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Surgical Intensive Care Medicine

SECOND EDITION

Springer

Surgical Intensive Care Medicine

Second Edition

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Edited by

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This book is dedicated to my wife, Rocky, and daughter, Jacquelyn, who give me purpose; to my beloved parents, Kay and Frank "Shorty" O'Donnell, who never lost faith; to my mentors, whose patience was tested every day; and to all of the nurses who have ever cared for patients in the surgical intensive care unit at the Lahey Clinic Medical Center.

John M. O'Donnell, M.D.

To my parents Lilian and Jacob, and my wife Alessandra, for their unconditional love; to my daughter Mariana, for the joy she brings to my life; and to my brother Luis and my uncle Sabino, for their support.

Flávio Eduardo Nácul, M.D.

Preface to the Second Edition

We are honored to present the second edition of *Surgical Intensive Care Medicine*. Our first edition was considered to be an important contribution to the critical care literature and received excellent reviews from *Critical Care Medicine*, *Chest*, and *Anesthesiology*. In the second edition, the basic organization of the book remains unchanged, being composed of 60 carefully selected chapters divided into 11 sections. The book begins with general topics in primary intensive care, such as airway management and vascular cannulation, followed by categories based on medical and surgical subspecialties. While the chapters discuss definitions, pathophysiology, clinical course, complications, and prognosis, the primary emphasis is devoted to patient management. The contents of the current edition have been comprehensively upgraded and the chapters retained from the first edition have been thoroughly updated, revised, or rewritten.

In this second edition, some new topics have been added including Postoperative Care of the Obese Patient, Postoperative Care of the Pancreas Transplant Patient, Optimization of High-Risk Surgical Patients, Postoperative Alcohol Withdrawal Syndrome, Ethics and End of Life Issues, Improving the ICU, and Continuous Medical Education in Intensive Care Medicine. We are extremely fortunate to have high-quality contributors, many of whom are nationally and internationally recognized researchers, speakers, and practitioners in Critical Care Medicine. An important feature of this latest edition is the geographical diversity of its authors. Most are based in the United States, but colleagues from Canada, England, Ireland, Germany, Belgium, Holland, France, Italy, Portugal, and Australia have also made notable contributions.

The book is written for medical students, residents, and critical care fellows in training, and its purpose is to educate, stimulate, and serve as a resource for all professionals caring for the critically ill. Those who are not involved in the daily care of the acutely ill patient but who seek information will also find this book a valuable resource. We are very fortunate to have Springer as our publisher and we are especially thankful to our chapter authors and their families. We anticipate that our book will be both educational and enjoyable and we hope that both our readers and their patients will benefit.

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Part I
Resuscitation and General Topics

Chapter 1
Supplemental Oxygen Therapy

Andrew G. Villanueva

Intensivists caring for critically ill patients in a surgical intensive care unit continually face multiple diverse and challenging problems. While the specific disease processes in these patients are myriad, a fundamental goal is to provide adequate cellular respiration and thereby maintain sufficient tissue oxygenation and normal organ function. Successful cellular respiration depends on the maintenance of several factors, including adequate alveolar ventilation, a functioning gas-exchange surface, the capacity to transport oxygen to the tissue, and intact tissue respiration (the mitochondrial cytochrome oxidase system). Subsequent chapters in this textbook describe problems with each of these factors and how intensivists should approach and manage them. This chapter focuses on alveolar ventilation and how to use supplemental oxygen therapy to improve arterial oxygenation in patients who are hypoxemic but do not require mechanical ventilation.

Pathophysiology of Hypoxemia

Hypoxemia is defined as a relative deficiency of oxygen in the arterial blood as measured by arterial oxygen tension (PaO_2). Hypoxia is defined as inadequate oxygen tension at the cellular level. Currently, there is no way for clinicians to directly measure hypoxia and the diagnosis must be made indirectly based on the assessment of organ function, oxygen delivery, and mixed venous oxygen tension. Hypoxemia and hypoxia are therefore not synonymous—patients may have hypoxia without hypoxemia, but patients cannot have sustained severe hypoxemia without developing hypoxia. It is thus imperative to promptly treat patients who have significant hypoxemia with supplemental oxygen.

The PaO_2 is determined by the inspired oxygen tension, the alveolar ventilation, and the distribution of ventilation and perfusion (V/Q) in the lungs. The five major mechanisms of hypoxemia are (1) decreased ambient fraction of inspired oxygen (FiO_2), (2) alveolar hypoventilation, (3) diffusion limitation across the alveolar-capillary membrane, (4) shunt, and (5) V/Q mismatch[1]. Decreased ambient FiO_2 is generally not a cause, unless the altitude is very high.

Pure alveolar hypoventilation in critically ill patients is often related to drug overdose; the excess use of medications that suppress the respiratory drive such as opiates or benzodiazepines; or catastrophic events of the central nervous system such as head trauma, stroke, subarachnoid hemorrhage, subdural hematoma, or cerebral edema. The hypoxemia is caused by a decrease in the alveolar oxygen tension (P_AO_2), which can be measured using the alveolar gas equation:

$$P_AO_2 = F_IO_2\,(PB - 47) - PaCO_2/R$$

where F_IO_2 is the fraction of inspired oxygen (expressed as a decimal), (PB – 47) is the barometric pressure minus water vapor pressure, $PaCO_2$ is the arterial carbon dioxide tension, and R is the respiratory quotient (usually 0.8). Clinically, hypoventilation results in a decreased PaO_2 and an elevated $PaCO_2$. With hypoventilation, however, the alveolar-arterial oxygen gradient ($[A\text{-}a]O_2$) and the arterial-alveolar ratio (PaO_2/P_AO_2) are normal (2.5 + [0.21 x age] mmHg, and 0.77-0.82, respectively). Diffusion limitation across the alveolar-capillary membrane, shunt, and V/Q mismatch all cause an abnormal $[A\text{-}a]O_2$ and PaO_2/P_AO_2.

Diffusion limitation across the alveolar-capillary membrane can be caused by pulmonary edema fluid or interstitial fibrotic tissue between the alveolar epithelium and the capillary endothelium. This impaired oxygen exchange is worsened as blood transit time through the pulmonary capillaries decreases, such as during exercise. Arterial hypoxemia secondary to diffusion defects is not common but is responsive to an increase in P_AO_2 using supplemental oxygen therapy.

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True shunt occurs when right-heart blood enters the left heart without an increase in oxygen content because the blood does not interact with alveolar gas (zero V/Q). The shunt can be intracardiac (e.g., atrial septal defect, patent foramen ovale) or intrapulmonary. Causes of intrapulmonary shunting include alveolar collapse, which occurs with acute lung injury or acute respiratory distress syndrome (ARDS); complete lobar collapse due to retained respiratory secretions; pulmonary arterial-venous malformations; and pulmonary-capillary dilatation, as is sometime seen in liver disease (the so-called "hepatopulmonary syndrome").[2] Oxygen therapy is of limited benefit with significantly increased shunt because, regardless of the F_IO_2, oxygen transfer cannot occur when blood does not come into contact with functional alveolar units. Therefore, true shunt pathology is refractory to oxygen therapy. The shunt, however, can be improved if the cause is lobar or alveolar collapse. Lobar lung collapse can often be reversed with appropriate bronchial hygiene or removal of the source of obstruction. Alveolar collapse resulting from destabilization of the alveolar architecture due to disruption of the surfactant layer, such as with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), can improve with the use of positive end expiratory pressure (PEEP), but this requires mechanical ventilation.

V/Q mismatch is defined as an imbalance between alveolar ventilation and pulmonary capillary blood flow. A detailed explanation of why V/Q mismatch results in hypoxemia is beyond the scope of this chapter, but this mechanism is believed to be the most common cause of hypoxemia.[3,4] V/Q mismatching can result from an array of disorders such as bronchospasm, chronic obstructive pulmonary disease (COPD), bronchial secretions, mild pulmonary edema, interstitial lung disease, venous thromboembolism, pleural effusion, pulmonary contusion, aspiration of gastric contents, and pneumonia, to name just a few. The hallmark of hypoxemia due to V/Q mismatch is that it improves with oxygen therapy. In contrast to shunt, an increase in the F_IO_2 causes a substantial increase in PaO_2.

Goals of Supplemental Oxygen Therapy

In general, the purpose of oxygen therapy is to correct hypoxemia by achieving a $PaO_2 \geq 60$ mmHg or an arterial oxygen saturation of $\geq 90\%$.[5] Little additional benefit is gained from further increases because of the functional characteristics of hemoglobin (Fig. 1.1). Different criteria are used for patients with COPD and chronic carbon dioxide retention. In these patients, values that define hypoxemia are PaO_2 of 50 to 55 mmHg, corresponding to an arterial oxygen saturation 88% to 90%.[6] These target values for PaO_2 or arterial oxygen saturation assume the presence of normally functioning hemoglobin. In situations with abnormal hemoglobins that cannot effectively bind oxygen, such as methemoglobinemia or carbon monoxide poisoning, even supranormal PaO_2 values may be associated with a reduction in available hemoglobin and resultant lower oxygen content.[7,8,9]

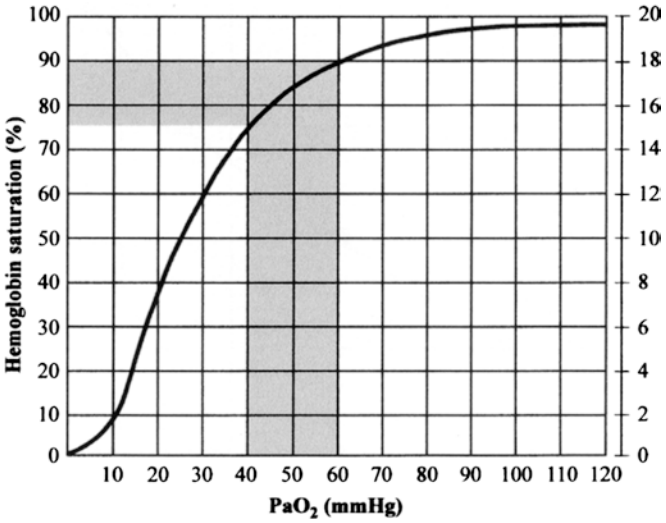

FIG. 1.1. The normal oxyhemoglobin dissociation curve for humans. The reversible chemical reaction between O_2 and hemoglobin is defined by the oxyhemoglobin equilibrium curve, which relates the percent saturation of hemoglobin to the PaO_2. Because of the characteristic sigmoid shape, the affinity for O_2 progressively increases as successive molecules of O_2 combine with hemoglobin. There are physiologic advantages in that the flat upper portion allows arterial O_2 content to remain high and virtually constant (>90%) despite fluctuations in arterial PaO_2 (60-100 mmHg), and the middle steep segment enables large quantities of O_2 to be released at the PaO_2 prevailing in the peripheral capillaries. Illustrations by Paul Singh-Roy reprinted from the Journal of Critical Illness Vol. 4, No. 6 June 1989 with permission from CMP Medica.

Other indications for oxygen therapy include suspected hypoxemia, acute myocardial infarction, severe trauma, and postoperative recovery from anesthesia.[5] Early clinical findings associated with hypoxemia include tachycardia, tachypnea, increased blood pressure, restlessness, disorientation, headache, impaired judgment, and confusion. Some patients may become euphoric and lack the classic signs and symptoms of hypoxemia. Severe hypoxemia is associated with slow, irregular respirations, bradycardia, hypotension, convulsions and coma.

Oxygen Delivery Systems

Oxygen delivery systems can be classified as low-flow (or variable-performance) and high-flow (or fixed performance) systems. Low-flow systems provide small amounts of 100% oxygen as a supplement, with F_IO_2 determined by the patient's pattern of breathing and minute ventilation. The greater portion of the inspired volume is obtained from room air. High-flow systems, on the other hand, are designed to supply premixed oxygen in volumes that provide the patient's total ventilatory requirements. An advantage of high-flow systems is that the level of F_IO_2 remains constant regardless of any changes that may occur in the ventilatory pattern.[10] In this section these two types of oxygen

delivery systems will be discussed, as well as delivery systems for helium-oxygen gas mixtures and for oxygen via positive pressure devices using a mask device instead of an endotracheal tube—so-called non-invasive ventilation (NIV).

Low-Flow Systems

Low-flow oxygen devices are the most commonly used because of their simplicity and ease of use, healthcare providers' familiarity with the system, low cost, and patient acceptance.

Nasal Cannula

The most frequently used low-flow oxygen delivery system consists of a pronged nasal cannula to deliver 100% oxygen at flow rates of 0.5 to 6 L/min, delivering an F_IO_2 ranging from 0.24 to 0.40. Patients generally cannot tolerate an oxygen flow rate of more than 6 L/min from the nasal cannula because of nasal discomfort. If the oxygen flow rate exceeds 4 L/min, the gases should be humidified to prevent drying of the nasal mucosa. As a rule, F_IO_2 increases by approximately 0.03 to 0.04 for each increase of 1 L/min in the oxygen flow rate, up to about 0.40 at 6 L/min (Table 1.1). However, in clinical practice this rule of thumb cannot be applied with confidence, because of variations in individual patients' breathing patterns. To be effective, the patient's nasal passages must be patent to allow filling of the anatomic reservoir. The patient, however, does not need to breathe through the nose, because oxygen is entrained from the anatomic reservoir even in the presence of mouth breathing.

The nasal cannula is advantageous because of the comfort and convenience it affords—the patient may eat, speak, and cough with it in place. Except for irritation of the nasal mucosa at higher flow rates and an occasional reaction to chemical components of the tubing, cannulas are well tolerated.

TABLE 1.1. Flow rates and F_IO_2 with low-flow oxygen-delivery devices. Predicted F_IO_2 values for low-flow systems assume a normal and stable pattern of ventilation.[12]

Low-flow system	Oxygen flow rates (L)	F_IO_2
Nasal cannula	1	0.24
	2	0.28
	3	0.32
	4	0.36
	5	0.40
	6	0.44
Simple fa ce mask	5-6	0.40
	6-7	0.50
	7-8	0.60
Partial-rebreathing mask	6	0.60
	7	0.70
	8	0.80
	9	0.80+
	10	0.80+
Nonrebreathing mask	10	0.80+
	15	0.90+

The physiologic disadvantage of cannula use is that F_IO_2 varies with the patient's breathing pattern, and calculations requiring accurate F_IO_2 data cannot be made. In most patients with mild hypoxemia, precise knowledge of F_IO_2 is unnecessary and clinical improvement occurs rapidly.

Simple Face Mask

A simple oxygen mask is a low-flow system that delivers approximately 35% to 50% oxygen at flow rates of 5 L/min or greater. The mask provides a reservoir (100 to 200 mL) next to the patient's face to increase the fraction of oxygen in the tidal volume. The open ports in the sides of the mask allow entrainment of room air and venting of exhaled gases. Because the mask fits over the nose and mouth, the volume it contains may increase ventilatory dead space; flow rates of 5 L/min or greater are required to keep the mask flushed.[11] Flow rates greater than 8 L/min do not increase the F_IO_2 significantly above 0.6 (Table 1.1). The disadvantages of using this device include the resultant variable F_IO_2 and the fact that it must be removed for eating or drinking.

Partial-Rebreathing Mask

Partial rebreathing and nonrebreathing masks with 600- to 1,000-mL reservoir bags (Fig. 1.2) can deliver high inspired

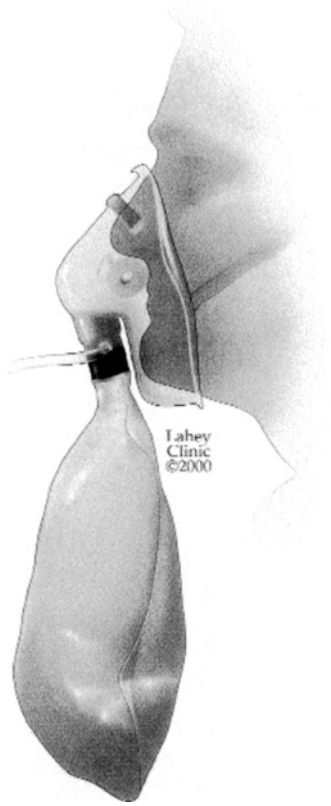

FIG. 1.2. Rebreathing mask with reservoir bag.

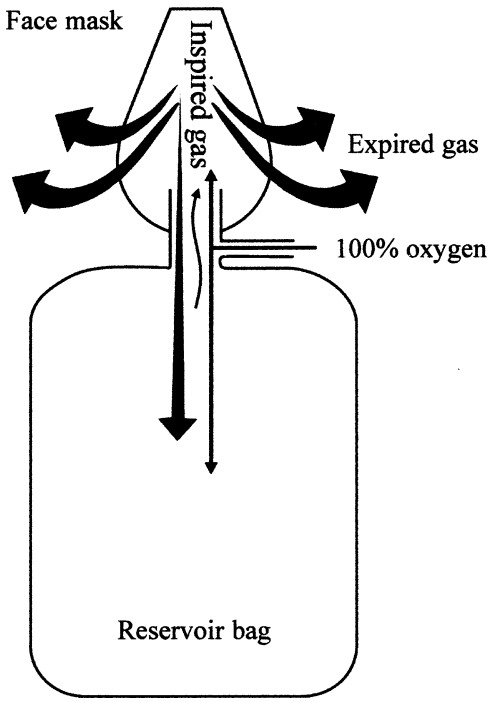

FIG. 1.3. Partial-rebreathing mask. The mask captures the first portion of exhaled gas (dead-space gas) in the reservoir bag. The remainder of the reservoir bag is filled with 100 percent oxygen. Reprinted from Shapiro BA, Kacmarek RM, Cane RD, et al. Clinical application of respiratory care. 4th edition. St. Louis: Mosby Year Book 1991 with permission from Elsevier.

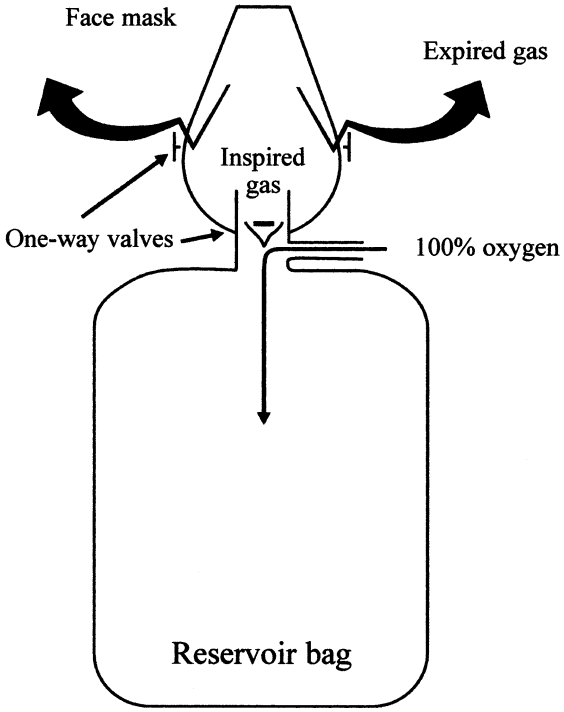

FIG. 1.4. Nonrebreathing mask. The one-way valves of the nonrebreathing mask prevent expired gases from reentering the reservoir bag. The tidal volume with this device should be nearly 100% oxygen. Reprinted from Shapiro BA, Kacmarek RM, Cane RD, et al. Clinical application of respiratory care. 4th edition. St. Louis: Mosby Year Book 1991 with permission from Elsevier.

oxygen concentrations of greater than 50% with low flow rates.[6] In partial rebreathing masks, the first one-third of the patient's exhaled gas fills the reservoir bag (Fig. 1.3). Because this gas is primarily from anatomic dead space, it contains little carbon dioxide. With the next breath, the patient inhales a mixture of the exhaled gas and fresh gas. If the fresh gas flows are equal to or greater than 8 L/min and the reservoir bag remains inflated throughout the entire respiratory cycle, adequate carbon dioxide evacuation and the highest possible F_IO_2 should occur (Table 1.1). The rebreathing capacity of this system allows some degree of oxygen conservation, which may be useful while transporting patients with portable oxygen supplies.[12]

Nonrebreathing Mask

A nonrebreathing mask is similar to a partial-rebreathing mask but with the addition of three unidirectional valves (Fig. 1.4). Two of the valves are located on opposite sides of the mask; they permit venting of exhaled gas and prevent entrainment of room air. The remaining unidirectional valve is located between the mask and the reservoir bag and prevents exhaled gases from entering the fresh gas reservoir. As with the partial-rebreathing mask, the reservoir bag should be inflated throughout the entire ventilatory cycle to ensure adequate carbon dioxide clearance from the system and the highest possible F_IO_2.[12] Because its bag is continuously filled with 100% oxygen and expired gases do not enter the reservoir, the tidal volume should be nearly 100% oxygen (Table 1.1). To avoid air entrainment around the mask and dilution of the delivered FIO_2, masks should fit snugly on the face, but excessive pressure should be avoided. If the mask is fitted properly, the reservoir bag should partially deflate and inflate with the patient's inspiratory efforts.

The disadvantages of high F_IO_2 masks include the risk of absorption atelectasis and the potential for oxygen toxicity if they are used for longer than 24 to 48 hours. Therefore, these masks are only recommended for short-term treatment. Critically ill patients with profound hypoxemia usually require ventilatory assistance as well, because pure hypoxic respiratory failure rarely occurs without concomitant or subsequent ventilatory failure.

Tracheostomy Collars

Tracheostomy collars primarily are used to deliver humidity to patients with artificial airways. Oxygen may be delivered with these devices, but as with other low-flow systems the F_IO_2 is unpredictable, inconsistent, and depends on the patient's ventilatory pattern.

High-Flow Systems

In contrast to low-flow systems, high-flow systems are designed to deliver a large volume of premixed gas. Because the patient is breathing only gas applied by the system, the flow rate must exceed the patient's minute ventilation and meet the patient's peak inspiratory demand. The advantages of a high-flow system include the ability to deliver relatively precise oxygen concentrations, control the humidity and temperature of the inspired gases, and maintain a fixed inspired oxygen concentration despite changes in the ventilatory pattern.

Air-entrainment (Venturi) Mask

Air-entrainment masks (Fig. 1.5), commonly called "Venturi masks," entrain air using the Bernoulli principal and constant pressure-jet mixing.[13] A jet of oxygen is forced through a small opening that because of viscous shearing forces creates a subatmospheric pressure gradient downstream relative to the surrounding gases (Fig. 1.6). The proportion of oxygen can be controlled by enlarging or reducing the size of the injection port. A smaller opening creates greater pressure of oxygen flow, resulting in more room air entrained and a lower percentage of inspired oxygen. As the desired F_IO_2 increases, the air-to-oxygen-entrainment ratio decreases with a net reduction in total gas flow. Therefore, the probability of the patient's ventilatory needs exceeding the total flow capabilities of the device increases with higher F_IO_2 settings.[12]

Occlusion of or impingement on the exhalation ports of the mask can cause back-pressure and alter gas flow. The oxygen-injector port also can become clogged, especially with water droplets. Aerosol devices should therefore not be used with Venturi masks; if humidity is necessary, a vapor-type humidifier should be used.[12]

The major indication for the use of Venturi masks is the need for precise control of the F_IO_2 between 0.24 and 0.40 when providing oxygen therapy to patients with COPD who are hypercarbic (Table 1.2). For patients with COPD who have a $PaCO_2$ greater than 45 mmHg, it is generally recommended that the F_IO_2 be low initially (0.24 to 0.28) and then adjusted upward to maintain an oxygen saturation of 88% to 90%. Using devices that deliver a high F_IO_2 to patients with

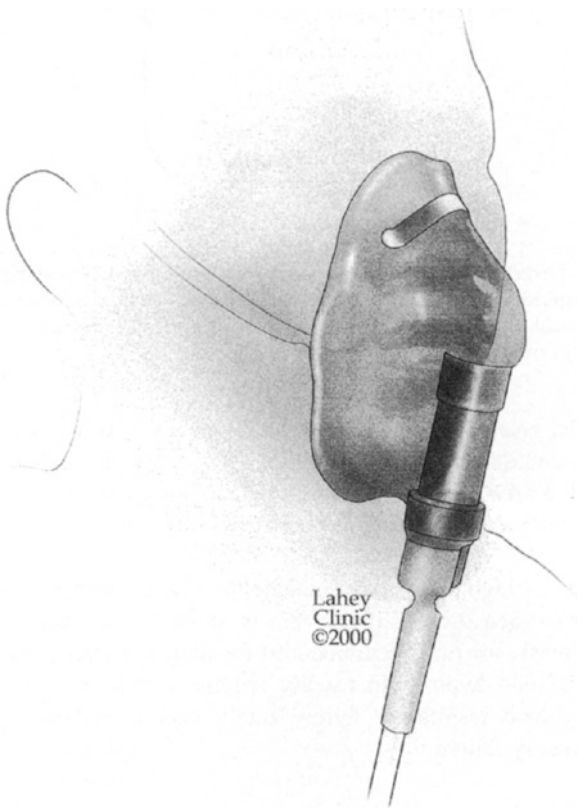

FIG. 1.5. Air-entrainment (Venturi) mask.

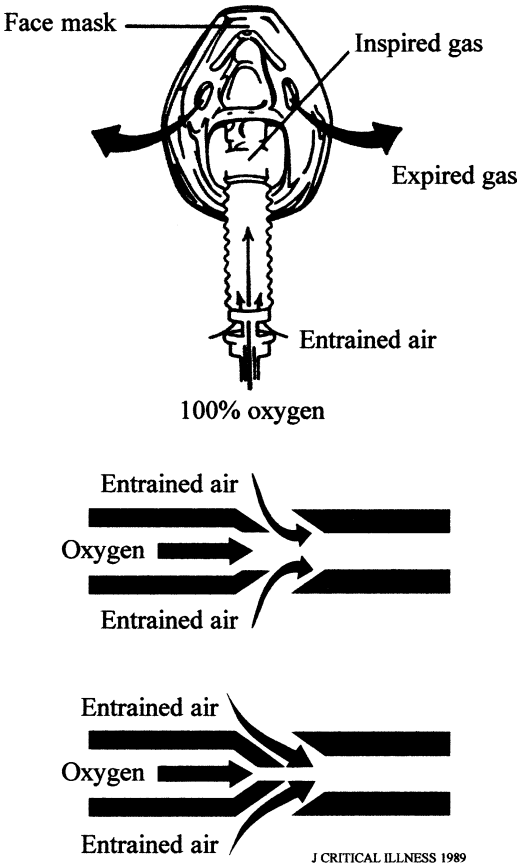

FIG. 1.6. Air-entrainment (Venturi) mask and the Bernoulli principal. A jet of oxygen is forced through a small opening, which creates a low-pressure area around it and entrains ambient air. The proportion of oxygen can be controlled by enlarging or reducing the size of the injection port. A smaller opening creates pressure of oxygen flow, resulting in more room air entrained and a lower percentage of inspired oxygen. Illustrations by Paul Singh-Roy reprinted from The Journal of Critical Illness Vol. 4, No. 6 June 1989 with permission from CMP Medica.

TABLE 1.2. Air entrainment ratios and total gas outflows of commercially available Venturi masks.[14]

O_2 concentration of delivered gas	Liters of air entrained per liter O_2	Total gas outflow (liter/min)
24	25.3	105(DF=4)
28	10.3	68 (DF=6)
31	6.9	63 (DF=8)
35	4.6	56 (DF=10)
40	3.2	50 (DF=12)
50	1.7	33 (DF=12)

DF, highest driving flow of oxygen, in liters per minute, recommended by the manufacturer for a given concentration. In general, the highest driving flow should be used to provide the highest total gas outflow.

COPD and elevated $PaCO_2$ can result in a high PaO_2, which can lead to further elevations in $PaCO_2$ and worsening respiratory acidosis. (See "Complications of Oxygen Therapy.")

Aerosol Mask

An F_IO_2 greater than 0.40 with a high-flow system is best provided with a large-volume nebulizer and wide-bore tubing. Aerosol masks, in conjunction with air-entrainment nebulizers or air/oxygen blends, can deliver a consistent and predictable F_IO_2 regardless of the patient's ventilatory pattern. An air-entrainment nebulizer can deliver an F_IO_2 of 0.35 to 1.0, produce an aerosol, and generate flow rates of 14 to 16 L/min. Air/oxygen blenders can deliver a consistent F_IO_2 ranging from 0.21 to 1.0, with flows up to 100 L/min. These devices are generally used in conjunction with humidifiers.[12]

Helium-Oxygen Therapy

There are situations in which it may be beneficial to combine oxygen with a gas other than nitrogen. Helium and oxygen, for instance, can be combined to form a therapeutic gas mixture known as "heliox." Heliox reduces the density of the delivered gas, thereby reducing the work of breathing and improving ventilation in the presence of airway obstruction.[15,16,17] When there is airflow obstruction due either to an obstructing lesion in the central airways or narrowing of the peripheral airways from bronchospasm, turbulent flow of the airway gases predominates over the usual laminar flow. Turbulent flow requires a greater driving pressure than laminar flow does and is inversely proportional to the density of the gas being inspired. Clinically, a 60:40 or 70:30 ratio of helium to oxygen is generally recommended. The combination is administered through a well-fitted nonrebreathing mask with a complete set of one-way valves. The reported clinical benefits of administering heliox to patients with severe asthma include improved ventilation, avoidance of mechanical ventilation, decreased paradoxical pulse, and increased peak expiratory flow rates.[18,19] Because the benefits of heliox dissipate if the ratio for helium to oxygen is less than 60:40, it should not be used if a high F_IO_2 is required to treat the patient's hypoxemia.

Noninvasive Ventilation

All of the oxygen delivery devices previously mentioned are used in patients who are spontaneously breathing and require no assisted ventilation. The use of mechanical ventilation via an endotracheal tube to treat patients with hypoxemic or hypercarbic respiratory insufficiency are described elsewhere in this text. Oxygen also can be delivered using mechanical ventilators via a mask strapped to the patient's face, without the need for tracheal intubation. The mask can either be a nasal mask, which fits snugly around the nose, or a full facial mask, which covers both the nose and mouth. Success for this mode of oxygen delivery depends in large part on the patient's acceptance and tolerance to the tight-fitting mask (Fig. 1.7).

Continuous Positive Airway Pressure (CPAP)

A continuous positive pressure is delivered throughout the respiratory cycle, either by a portable compressor or from a

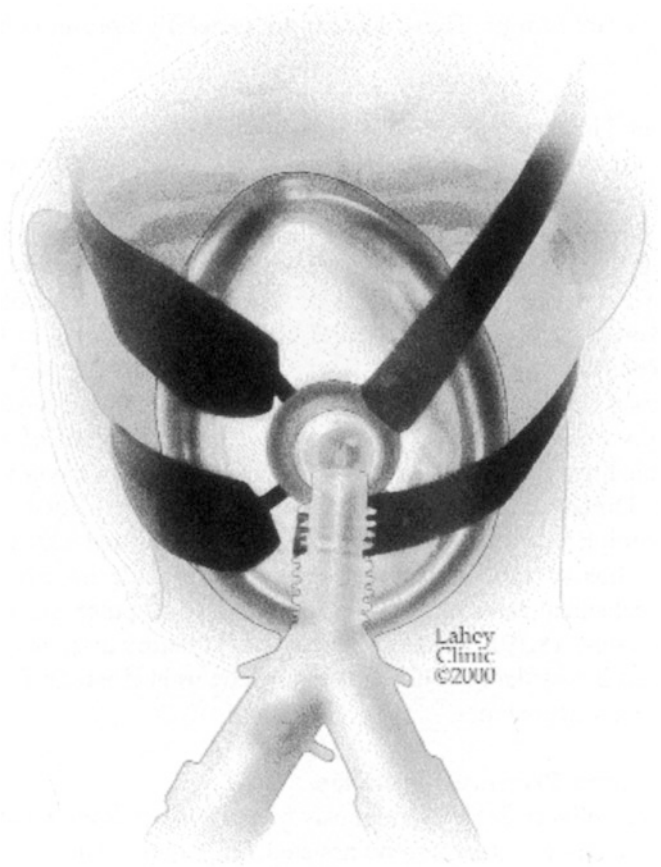

FIG. 1.7. Full-face mask used for noninvasive positive pressure ventilation.

flow generator in conjunction with a high-pressure gas source. Oxygen can be delivered by attaching a low-flow system to the mask or by adjusting the F_IO_2 delivered by the mechanical ventilator. The major use of CPAP, particularly when delivered by a nasal mask, is to treat obstructive sleep apnea. It does, however, also have a role in the critically ill patient because it can improve oxygenation by opening collapsed alveoli and reduce the work of breathing by increasing functional residual capacity, thus moving the patient onto the more compliant portion of the pressure volume curve.[20,21,22] Mask CPAP is also an effective treatment for cardiogenic pulmonary edema, because positive intrathoracic pressure reduces both cardiac preload and afterload; it has been shown to decrease the need for intubation.[23,24,25] Typically, pressures of 5 to 15 cm H_2O of CPAP are applied, depending on the effect on oxygenation and patient comfort. Mask CPAP can only be used in patients who are breathing spontaneously, and is contraindicated in those who are hypoventilating. For these patients, noninvasive ventilation (NIV) may be a treatment option. Indeed, some recent studies comparing mask CPAP and NIV in the treatment of cardiogenic pulmonary edema showed that while both modalities reduced intubation rates[26], there may be more rapid improvement in gas exchange with NIV than with CPAP alone.[27,28] NIV may therefore be preferable for patients with persisting dyspnea or hypercapnia after the initiation of mask CPAP.

Noninvasive Ventilation (NIV)

NIV is defined as the delivery of mechanically assisted or generated breaths without placement of an artificial airway (endotracheal or tracheostomy tube). The benefits are similar to those of mechanical ventilation delivered through an artificial airway without the risks associated with endotracheal intubation, including the risk of ventilator-associated pneumonia. As with mask CPAP, oxygen can be delivered via a low-flow device attached to a nasal or full facial mask, or by adjusting the F_IO_2 delivered by the mechanical ventilator. Several early studies of NIV in acute respiratory failure used volume-controlled ventilators, but most clinical trials have been performed with pressure-controlled ventilation, delivered either in the pressure support mode or with bi-level positive airway pressure ventilation.[29] Bi-level positive airway pressure ventilation delivers both inspiratory pressure support and an expiratory pressure. "BiPAP" refers to a specific bi-level positive airway pressure ventilator manufactured by the Respironics Corporation, which has been used in some trials. The term BiPAP is often erroneously used interchangeably with bi-level positive airway pressure ventilation, which can also be delivered by most conventional ventilators.

Prospective, randomized, controlled trials over the last two decades have shown that the technique is efficacious in the treatment of many forms of acute respiratory failure. There is strong evidence for its use in COPD exacerbations[30,31,32], acute cardiogenic pulmonary edema[33], immunocompromised patients, and for the facilitation of weaning in COPD patients.[34,35,36] Recent reviews on the use of NIV for COPD exacerbations have summarized the benefits of reduced intubation rate, mortality, and hospital length of stay[37,38] and suggest that the use of NIV in many of these patients should be the standard of care.[39] NIV produces few complications other than local damage related to pressure effects of the mask and straps.[40] Cushioning the forehead and the bridge of the nose before attaching the mask can decrease the likelihood of these problems. Mild gastric distention occurs with some frequency but is rarely significant at routinely applied levels of inspiratory pressure support (10-25 cm H_2O), and the routine use of a nasogastric tube is not warranted. Ocular irritation and sinus pain or congestion may occur and require lower inspiratory pressure or the use of a face mask rather than a nasal mask.

Bedside Monitoring of Oxygenation

As mentioned previously, the purpose of oxygen therapy is to correct hypoxemia by achieving a $PaO_2 \geq 60$ mmHg or an arterial oxygen saturation $\geq 90\%$.[5] The readily available tools to measure oxygenation of arterial blood are arterial blood gas analysis and pulse oximetry.

Arterial Blood Gas Analysis

Arterial blood gas analysis allows the intermittent, direct measurement of pH, PaO_2, $PaCO_2$, and O_2 saturation of hemoglobin in arterial blood. While oxygenation cannot be continuously monitored with this method, the measurement of pH and $PaCO_2$ helps determine a patient's acid-base status and the adequacy of the alveolar ventilation, because the $PaCO_2$ is inversely proportional to the alveolar ventilation. Arterial blood gas analysis also allows a more sensitive means to detect subtle degrees of hypoxemia, compared with pulse oximetry. By knowing the F_IO_2 being administered to the patient and the patient's $PaCO_2$ and PaO_2, the alveolar gas equation can be used to measure the alveolar-arterial oxygen gradient (see "Pathophysiology of Hypoxemia"). The normal $(A\text{-}a)O_2$ gradient varies with age and ranges from 7 to 14 mmHg when the patient is breathing room air; the gradient increases in cases of diffusion impairment, right-to-left shunt, and V/Q mismatch. The following equation can be used to estimate the expected $(A\text{-}a)O_2$ gradient[41]:

$$(A\text{-}a)O_2 = 2.5 + 0.21 \times \text{age in years}$$

Measurement of the $(A\text{-}a)O_2$ is most useful when the patient is breathing room air, because it increases with higher inspired oxygen concentrations.[42] Another useful index for measuring arterial oxygenation is the ratio of PaO_2 to P_AO_2 (PaO_2/P_AO_2), which also can be calculated using data from arterial blood gas measurements.[43,44] The lower limit of normal PaO_2/P_AO_2 is 0.77 to 0.82.[43]

Pulse Oximetry

The use of pulse oximetry is now considered the standard of care when monitoring patients being treated for hypoxemia.

It is noninvasive, inexpensive, and simple, and requires only the placement of a probe on a finger, toe, or ear. The convenience of pulse oximetry measurements may improve patient monitoring and reduce the number of samples that must be obtained for arterial blood gas analysis. However, PaO_2 and arterial oxygen saturation (SaO_2) should always be measured directly via arterial blood gas analysis at the inception of pulse oximetry monitoring of critically ill patients. SaO_2 is measured by CO-oximetry, a technique that quantifies four species of hemoglobin in arterial blood: oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin.[45] Pulse oximeters can detect only two hemoglobin species: oxyhemoglobin and deoxyhemoglobin.[46,47,48]

The pulse oximeter functions when any pulsating arterial vascular bed is positioned between a dual-wavelength light-emitting diode (LED) and a detector. The LED emits red light (wavelength, 660 nm) and infrared light (wavelength, 900 to 940 nm). As the pulsating bed expands and relaxes, it creates a change in the length of the light path, modifying the amount of light detected. A plethysmographic waveform results. Photodiodes are switched on and off several hundred times per second by a microprocessor, while the photodetector records changes in the amount of red and infrared light absorbed. The pulsatile component (reflecting absorption by pulsatile arterial blood) is divided by the baseline component (reflecting absorption by nonpulsatile arterial blood, venous and capillary blood, and tissue) for both wavelengths. Ratios are used to obtain a signal that is related to saturation.[46,47,48]

Pulse oximetry has been shown to be accurate to within 3% to 4% in the range of 70% to 100% saturation.[49] Loss of pulsation, which can occur with hypotension, hypothermia, or vasoconstriction, causes a loss of signal. Because pulse oximetry is dependent on perfusion, it works well during primary respiratory arrest but is unreliable during cardiac arrest. Pulse oximetry is more accurate in light-skinned than in dark-skinned patients. For light-skinned patients, a less conservative target SaO_2 of 90% to 92% is recommended for oxygen titration. For dark-skinned patients, a target value of 95% should be adequate.[50]

Carbon monoxide is not detected by pulse oximetry, so that pulse oximetry overestimates oxygen saturation in patients who have been exposed to smoke or who actively smoke cigarettes. Pulse oximetry is also inaccurate in the presence of methemoglobinemia, which results from exposure to chemicals or drugs (such as dapsone, benzocaine, nitrates, and sulfonamides) that oxidize the iron in hemoglobin of susceptible patients from its ferrous to its ferric state.[49] Oxyhemoglobin absorbs more light at 940 nm than at 660 nm, reduced hemoglobin has the opposite property, and methemoglobin absorbs light equally at both wavelengths. These facts underlie the miscalculation of oxygen saturation in the presence of methemoglobin. When light absorption at both wavelengths is equal, the pulse oximeter records an oxygen saturation of 85%. Therefore, increasing levels of methemoglobin cause the pulse oximetry reading to gravitate toward 85%. If the actual oxygen saturation of a patient with methemoglobinemia is over 85%, the pulse oximeter underestimates it; if it is less than 85%, the pulse oximeter overestimates it.[49]

Despite these potential problems, pulse oximetry is extremely useful when monitoring hypoxemic patients being treated in the intensive care unit. It should be remembered that the technique does not assess arterial pH or $PaCO_2$ and that marked changes in PaO_2 can occur with only modest changes in SaO_2 if the latter is above 90%. Pulse oximetry, therefore, does not eliminate the need for arterial blood gas determinations in acutely ill patients.

Complications of Oxygen Therapy

While the benefits of supplemental oxygen therapy for hypoxemic patients heavily outweigh the risks in most cases, there are potential problems of which the intensivist should be aware.

Worsening Acute on Chronic Respiratory Acidosis

Acute respiratory failure in patients with COPD is characterized by increased $PaCO_2$ and severe hypoxemia. When oxygen is administered to these patients, their $PaCO_2$ levels commonly increase.[51,52] Hypothesized mechanisms for oxygen-induced hypercarbia include a decrease in minute ventilation caused by removal of the hypoxic stimulus[53,54], increased V/Q inequality in the lung caused by release of hypoxic vasoconstriction[55,56,57], and the effect of oxygen on the hemoglobin-carbon dioxide dissociation curve of blood[56], the so-called "Haldane effect." There is still ongoing debate as to which of these mechanisms is most important[58,59] in causing the hypercarbia, but it is now accepted that supplemental oxygen does not cause these patients to "stop breathing."[60] If worsening respiratory acidosis occurs with the initiation of oxygen therapy in a patient with severe hypoxemia, treatment choices include decreasing the F_IO_2 to achieve a lower but acceptable SaO_2, noninvasive positive pressure ventilation to improve oxygenation while maintaining a satisfactory minute ventilation, and tracheal intubation for assisted ventilation.

Absorption Atelectasis

Absorption atelectasis occurs when high alveolar oxygen concentrations cause alveolar collapse. Ambient nitrogen, an inert gas, remains within the alveoli and splints alveoli open. When a high FIO2 is administered, nitrogen is "washed out" of the alveoli, and the alveoli are filled primarily with oxygen. In areas of the lung with reduced V/Q ratios, oxygen is absorbed into the blood faster than ventilation can replace it. The affected alveoli then become progressively smaller until they reach the critical volume at which surface-tension forces cause alveolar collapse. This problem is most frequently

encountered in spontaneously breathing patients who are given oxygen in concentrations greater than 0.70.

Oxygen Toxicity

A high F_IO_2 level can be injurious to the lungs. The mechanism of oxygen toxicity is related to a significantly higher production rate of oxygen free radicals such as superoxide anions, hydroxyl radicals, hydrogen peroxide, and singlet oxygen. These radicals affect cell function by inactivating sulfhydryl enzymes, interfering with DNA synthesis, and disrupting the integrity of cell membranes. During period of lung-tissue hyperoxia, the normal oxygen-radical-scavenging mechanisms are overwhelmed, and toxicity results.[61,62] The F_IO_2 at which oxygen toxicity becomes important is controversial and varies depending on the animal species, degree of underlying lung injury, ambient barometric pressure, and duration of exposure. In general, it is best to avoid exposure to an F_IO_2 greater than 0.6 for more than 24 hours, if possible. However, correction of severe hypoxemia takes precedence over the potential of oxygen toxicity.

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2
Airway Management in the Intensive Care Unit

Denis H. Jablonka and William Rosenblatt

Securing the patient's airway is one of the most basic skills an intensivist must master. Mishandling the airway in critical care patients may result in severe if not fatal complications. This chapter will focus on understanding how the clinician chooses basic or advanced airway techniques.

Critical care patients who require ventilatory support present with unique concerns that make them vulnerable during airway management. Patients in the intensive care unit may have compromised cardiopulmonary function, which will limit their ability to tolerate even short periods of apnea. Septic shock, the need for hemodynamic support, and the anticipation of positive pressure ventilation may also limit the use of drugs to provide adequate sedation and relaxation of the airway. Prolonged intubation, post extubation stridor, and self extubation are common events that may make airway management particularly challenging in the intensive care setting.

Review of Airway Anatomy

The human airway is a complex anatomical entity since it is comprised of structures from both the respiratory as well as the digestive system. The airway is derived from the primitive pharynx with the appearance of the laryngo-tracheal groove at about 4 weeks of gestation.

The airway can also be classified as the upper airway, also known as the upper respiratory system, and includes the nose, the nasal cavity, the paranasal sinuses, the nasopharynx, and the oropharynx. The lower respiratory system includes the larynx, trachea, bronchi, and lungs.

Because the oroesophageal and nasotracheal passages intersect each other, anatomic and functional complexities have evolved for the protection of the sublaryngeal airway against aspiration of food that passes through the pharynx.Similar to other systems in the body, it is not immune from the influence of genetic, nutritional, and hormonal factors.

The laryngeal skeleton consists of nine cartilages (three paired and three unpaired); together, these house the vocal folds, which extend in an anterior–posterior plane from the thyroid cartilage to the arytenoid cartilages. The shield-shaped thyroid cartilage acts as the anterior "protective housing" of the vocal mechanism. Movements of the laryngeal structures are controlled by two groups of muscles: the extrinsic muscles, which move the larynx as a whole, and the intrinsic muscles, which move the various cartilages in relation to one another. The larynx is innervated bilaterally by two branches of each vagus nerve: the superior laryngeal nerve and the recurrent laryngeal nerve. Because the recurrent laryngeal nerves supply all the intrinsic muscles of the larynx (with the exception of cricothyroid), trauma to these nerves can result in vocal cord dysfunction. As a result of unilateral nerve injury, airway function is usually unimpaired, but the protective role of the larynx in preventing aspiration may be compromised.

The cricothyroid membrane (CTM) provides coverage to the cricothyroid space. The membrane, which is typically 9 mm in height and 3 cm in width, is composed of a yellow elastic tissue that lies directly beneath the skin and a thin fascial layer. It is located in the anterior neck between the thyroid cartilage superiorly and the cricoid cartilage inferiorly. It can be identified 1 to 1.5 fingerbreadths below the laryngeal prominence (thyroid notch, or Adam's apple). It is often crossed horizontally in

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its upper third by the anastomosis of the left and right superior cricothyroid arteries. The membrane has a central portion known as the conus elasticus and two lateral portions, which are thinner and located directly over the laryngeal mucosa. Because of anatomic variability in the course of veins and arteries and its proximity to the vocal folds (which are 0.9 cm above the ligaments' upper border), it is suggested that any incisions or needle punctures to the cricothyroid membrane be made in its inferior third and be directed posteriorly.

At the base of the larynx is the signet ring–shaped cricoid cartilage suspended by the underside of the cricothyroid membrane. This cartilage is approximately 1 cm in height anteriorly, but almost 2 cm in height in its posterior aspect as it extends in a cephalad direction, behind the cricothyroid membrane and the thyroid cartilage. The trachea is suspended from the cricoid cartilage by the cricotracheal ligament (CTL). The trachea measures ~15 cm in adults and is circumferentially supported by 17 to 18 C-shaped cartilages, with a posterior membranous aspect overlying the esophagus.

The first tracheal ring is anterior to the sixth cervical vertebrae. The trachea ends at the carina at the level of the fifth thoracic vertebra, where it bifurcates into the principal bronchi. The right principal bronchus is larger in diameter than the left and deviates from the plane of the trachea at a less acute angle. Aspirated materials, as well as a deeply inserted tracheal tube, tend to gain entry into the right principal bronchus though a left-sided position can not be excluded. Cartilaginous rings support the first seven generations of the bronchi.

Patient History and Physical Exam

Airway History

Airway evaluation should include a thorough history of airway-related events as well as symptoms of airway compromise. A search for documentation to confirm or elucidate these problems should be conducted. The patient's medical chart may provide important information in the Pre-hospital, Emergency Room, and Anesthesia records when available. They may describe whether intubation was performed in an awake, sedated, or anesthetic state; which device was used; how many intubation attempts were made; and what sedatives and muscle relaxants were administered, if any.

Physical Exam

Clues to potential difficult airway can be quickly identified at the first patient encounter. Obvious signs such as airway bleeding or severe facial and neck swelling, as well as subtle signs such as a tracheostomy scar or a small jaw may alert the expert clinician to seek more advanced airway equipment and extra help. Almost any systemic disease may affect the airway. Endocrine diseases such as diabetes, for example, may impair neck mobility due to joint stiffness. Thyroid masses may distort the airway. Lymphomas may cause life threatening airway compression by mediastinum involvement. Scleroderma may limit oral aperture. Digestive problems may increase the risk of pulmonary aspiration and the list continues (Table 2.1).

The Mallampati Airway classification is the most commonly used physical exam index for assessing the likely difficulty of direct laryngoscopy (DL).[1] This classification is based in the operator's ability to see the oropharynx with a patient sitting upright, with the mouth open as wide as possible, and the tongue extended (without phonation). A class III is defined as the view of only the soft palate as opposed to a class I in which the faucial pillars, the uvula, and the soft palate are fully visualized. The Mallampati classification is far from being the only criteria upon which the airway care provided should be evaluated. A Mallampati class III view has a positive predictive value of 4.5% in some studies.[2]

Other parameters have also been correlated with a difficult laryngoscopy.[2,3] An oral aperture of less than 4 cm is associated with difficult DL. It is best described as the distance between

Table 2.1. Syndromes associates with difficult airway management.

Pathological condition	Airway features
Congenital	
Pierre Robin sequence	Micrognathia, macroglossia, glossoptosis, cleft soft palate
Treatcher Collins syndrome (mandibulofacial dysostosis)	Eye and ear defects, microstomia, choanal atresia, malar and mandi-bular hypoplasia
Goldenhar's syndrome (oculo-auriculo-vertebral syndrome)	Ear and eye defects; malar and mandibular hypoplasia, occipitalization of the atlas
Down's syndrome (mongolism)	Macroglossia, microcephaly, cervical spine abnormalities (atlantoaxial subluxation)
Acquired	
Neoplasic: benign	
Cystic hygromas, goiter, lipomas, adenomas	Airway distortion, airway obstruction
Neoplasic: malignant	
Tongue CA, larynx CA, thyroid CA	Stenosis, anatomy distortion, SVC syndrome (airway edema), tissue fibrosis (radiation therapy)
Inflammatory	
Rheumatoid disease	Cervical spine instability and restriction, temporomandibular joint (TMJ) ankylosis, larynx deviation
Ankylosing Spondylitis	Cervical spine restriction, TMJ ankylosis
Traumatic	
Head and neck trauma, facial Injury	Airway edema, hemorrhage, skull base fracture, C-spine trauma, maxillary, mandibular fracture
Infectious	
Supraglottitis, croup, abscess, papillomatosis, Ludwig's angina	Laryngeal edema, airway distortion, trismus
Miscellaneous	
Morbid obesity	Short neck, large tongue
Acromegaly	Macroglossia, prognathism
Acute burn	Airway edema

the upper and lower incisor teeth or between the upper and lower alveolar ridge in the edentulous patient. Patients with trismus, temporomandibular joint disease, or long-standing mandibular fractures may have their oral apertures severely restricted during the laryngoscopy making it difficult to intubate. Inability to fully open the mouth has a stronger predictive value for a difficult intubation than the Mallampati class.

Limited range of neck motion of less than 35° from the neutral position makes DL difficult. Patients with cervical spine disease or cervical spine trauma cannot be optimally positioned for intubation due to both restrictions of movement and because of risk of further spinal cord injury. These patients should have the c-spine protected by neck collar and/or inline stabilization during laryngoscopy. A fiber-optic device is strongly warranted in these cases.

The distance from the mental prominence to the thyroid cartilage (TMD) of less than 6 cm has been strongly linked with difficult laryngoscopy (Fig. 2.1). A small mandible may be associated with extra tongue tissue in the hypopharynx, making airway visualization difficult. A TMD of less than 6 cm has the strongest predictive value for an impossible laryngoscopy when compare to all other physical parameters. The clinician should have a high index of suspicion when assessing a patient with acquired or congenital disorders of the mandible.

Inability to prognath is another important finding in a cooperative patient (Fig. 2.2). Laryngoscopy often requires a forward movement of the jaw in order to obtain proper airway visualization. Temporomandibular joint disease has been associated with unexpected difficult DL.[4]

In addition to difficult DL, difficult mask ventilation should also be considered when evaluating a patient for airway management. Risk factors for difficult mask ventilation are independent of difficult DL risk factors. These include: (1) presence of a full beard, (2) a history of snoring, (3) the edentulous patient, (4) a body mass index of greater than 26, and (5) age greater than 56.[5,6]

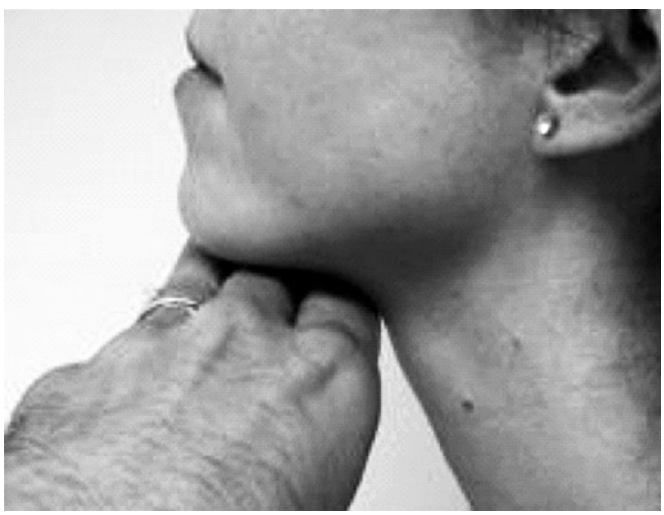

FIG. 2.1. Normal thyromental distance of 6 cm.

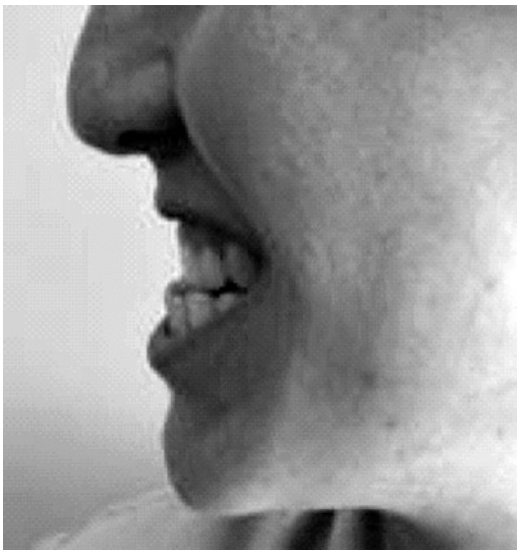

FIG. 2.2. The ability to prognath.

Clinical Management of the Airway

Preoxygenation

In order to improve tolerance to apnea during airway management, preoxygenation should be attempted in every patient. This is best accomplished by having the patient breathe 100% oxygen for 5 min or more. In patients without compromised cardiopulmonary function, this maneuver may allow apnea of up to 10 min before the patient becomes hypoxemic.

Patients with compromised cardiopulmonary function and those who are in septic or cardiogenic shock may not respond profoundly to preoxygenation. The presence of pulmonary edema, ventilation/perfusion mismatch, or increased metabolism will impair the ability to increase the arterial oxygen tension and/or shorten the time to hypoxemia. For this reason, extreme care should be taken not to expose these patients to prolonged apnea and to minimize the number of laryngoscopy attempts.[7]

Intravenous Sedatives and Muscle Relaxants

When appropriate, intravenous hypnotics and muscle relaxation should be administered to a patient prior to intubation. The combination of sedative-hypnotic agents and muscle relaxants provides protection against hypertension, and assures airway relaxation, and unconsciousness during intubation.

It is important to understand that by using these agents the patient will lose his protective reflexes and his ability to breathe. Hypotension and life-threatening arrhythmias can also occur and should be treated accordingly. A thorough checklist of the airway equipment and resuscitation drugs should be performed before administering these agents.

Propofol

Propofol is one of the most commonly used agents in elective patients undergoing surgery. It should be used with extreme caution in the critical care setting due to its depression of both myocardial function and vascular resistance, which can lead to life threatening hypotension. It offers some airway relaxation even when not combined with a muscle relaxant, as well as some protection against bronchospasm. Propofol decreases cerebral blood flow, which is matched by a decrease in cerebral metabolism – well suited for patients with increased ICP. The recommended dose is 1.5–2.5 mg/kg.[8]

Etomidate

Etomidate is a commonly used sedative-hypnotic in critical patients. When compared to sodium thiopental or propofol, etomidate causes less hypotension and less tachycardia making it additionally attractive in patients with compromised cardiac function or sepsis. When used in repeated doses or by continuous infusion, it has the ability to decrease the synthesis of adrenal hormones – cortisol in particular. If used without a muscle relaxant, etomidate may provoke myoclonic movements. The recommended bolus injection dose for adults is 0.2–0.6 mg/kg.[8]

Ketamine

Ketamine has been gaining recent popularity as an alternative agent to etomidate in critical patients. It causes minimal changes in the arterial blood pressure, being ideal in patients with severe hemodynamic instability. It is indicated in patients with active bronchospasm since it has potent bronchodilating effects. Ketamine should be avoided in patients with increased intracranial or intraocular pressure. Some patients report vivid hallucinations or dysphoria after receiving ketamine. These untoward effects can usually be offset by pretreatment with a benzodiazepine. The recommended dose in adults is 1–2 mg/kg intravenously.[8]

Succinylcholine (SCh)

Succinylcholine (SCh) is one of the most commonly used muscle relaxants for tracheal intubation. It has no hypnotic effect and should be used with a sedation agent. It is the only depolarizing muscle relaxant available in the United States. SCh has a rapid onset of only 30–60 s, making it ideal for patients with increased risk of gastric contents aspiration. SCh can cause a transient increase in the plasma levels of potassium and should be used with caution in patients with preexisting hyperkalemia. SCh should also be avoided in patients with acute denervation injuries, such as spinal cord trauma, severe burn injuries, and muscle trauma due to the risk of hyperkalemic arrest – an event related to formation of extrajunctional acetyl-choline receptors.[9] SCh may increase ICP and IOP. The recommended dose is 0.5–1 mg/kg intravenously and 1.5 mg/kg during a rapid sequence induction (see below). It can also be administered intramuscularly at a dose of 3–4 mg/kg in an emergency when no intravenous access is available. Since SCh is metabolized by nonspecific plasma esterases, its clinical duration is between 7 and 10 min.[8]

Rocuronium

Rocuronium is the closest alternative to SCh among the nondepolarizing agents. It also has a rapid onset, similar to SCh, but does not share the same mechanism of action and, therefore, the side effects of SCh. Its prominent disadvantage is its clinical duration of 30–40 min, which could be problematic in case of failure to intubate. The recommended dose ranges from 0.6 mg/kg to the rapid sequence induction dose of 1.2 mg/kg intravenous bolus.[8]

Opioid Agents

Opioid agents are commonly used as sedative agents as well, to improve airway relaxation. Fentanyl is synthetic opioid 100 times more potent than morphine. It can be used for sedation with bolus doses of 1–2 mcg/Kg. Fentanyl helps in minimizing the hemodynamic response to laryngoscopy and does not lower the blood pressure significantly in stable euvolemic patients. Fentanyl - as any other opioid agent - may exacerbate hypotension in patients with clinical shock. Higher doses of fentanyl may produce severe respiratory depression, chest rigidity, and respiratory arrest.

Remifentanil, one of the most recent opioid agents introduced in clinical practice, has an analgesic potency similar to that of fentanyl. It has been used during rapid sequence intubation when combined with propofol (1.2–2.5 mcg/Kg), at a dose of 4 mg/kg without the need for muscle relaxants. This combination achieves laryngoscopy conditions comparable to propofol and succinylcholine. Alfentanil at a dose of 30–40 mcg/kg intravenous bolus combined with propofol has also been used during rapid sequence intubation without the use of muscle relaxants.[10] Remifentanil and Alfentanil have rapid onset after intravenous administration when compared to fentanyl. Severe bradycardia may occur and should be treated with atropine 0.02 mg/kg bolus (maximum of 3 mg dose). Remifentanil is metabolized by plasma esterases, making it a suitable agent in patients with compromised renal or hepatic function.

Local Anesthetics and the Airway

Considered the cornerstone of awake airway techniques, local anesthetic can be used in a variety of ways. They can be directed to the pharynx and base of the tongue by aerosolized solution or voluntary swish and swallow. Anesthetic-soaked cotton swabs can be applied to the nasal cavity. The larynx can be anesthetized by transtracheal injection, nebulized local anesthetic, or by superior laryngeal nerve block.

Topical anesthesia will provide the necessary analgesia and blunt airway reflexes such as coughing or laryngospasm. Exercising caution is important since these medications can sometimes reach toxic plasma levels through mucosal and alveolar absorption.

Lidocaine is available in many different preparations. The most common are the viscous and ointment forms, available in concentrations ranging from 1 to 5%. Peak effect is achieved in 15 min. Toxic levels can lead to seizures and life threatening arrhythmias.

Benzocaine has a rapid onset of less than 1 min. The commercially available preparation HurriCaine, which adds tetracaine to benzocaine, has a longer clinical duration. Each spray of HurriCaine delivers 30 mg of benzocaine. The toxic dose is 100 mg. Cetacaine is another popular preparation, which is similar to HurriCaine with the addition of butyl-aminobenzoate, benzalkonium chloride, and cetyldimethylethyl ammonium bromide. Benzocaine may produce methemoglobinemia, a condition characterized by acute cyanosis and tissue hypoxia. The treatment for methemoglobinemia is supplemental oxygen therapy plus the administration of methylene blue 1–2 mg/kg dose over 5–10 min in more severe cases.[11]

Tracheal Intubation

When performing direct laryngoscopy for intubation, one should keep in mind the risks associated with this procedure. Outside the operating room, the risk of cardiac arrest has been reported to be 1.4%, hypoxemia being the most common offender.[12] The advent of endotracheal tube-verifying devices and advanced airway equipment has helped decrease unrecognized esophageal intubation.[13] Special attention should always be paid to the number of direct laryngoscopy (DL) attempts in order to minimize hypoxemia and airway trauma. The American Society of Anesthesiologists recommends no more than three attempts at direct laryngoscopy.

As described earlier, successful laryngoscopy involves distortion of the normal anatomic planes of the supralaryngeal airway to produce a line of direct visualization to the vocal cords. In other words, the operator's eye should have a direct view of the larynx once he or she aligns the oral, pharyngeal, and tracheal axes. The use of external cricoid pressure is sometimes applied to improve the view of the larynx. The acronym BURP describes one way in which an assistant can manipulate the larynx to improve the laryngeal view for the laryngoscopist. BURP stands for backward, upward, rightward pressure. As implied, the assistant pushes the larynx back against the cervical spine, upward toward the pharynx, and rightward because the laryngoscope is sweeping the tongue to the left.[14]

The most popular laryngoscope blades used in adults are the Macintosh blade, or the curved blade, and the Miller blade, or the straight blade. During laryngoscopy the Macintosh blade's tip is placed in the vallecula, whereas the Miller blade tip goes underneath the epiglottis. After placing the patient's head in the "sniff position" (head elevated by a pillow and neck extended) (Fig. 2.3), the operator opens the patient's mouth with the right hand and the laryngoscope, held in the left hand, is inserted into the right side of the mouth. The tongue is displaced to the left side as the blade advances toward the hypopharynx. Once the epiglottis is seen, the operator should lift the laryngoscope handle in a forward and caudad direction, avoiding the wrist movement so as not to damage the upper teeth. The endotracheal tube is then advanced through the vocal cords until the proximal aspect of the tracheal tube cuff is 2 cm beyond the vocal cords. This should correspond to a distance of approximately 18–22 cm from the tip of the tube to the patient's lips.

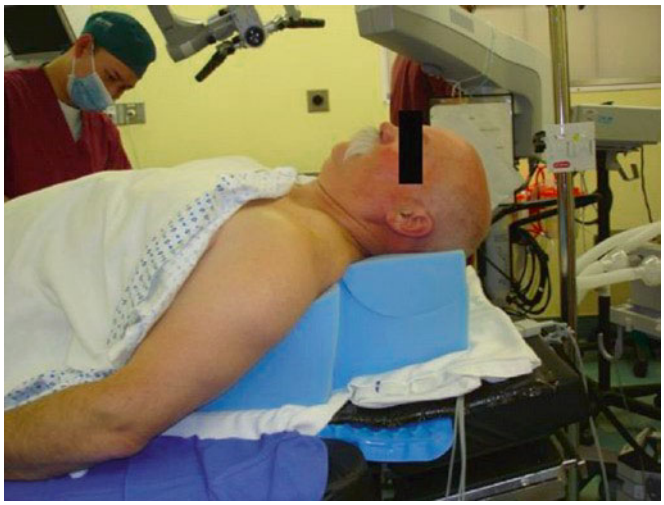

FIG. 2.3. The "Sniff" position, using a commercial positioning device: Pi's Pillow.

When using a cuffed endotracheal tube, the cuff should be inflated before resuming or starting positive pressure ventilation. The cuffed pressure is usually maintained at a minimum – enough to provide an adequate tracheal seal. The cuffed pressure should be constantly monitored in order to minimize injury to the tracheal epithelium. High cuff pressures, above 60 cmH_2O pressure, can be a risk factor for post-extubation stridor.[15]

Verifying the endotracheal tube position is a critical task, since failed tracheal intubation is only hazardous if unrecognized. Endotracheal tube verifying devices should be available at any hospital location where intubation is performed. The CO_2 detector and the suction bulb are the most common devices used. Although CO_2 can sometimes be detected while ventilating a tube placed in the esophagus, the CO_2 concentration will fade after several breaths. Sustained CO_2 will accompany tracheal intubation. False negatives may occur. For example, CO_2 may not be present in a tracheal tube during impaired blood flow states (e.g., cardiopulmonary arrest, massive pulmonary embolism). The suction bulb does not depend on the presence of blood flow. It is attached to the tracheal tube connector and should not remain collapsed after being

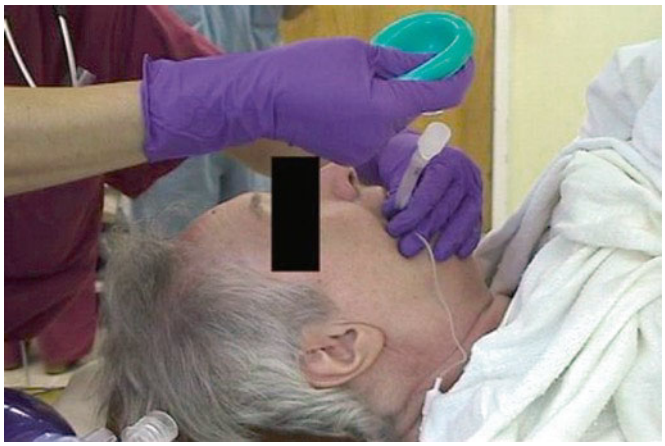

Fig. 2.4. Suction bulb.

Table 2.2. Patients at risk for aspiration.

Full stomach	Recent meal (8 h)
	Trauma
	Delayed gastric emptying (diabetic, opioid induced, high ICP, sepsis)
	Intra-abdominal insult
	Ascites
	Upper gastrointestinal bleeding
Esophageal pathology	Zenker's diverticulum
	Severe gastroesophageal reflux
Head and neck pathology	Post-tonsillectomy bleeding
	Nasal bleeding
	Retropharyngeal abscess

.squeezed (Fig. 2.4). If the bulb remains collapsed, esophageal intubation should be suspected.[16]

Rapid Sequence Intubation

When intubation of the patient's airway is deemed immediately necessary, but the patient is considered an aspiration risk, a rapid sequence intubation (RSI) should be considered (Table 2.2).

RSI is defined as the simultaneous use of a potent hypnotic agent followed immediately by a rapidly acting neuromuscular blocking agent, and tracheal intubation. The purpose of RSI is to produce ideal laryngoscopic conditions for securing the airway, while minimizing the time between the loss of protective glottic reflexes and intubation, and avoiding gastric distention with bag-valve mask ventilation. The advantages of RSI over other techniques (e.g., awake, nasal, tracheal intubation) include rapid attainment of airway control and protection, control of the uncooperative and combative patient, a high success rate, and a blunting of systemic responses to intubation including cardiovascular, intracranial, and intraocular pressure changes. RSI is contraindicated in patients whom the clinician judges to have impossible-to-mask airways. It is relatively contraindicated in patients with severe trauma to the mouth, upper or lower airways, stridor, morbid obesity, evidence of possible difficult laryngoscopy, and when no appropriate rescue airway is available.

Table 2.3. Rapid sequence intubation.

Sequence	Components
Prepare	Evaluation, equipment, position, monitoring, IV access, preoxygenation, blunting agents
Commit	Injection of hypnotics and muscle relaxants
Confirm	End tidal CO_2 measurement, auscultation
Care	Care for consequences of drugs injection and tracheal intubation

RSI should be considered in two distinct phases: patient preparation and the sequence of the intubation events, which can be described in the mnemonic PC3, which stands for prepare, commit, confirm, and care (Table 2.3).

The elements of preparation include evaluating the airway; checking and knowing what equipment is available; preparing the patient; choosing systemic response blunting agents, as well as hypnotic drugs and muscle relaxants; and being prepared to verify tracheal intubation.

In assessing the location where the RSI will be performed, the environment should allow monitoring and unimpeded access to the patient. The electrocardiogram, blood pressure, expired CO_2, and oxygen saturation should be monitored continuously before, during, and after RSI. The patient should be accessible from all sides in the event there may be a failure of the IV line, and there is the need for a surgical airway, cardiopulmonary resuscitation, or other interventions. Equipment which should be available includes laryngoscopes with two handles and blades with two sizes each of curved and straight blade designs. All blades and all handles should be tested and working. Tracheal tubes should include the appropriate size for the patient and smaller. The cuff and pilot balloon should be tested and the tracheal tube should be styleted and shaped to the clinician's liking. A self-inflating ventilation bag that does not require a compressed gas source should be available, as well as a suction device to remove airway secretions, blood, or vomitus. Nasal airways, oral airways, and other adjuncts such as malleable intubating stylets should be available, as well as supraglottic rescue airways such as the laryngeal mask airway, the intubating laryngeal mask airway, or the tracheal esophageal Combitube. Finally, the equipment used to perform emergency cricothyroidectomy should also be available.

Patient preparation for RSI includes positioning of the head after the clinician has taken into consideration the possibility of cervical spine instability. If no cervical spine injury is suspected, the patient is put into a sniffing position. This is especially helpful if the patient is obese. Once positioned, the patient is preoxygenated in order to maximize the oxygen reservoir of the lungs, as discussed elsewhere in this chapter.

Before proceeding with the RSI, the clinician must choose if and how systemic responses to laryngoscopy and intubation should be blunted. Systemic responses include hypertension (both systemic and pulmonary), tachycardia, bronchospasm,

intracranial and intraocular hypertension, and vagal reflexes (in the child).

The next two classes of drugs to be considered in RSI include hypnotics and muscle relaxants, which are discussed in detail elsewhere in this chapter. Ideal drugs for the induction of RSI are those that act rapidly, achieving unconsciousness and muscle relaxation and, subsequently, dissipate rapidly. RSI is not "titration to effect" where small doses of a drug are given until ideal conditions are achieved, nor is RSI sedation where unconsciousness and complete muscle relaxation are never achieved. Due to the speed of onset of the drugs used for RSI, there is minimal time when the airway is unprotected, unlike during titration and sedation. Common hypnotic agents that are used for RSI include etomidate, which typically has little effect on the cardiovascular status of the patient, and ketamine, which, in the hypovolemic or otherwise hemodynamically impaired patient, may increase blood pressure. Succinylcholine is the most common rapidly acting muscle relaxant to be used in RSI. It must be used with caution in patients at risk of hyperkalemia; for example, patients with burns, major trauma, uncorrected renal failure, peripheral neuropathy, or muscular dystrophy. A family history of malignant hyperthermia is a contraindication for succinylcholine and should be sought. When succinylcholine cannot be used, several nondepolarizing muscle relaxants can be administered. The clinician should be aware that rapid recovery from these drugs should not be expected.

The next phase of the sequence is termed "commit." This refers to the injection of drugs, which will affect the patient's level of consciousness. Cricoid pressure should be immediately applied. This procedure, also known as the Sellick maneuver, is pressure on the cricoid performed by a second operator who presses on the cartilage with the intent of compressing the esophagus against the C4-5 vertebral body. This has the effect of occluding the esophagus so that passive regurgitation is prevented as the patient loses consciousness. Contraindications to cricoid pressure include suspicion of an unstable cervical spine, active vomiting, and suspicion that there may be a foreign body present in the hypopharynx, larynx, trachea, or esophagus Hypnotic agents and relaxants are injected forty-five seconds to one minute after the injection of the blunting agents,. These drugs are given rapidly. The muscle relaxant is given, without pause, immediately after the injection of the hypnotic agent. It is not necessary to wait for the loss of consciousness before giving the relaxant drug.

With the rapid onset of apnea, bag-valve-mask ventilation is not performed. (Mask ventilation is avoided because it can cause air insufflation of the stomach, which may result in forced regurgitation and subsequent aspiration.)

Forty-five seconds after the hypnotic and muscle relaxant drugs are administered, the clinician checks for relaxation of the jaw. If that relaxation has not occurred, the clinician waits another 15 s. After this time period, direct laryngoscopy is performed. Importantly, throughout this waiting period and during direct laryngoscopy, the Sellick maneuver is maintained.

After intubation has been performed, the clinician must confirm that the endotracheal tube has been successfully placed into the trachea. The gold standards of this confirmation are direct visualization of the endotracheal tube passing between the vocal cords, and the detection of end tidal CO_2.

Only after successful endotracheal intubation has been confirmed, cricoid pressure may be released.

During the care phase of rapid sequence intubation, there is continued monitoring of exhaled carbon dioxide and neurologic status. At this time, the clinician may consider the use of long-acting muscle relaxants and sedative hypnotics.

If direct laryngoscopy and intubation are unsuccessful, or correct tube placement cannot be confirmed, cricoid pressure is maintained. Mask ventilation may now be resumed with the goal of preventing oxyhemoglobin desaturation. The clinician may consider a second and third attempt at laryngoscopy. A change in the patient's head position or the laryngoscope blade, external manipulation of the larynx by a second operator, or the use of an assistant to help with endotracheal intubation may be considered in order to make these further attempts successful.

Should oxyhemoglobin desaturation occur or appear imminent, the clinician may also consider superlaryngeal rescue devices including the laryngeal mask airway or Combitube. Success of airway rescue with these devices should also be confirmed with capnography (to be discussed later in this chapter).

If adequate superlaryngeal ventilation is not achieved, mask ventilation may be resumed and the clinician may consider surgical or percutaneous airway procedures.

The worst complication of rapid sequence intubation is the unrecognized esophageal intubation. In this situation, the clinicians would have moved on to other tasks in the care of the patient, not recognizing that the airway has not been secured.

The second worst complication is failure to intubate or failure to bag/valve/mask ventilate the patient. In this case, the airway has not been secured but the clinician is still focused on the problem at hand.

The third worst situation is the failure to intubate but bag/valve/mask ventilation can be accomplished. Though the patient is not protected from the aspiration of gastric contents, oxygen and CO_2 exchange is occurring and the clinician is working toward securing the airway.

Other complications of rapid sequence intubation include the aspiration of blood, debris or gastric contents, and airway trauma.

There are also complications of successful intubation. These include hypotension which can occur when the hypovolemic patient is ventilated with positive pressure; tension pneumothorax; and untoward effects of the induction agents used during the RSI. The clinician must be prepared to treat these reactions. Bradycardia can occur as a result of hypoxia or from the use of a second dose of succinylcholine, and hypertension or tachycardia can occur due to inadequate sedation.

Awake Intubation Techniques

Awake intubation techniques should be considered whenever there is a desire to preserve spontaneous breathing and protective airway reflexes in a patient whose airway is deemed difficult to manage. Minimizing trauma, bleeding, and secretions are important to ensure the best airway visualization. Pretreatment with an antisialogogue (e.g., Glycopyrrolate 0.2 mg intravenously) is recommended.

The most ubiquitous intubation device used for awake intubations is the flexible fiber optic bronchoscope (FOB) (Fig. 2.5). The FOB allows excellent visualization of the airway structures, especially the larynx, the trachea, and the proximal bronchi. It can serve as a guide for the endotracheal tube insertion, be used through both oral and nasal routes, and can elucidate airway pathology such as tumors, masses, and diseases affecting the airway. The new generation of flexible bronchoscopes uses CCD technology instead of fiber-optic cables. Optic fibers tend to break with repetitive use, decreasing image resolution. CCD technology offers enhanced imaging resolution, clarity, and brightness.

In addition to the standard flexible fiber-optic scope, a new family of optic devices has been introduced for airway management. These devices incorporate the fiber-optic and CCD technologies into rigid airway scopes designed for a better view of the upper airway. They are simple to use, offering thorough airway visualization when compared to conventional laryngoscopes. Some devices like the C-trach offer the combined benefit of an LMA - an invaluable rescue device in cases of difficult mask ventilation-, and a guide for the endotracheal tube insertion (see below). Others like the Shikani (Fig. 2.6) and the Bullard Scope (Fig. 2.7) work well in cases where there is limited oral opening. Both the Bullard Scope as well as the Shikani have been successfully used in awake patients.

FIG. 2.5. The fiber-optic bronchoscope.

FIG. 2.6. The Shikani optical stylet. Permission for use granted by Clarus Medical, Minneapolis, Minnesota.

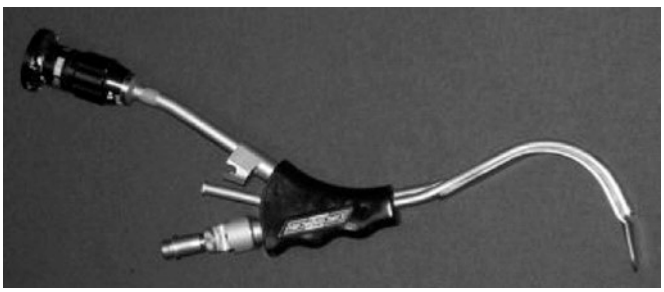

FIG. 2.7. The Bullard Laryngoscope.

The Difficult Extubation

Extubation of the trachea in the ICU setting should deserve special attention since a number of complications may occur during this vulnerable time. Postextubation stridor and acute respiratory failure may occur in 2–16% of intensive care patients. Laryngeal edema is the most common cause for this event.

Patients at risk of post-extubation stridor are those with a history of airway trauma by repeated intubation attempts (history of difficult intubation), prolonged duration of intubation, episodes of self-extubation, and high endotracheal cuff pressures.

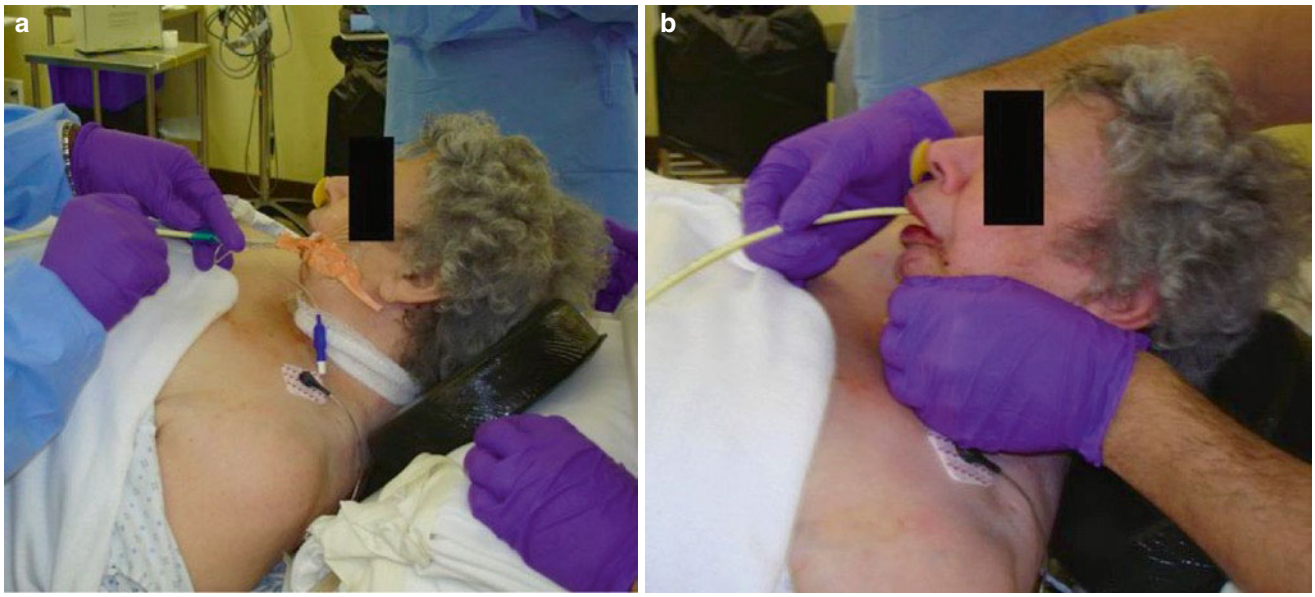

FIG. 2.8. (**a**, **b**) Tube exchanger device.

The cuff leak test has been a subject of controversy since the method was first reported. Jaber et al. described a positive cuff leak test as the calculated difference between the tidal volumes pre- and post-cuff deflation measured on a standard ICU ventilator.[15] A value smaller than 130 cc was strongly associated with post-extubation stridor.

A number of extubation techniques have been described for situations where potential for problems exist. Airway tube exchangers are well tolerated and serve as a guide for endotracheal tube reinsertion. They may be left in the trachea for an extended period of time after extubation (Fig. 2.8a, b). The use of a Laryngeal Mask Airway (LMA) placed before removing the endotracheal tube has also been described.

Rescue Airway Devices: The Supraglottic Airways

The supraglottic airways are a group of devices which are able to maintain airway patency by displacing the soft tissues of the nasal or oropharynx. There are ample anecdotal as well as controlled studies suggesting that these devices can be used in the rescue of a patient's airway when tracheal intubation fails. Some devices may also serve as a conduit to endotracheal intubation.

The Face Mask

Although a simple and readily available device, the face mask requires experienced and skilled hands to provide rescue breaths in an efficient manner (Fig. 2.9a).

The face mask is usually coupled with a self-inflating breathing bag (i.e., the AMBU bag) for positive pressure ventilation. A good mask seal should be assured to avoid substantial air leaks and small tidal volumes. As part of maintaining airway patency, a chin lift or jaw thrust is performed and, not infrequently, an oral or nasal airway is inserted as well. Signs of adequate mask ventilation include the lack of leaking sounds through the mask, chest expansion, presence of breath sounds on auscultation, presence of condensation in the mask, and the ability to maintain a patient's oxygen saturation above 90%.

If ventilation becomes difficult, two-person mask ventilation can be performed. One person should hold the mask with two hands maintaining a "jaw thrust" maneuver while the second person squeezes the ventilating bag (Fig. 2.9b).

Patients with a full stomach, such as those with a history of recent trauma or airway bleeding, may be at greater risk of pulmonary aspiration when ventilated by mask.

The Laryngeal Mask Airway (LMA)

Developed in England by Dr. Archie Brain, this airway device gained popularity in the early 1990s when the FDA approved it for use in US hospitals. The LMA was first introduced for use in the operating room as a substitute for a face mask or when tracheal intubation was not obtainable. The LMA is today considered one of the most useful rescue devices in a difficult airway situation.

The LMA is composed of a small "mask" designed to sit in the hypopharynx, with an anterior surface aperture overlying the laryngeal inlet. The rim of the mask is composed of an inflatable silicone cuff which fills the hypopharyngeal

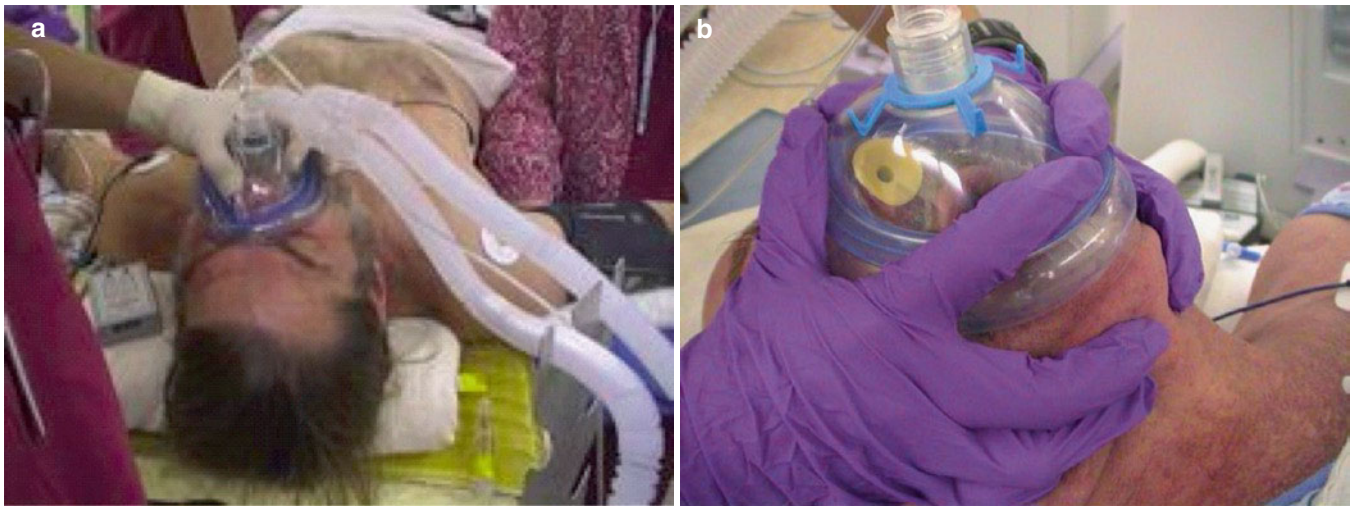

FIG. 2.9. (**a**) Mask ventilation. (**b**) Two-person mask ventilation technique.

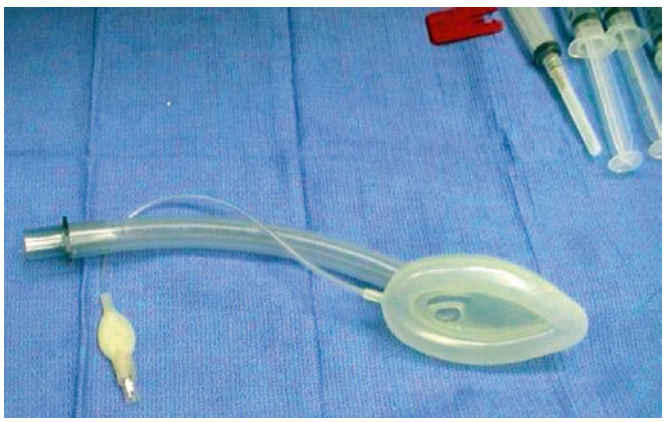

FIG. 2.10. The Laryngeal Mask Airway (LMA-Unique).

space, creating a seal that allows positive-pressure ventilation with up to 20 cmH_2O pressure (Fig. 2.10). The adequacy of the seal is dependent on correct placement and appropriate size. It is less dependent on the cuff filling pressure or volume. Attached to the posterior surface of the mask is a barrel (airway tube) that extends from the mask's central aperture through the mouth and can be connected to an Ambu bag or ventilator circuit.

The LMA is not designed to completely isolate the airway from the digestive tract, and therefore must be used in caution in a patient who may have a full stomach. Because hypoxia from a failed attempt at airway control is the primary indication for the LMA in the ICU, fears of aspiration must be a secondary consideration. Table 2.4 outlines conditions where the LMA may be contraindicated.

The LMA should be seen as a "bridge" for more definitive airway treatments such as percutaneous or surgical tracheostomy, or fiber-optic guided intubation while maintaining ventilation and oxygenation. Peak pressures should be kept below 20 cmH_2O and tidal volumes less than 8 ml/kg in order to minimize gastric insufflation.

TABLE 2.4. Contraindications for laryngeal mask airway.

Aspiration risk	Full stomach
	Bowel obstruction
	Delayed gastric emptying
	Severe gastroesophageal reflux
	Hiatus hernia
	Morbid obesity
Pulmonary disease	Poor lung compliance
Head and neck	Glottic or subglottic pathology
	Limited oral aperture (<1.5 mm)

The classic LMA can be used as a conduit for tracheal tube insertion. The technique involves passing a flexible bronchoscope (FOB) loaded with an appropriate size endotracheal tube (ETT) through the LMA and then through the vocal cords. Once the bronchoscope is positioned above the carina, the endotracheal tube is threaded past the vocal cords. The FOB and the LMA are carefully removed, paying attention not to accidentally displace the ETT.

In the ICU setting, the LMA has been used during diagnostic and therapeutic bronchoscopies and tracheostomies.[17] When compared to the ETT, the LMA offers more space for instrumentation, less work of breathing,[18] and access to the vocal cords and upper trachea.

A modified LMA device designed for endotracheal intubation is available in cases of difficult airway management. The LMA-Fastrach™ offers the benefit of maintaining a patent airway while the trachea is blindly intubated. The technique is done with or without the aid of an FOB. More recently, the LMA C-trach™ has been developed for difficult airway cases. It is similar to the LMA-Fastrach but coupled with a monitor that provides a clear view of the larynx (Fig. 2.11).

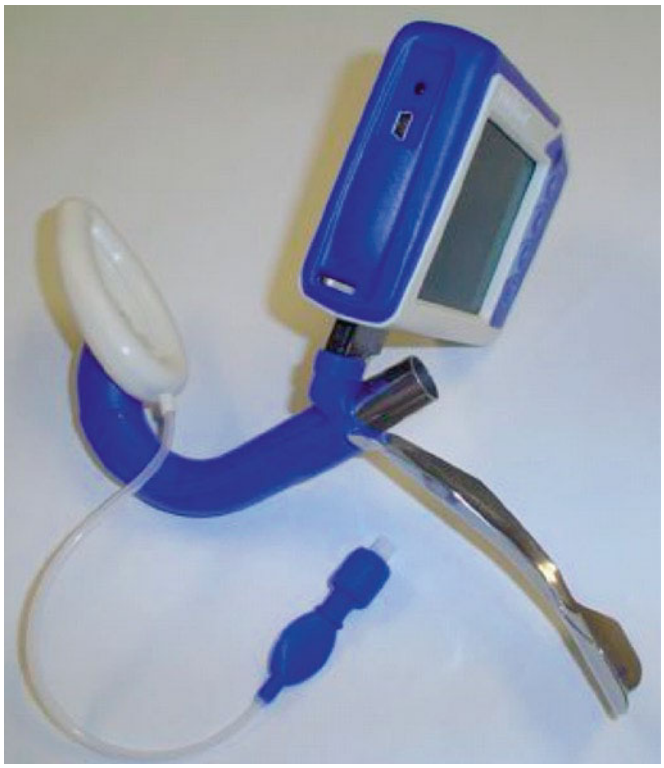

Fig. 2.11. The LMA C-trach.

The Combitube

Although less ubiquitous than the LMA in the USA at the time of this writing, the Combitube is a valuable supraglottic airway device for use in emergency airway situations.

The Combitube is a double lumen airway device with a distal (esophageal) and a proximal (pharyngeal) inflatable cuff. The distal cuff is important for prevention of gastric aspiration while the proximal cuff seals the pharynx and allows effective positive pressure ventilation. The Combitube is inserted blindly and can go either into the esophagus - as in most of the cases – or the trachea. For this reason both lumens should be inspected and ventilation should be provided through the appropriate lumen.

The Combitube is a simple device to use, with a very high rate of success in the first attempt, making it a suitable device for emergency care providers.[19]

Transtracheal Procedures

Transtracheal Ventilation (TTV or TTJV)

When access to the airway is unavailable either from the mouth or nose, the clinician should consider obtaining access through the extrathoracic trachea. With the development of supraglottic devices, emergency access to the trachea has become less common. Nevertheless, one should be familiar with these important airway management techniques since they can be lifesaving when intubation or ventilation by conventional means is not possible.

The percutaneous transtracheal ventilation technique (TTV) is a simple and safe means to sustain a patient's life during airway emergencies. A 12-, 14- or 16-gage intravenous catheter is attached to a partially filled 5 cc syringe (air or saline filled) and then inserted in the tracheal lumen through the cricothyroid membrane. Local anesthetic infiltration should be provided to an awake patient, if time permits. Intralumen location of the catheter tip should be verified with aspiration of air. The needle-catheter should be slightly advanced and, subsequently, the catheter alone should be fully advanced into the trachea.

Once the catheter is completely inserted in the airway, an oxygen source should be attached to the catheter. In the ICU setting, a low-pressure, but adequate system can be assembled using an oxygen flow meter and an Enk flow modulator (Cook Critical Care, Bloomington, Indiana). The Enk allows the clinician to control the flow of oxygen into the catheter (Fig. 2.12). Sufficient ventilation may not be possible due to the small diameter of the catheter, but oxygenation is possible with this technique until a more definitive airway can be obtained.

Percutaneous Cricothyroidotomy

Performing a cricothyroidotomy requires more time and skill than the TTV, but has a better potential for providing both oxygenation and ventilation. A number of devices have been developed for this task. The Melker emergency cricothyroidotomy catheter set utilizes the Seldinger technique (catheter-over-a-wire technique) to access the trachea. After a skin incision over the lower third of the cricothyroid membrane, an 18-gage catheter over needle attached to a syringe is advanced under constant aspiration for air until intratracheal lumen position is confirmed. The needle and syringe are removed while the catheter is advanced into the trachea. A wire is then threaded through the 18-gage catheter, and the catheter is removed. A trachea cannula fitted internally with a curve

Fig. 2.12. The ENK flow modulator. Permission for use granted by Cook Medical Incorporated, Bloomington, Indiana.

dilator is then threaded onto the wire. The dilator is advanced through the membrane using firm pressure. Once the cannula-dilator is fully inserted into the trachea, the wire and dilator are removed. A 15 mm circuit adaptor is attached to the Ambu bag or ventilator hoses.

Conclusion

Airway management must be considered a basic skill for the intensivist. Though a large number of tools are available, the critical care physician should concentrate on being skilled with a limited number. Critical skills include use of direct laryngoscopy, a fiber-optic device, a supraglottic airway, and some means of oxygenating through the extrathoracic airway. Though all morbidities have consequences, attention to oxygenation, ventilation, and finally, aspiration should dictate priorities.

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3
Vascular Cannulation

Shawn E. Banks and Albert J. Varon

Vascular cannulation is an essential tool for fluid and drug administration, accurate monitoring of hemodynamic parameters, and blood sampling in critically ill patients. Preparation, indications, contraindications, clinical utility, and techniques for vascular cannulation are reviewed in this chapter. The sites of catheterization and complications of arterial, central venous, and pulmonary artery catheterization are also presented.

Preparation

Patient and operator preparation is a crucial component of the vascular cannulation procedure.[1] It is advisable, if at all possible, to obtain informed consent from the patient or surrogate whenever an invasive procedure is to be performed. Vascular cannulation is no exemption to this rule. Benefits and potential complications should be discussed. The second aspect of preparation is selecting the site of catheterization. Operator experience is a major factor influencing this decision. Most vascular cannulations are performed percutaneously because of the ease of insertion and lower risk of infection. Cannulation under direct vision through a surgical cutdown may be performed in extremely difficult situations but is rarely necessary. Most central venous and arterial catheters are inserted by passing a guidewire through a needle (modified Seldinger technique).[2] The use of Doppler or ultrasound-guided vascular access has been reported to increase the success of cannulation and should be considered.[3,4] Vascular cannulation is likely to be successful and result in fewer complications if the patient is optimally positioned. Before catheter insertion, the operator should follow the same sterile preparations as in any other aseptic surgical procedure. Sterile sets containing the equipment needed for cannulation are routinely available. The insertion site is prepped with an antimicrobial solution. Povidone-iodine and chlorhexidine are most commonly used, although chlorhexidine appears to be more efficacious.[5,6] After skin preparation, the insertion site should be draped with a sterile field that allows adequate site access. To avoid patient's discomfort, local anesthesia, analgesia, and sedation should be considered.

Arterial Catheterization

Indications

Arterial catheterization is indicated whenever continuous monitoring of blood pressure or frequent sampling of arterial blood is required. Shock, hypertensive crisis, major surgical interventions, and high levels of respiratory support require precise and continuous blood pressure monitoring, particularly when vasoactive or inotropic drugs are being administered. An indwelling arterial catheter may be the only way to accurately determine blood pressure in these circumstances and may also provide ready access for blood gas analysis. Use of inaccurate pressure cuffs or oscillometric devices may lead to over- or underestimation of blood pressure[7,8]; further, indirect measurements of arterial pressure correlate poorly with direct measurements.[9,10]

Contraindications

Arterial cannulation is a relatively safe and inexpensive procedure with no absolute contraindications. Relative contraindications include bleeding diathesis and anticoagulant therapy (which may increase the risk of hemorrhagic complications and hematoma formation), severe occlusive arterial disease with distal ischemia, inadequate collateral blood flow, presence of a vascular graft, and skin infection.

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Clinical Utility

Systolic, diastolic, and mean arterial pressure can be continuously monitored. Analysis of the arterial pressure waveform obtained from an arterial catheter may allow qualitative assessment of cardiovascular status.[11] Further, systolic pressure variations during mechanical ventilation may guide fluid therapy in hypotensive patients.[12]

Technique and Sites of Catheterization

The radial, ulnar, axillary, brachial, femoral, dorsalis pedis, and superficial temporal arteries have been used to access the arterial circulation for continuous monitoring. Although the selection of anatomic site depends on its availability and the experience of the clinician, various advantages and disadvantages should be considered.

Radial Artery

Cannulation of the nondominant hand should be attempted first. The dual blood supply to the hand and the superficial location of the vessel make the radial artery the most commonly used site for arterial catheterization. Cannulation and securing the catheter in place are technically easy, and there is a low incidence of complications.[13,14]

Collateral blood flow may be inadequate in 15 to 20% of patients. The modified Allen test [15] is the most commonly used test to assess the adequacy of collateral circulation before cannulation of the radial artery. The patient elevates one hand, makes a fist, and clenches it firmly to squeeze the blood from the hand vessels. After the examiner simultaneously occludes the radial and ulnar arteries, the patient lowers and opens the hand in a relaxed fashion (without overextension). The pressure over the ulnar artery is then released. The capillary blush of the hand is normally complete within 6 s. Ultrasonic Doppler technique, plethysmography, and pulse oximetry have also been used to assess the adequacy of the collateral arterial supply.

The radial artery is palpated at a site slightly proximal to the planned entry site, usually 2 cm proximal to the flexion skin fold. A small-gage catheter is advanced through the puncture site along the course of the artery at a 30- to 45-degree angle to the skin (Fig. 3.1). Cannulation may be achieved by transfixing, direct threading, or by a modified Seldinger technique. In the direct threading technique the anterior wall of the artery is penetrated. When blood return is noted, the catheter is advanced further up the arterial lumen as the needle is withdrawn. The cannula is then connected to a pressure monitoring system.

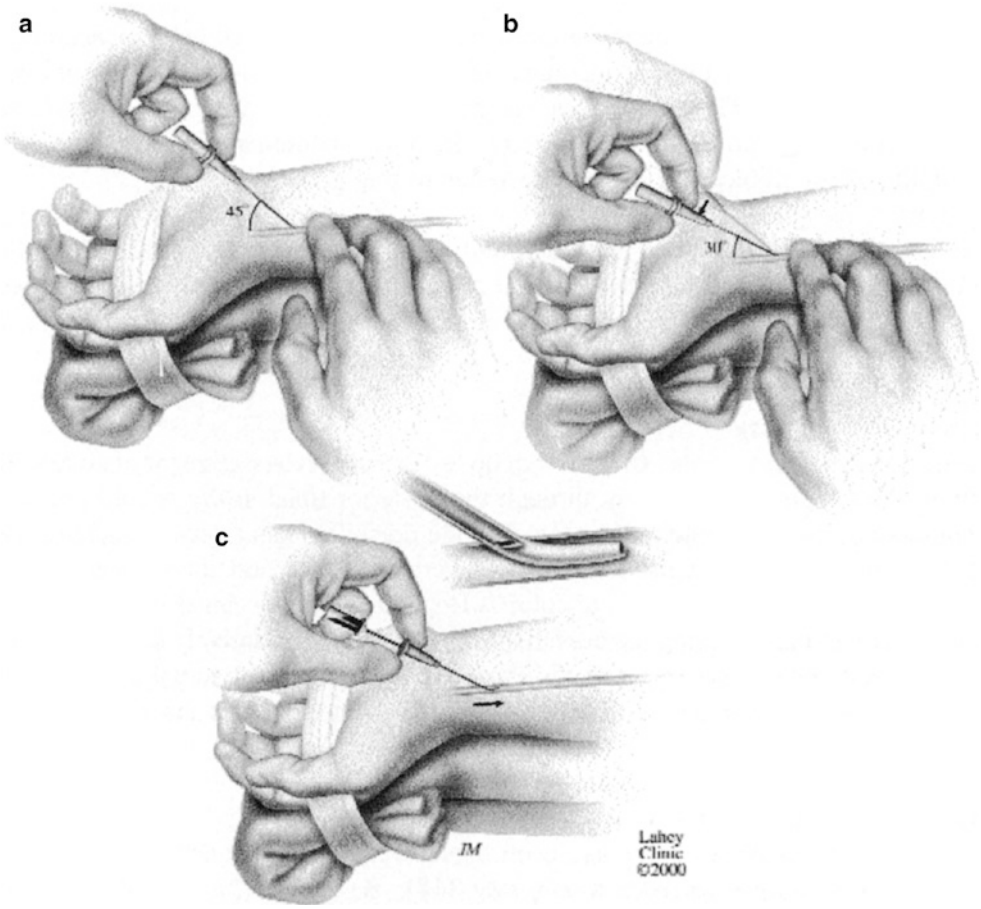

FIG. 3.1. Direct approach to cannulation of the radial artery (Sterile drapes omitted to illustrate anatomic landmarks).

Axillary Artery

This artery has been recommended for long-term direct arterial pressure monitoring because of its larger size, freedom for the patient's hand, and close proximity to the central circulation.[16] Pulsation and pressure are maintained even in the presence of shock with marked peripheral vasoconstriction. Thrombosis does not result in compromised flow in the distal arm because of the extensive collateral circulation. The major disadvantages are its low accessibility, visibility, and location within the neurovascular sheath, which may increase the risk of neurologic compromise if a hematoma develops.

The axillary artery is palpated with the arm extended and externally rotated. Cannulation is performed using a modified Seldinger technique. The artery is entered at its highest palpable point. Once free arterial flow is obtained, a guidewire is passed through the needle. The needle is then removed and a catheter is inserted over the wire.

Femoral Artery

The major advantages of using the femoral artery are its superficial location and large size, which allow easier localization and cannulation when the pulses are absent over more distal vessels. The major disadvantages are the decreased mobility of the patient, contamination from ostomies or draining abdominal wounds, and the possibility of occult bleeding into the abdomen or thigh.

The femoral artery should be identified and a site approximately 2 cm below the inguinal ligament chosen for insertion. The skin and artery are entered at a 45-degree angle, and a long 20-gage catheter is introduced using the modified Seldinger technique.

Dorsalis Pedis Artery

The dorsalis pedis artery may be absent in up to 12% of feet. Assessment of collateral flow to the remainder of the foot through the posterior tibial artery should precede cannulation. This can be done by occluding the dorsalis pedis artery, blanching the great toe by compressing the toenail for several seconds, and then releasing the toenail while observing the return of color. A Doppler technique can also be used. The major disadvantages of using the dorsalis pedis artery are its relatively small size and overestimation of systolic pressure (5–20 mmHg higher than the radial artery).[17] The technique for catheter insertion in this site is similar to that for insertion into the radial artery.

Superficial Temporal Artery

The superficial temporal artery has been extensively used in infants and in some adults for continuous pressure monitoring.[18] Because of its small size and tortuousity, however, surgical exposure is required for cannulation. Furthermore, a small but worrisome incidence of neurologic complications resulting from cerebral embolization has been reported in infants.

Brachial Artery

The brachial artery is not used often because of the high complication rate associated with arteriography. Although this artery has been successfully used for short-term monitoring, there are little data to support prolonged brachial artery monitoring, and its use has been discouraged. Disadvantages include the difficulty in maintaining the site and the possibility of hematoma formation in anticoagulated patients. The latter may lead to median nerve compression neuropathy and Volkmann's contracture. Compartment syndrome of the forearm and hand has also been reported.[19]

Complications

Major complications for all sites of arterial line insertion include bleeding, ischemia, distal embolization, sepsis, neuropathy, arteriovenous fistula, and pseudoaneurysm formation.[20] Inadvertent injections of vasoactive drugs or other agents into an artery can cause severe pain, distal ischemia, and tissue necrosis. Minor complications are thrombosis, skin ischemia, and local inflammation, infection, or hematoma. Factors associated with an increased risk of infection include placement of the catheter for more than 4 days, insertion by surgical cut-down rather than percutaneously, and local inflammation. Arterial catheter-related infection develops in less than 10% of radial or femoral sites used longer than 96 h.[21]

Central Venous Catheterization

Indications

The primary indications for central venous catheterization are to secure access for fluid therapy, parenteral nutrition, or vasoactive drug infusions, and for central venous pressure monitoring. Central venous catheters have also been used for hemodialysis, placement of pacemakers or cava filters, and for diagnostic procedures (e.g., cardiac catheterization).

Contraindications

There are no absolute contraindications for catheter placement. However, bleeding diathesis is a relative contraindication, because it may increase the risk of hemorrhagic complications. Thrombosis, local infection or inflammation, and distortion by trauma or previous surgery are considered contraindications to specific sites of catheterization.

Clinical Utility

Central venous catheters are placed primarily for fluid therapy. In addition, useful information can be obtained by monitoring the central venous pressure (CVP) and observing the pressure waveform. The CVP usually decreases in patients with hypovolemia. It increases in patients with hypervolemia,

right ventricular failure or infarction, tricuspid regurgitation, and pericardial tamponade. Although the CVP provides information about the relationship between intravascular volume and right ventricular function, it cannot be used to assess left ventricular function reliably in critically ill patients.

Technique and Sites of Catheterization

The most commonly chosen sites include the subclavian, internal jugular, external jugular, and femoral veins. The patient should be placed in the Trendelenburg position, and at minimum be monitored with pulse oximetry and continuous ECG. The depth and angle of insertion depend on the specific approach being used. When attempting to find the vein, slight negative pressure should be applied using a syringe. If the vein is not entered at this point, the needle/cannula should be withdrawn just under or totally out of the skin. Aspiration of venous blood is often obtained on withdrawal of the needle, since the initial pressure from needle insertion may collapse the vein, leading to unrecognized through-and-through puncture. Once the vein is located, the cannula over the needle is advanced or a guidewire inserted. The needle or cannula should never be left unoccluded because of the risk of air entering the vascular system. If resistance is met when advancing the guidewire, both the guidewire and needle should be withdrawn simultaneously. In most adult patients, 18 cm should be considered the upper limit when the guidewire should be introduced.[22] A catheter should be introduced over the guidewire without resistance and the distal end of the guidewire should be under control. After the guidewire is removed, the catheter is secured and the position confirmed by radiography.

Subclavian Vein

The subclavian vein can be cannulated with a high rate of success and may be the easiest site to cannulate in situations of profound volume depletion. In one prospective randomized controlled trial, subclavian vein cannulation offered an absolute risk reduction of 33% as compared to femoral cannulation.[23] It is still unclear if Doppler guidance increases success or decreases complications of subclavian vein catheterization.[24–26] Based on current CDC recommendations, the subclavian vein should be considered the site of choice to reduce the likelihood of catheter-related bloodstream infections.[27]

Access to the subclavian vein may be gained by the supraclavicular or infraclavicular approach.[28] The angle of insertion for all infraclavicular approaches is parallel to the coronal plane (Fig. 3.2). The insertion point can be made lateral to the midclavicular line at the junction of the lateral and middle thirds of the clavicle, in the mid clavicle, or at the junction of the middle and medial thirds of the clavicle. Infraclavicular subclavian venipuncture should be performed with the patient's shoulders in a neutral position and in slight retraction.[29] This approach has a success rate of

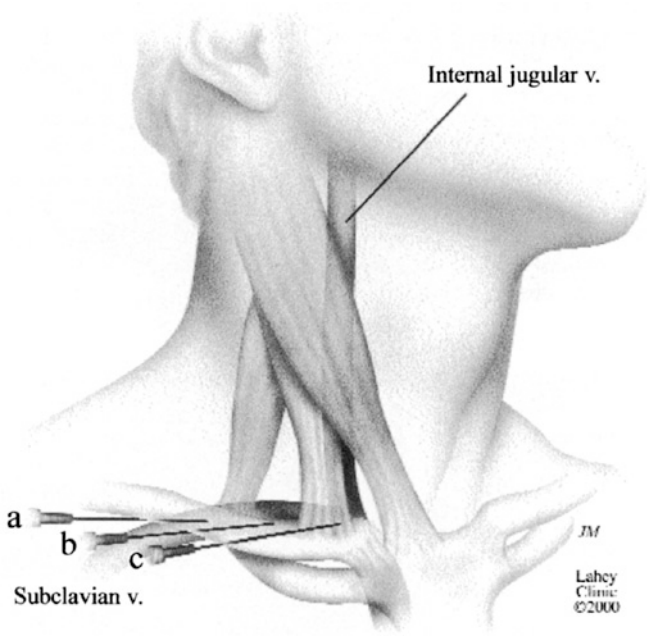

FIG. 3.2. Three approaches for infraclavicular access to the subclavian vein. (**a**) Junction of the lateral and medial third of the clavicle. (**b**) Mid clavicle. (**c**) Junction of the middle and medial third of the clavicle.

70–99%, is easier to maintain, and is preferably used when airway control is necessary. Disadvantages include difficulty in controlling bleeding, higher risk of pneumothorax, and interference with chest compressions during cardiopulmonary resuscitation.

Internal Jugular Vein

The internal jugular vein has been cannulated with success rates similar to that of the subclavian vein. It can be approached from three directions (Fig. 3.3): (a) anterior to the sternocleidomastoid (SCM), (b) central between the clavicular and sternal heads of the SCM, and (c) posterior to the SCM. The carotid artery lies posterior and medially to the vein. The vessel is cannulated at an angle of 45° or less. The major advantages of internal jugular vein catheterization are the lower risk of pneumothorax and the ability to compress the insertion site if bleeding occurs. In addition, the right internal jugular provides a straight path to the superior vena cava, facilitating placement of catheters and pacemakers. The posterior approach enables the physician to perform the procedure with the patient in the prone position. The internal jugular vein, however, may be difficult to cannulate in patients with volume depletion or shock. Dressing and maintaining catheters are also difficult.

External Jugular Vein

Cannulation of the external jugular vein has lower incidence of complications but higher incidence of failure.

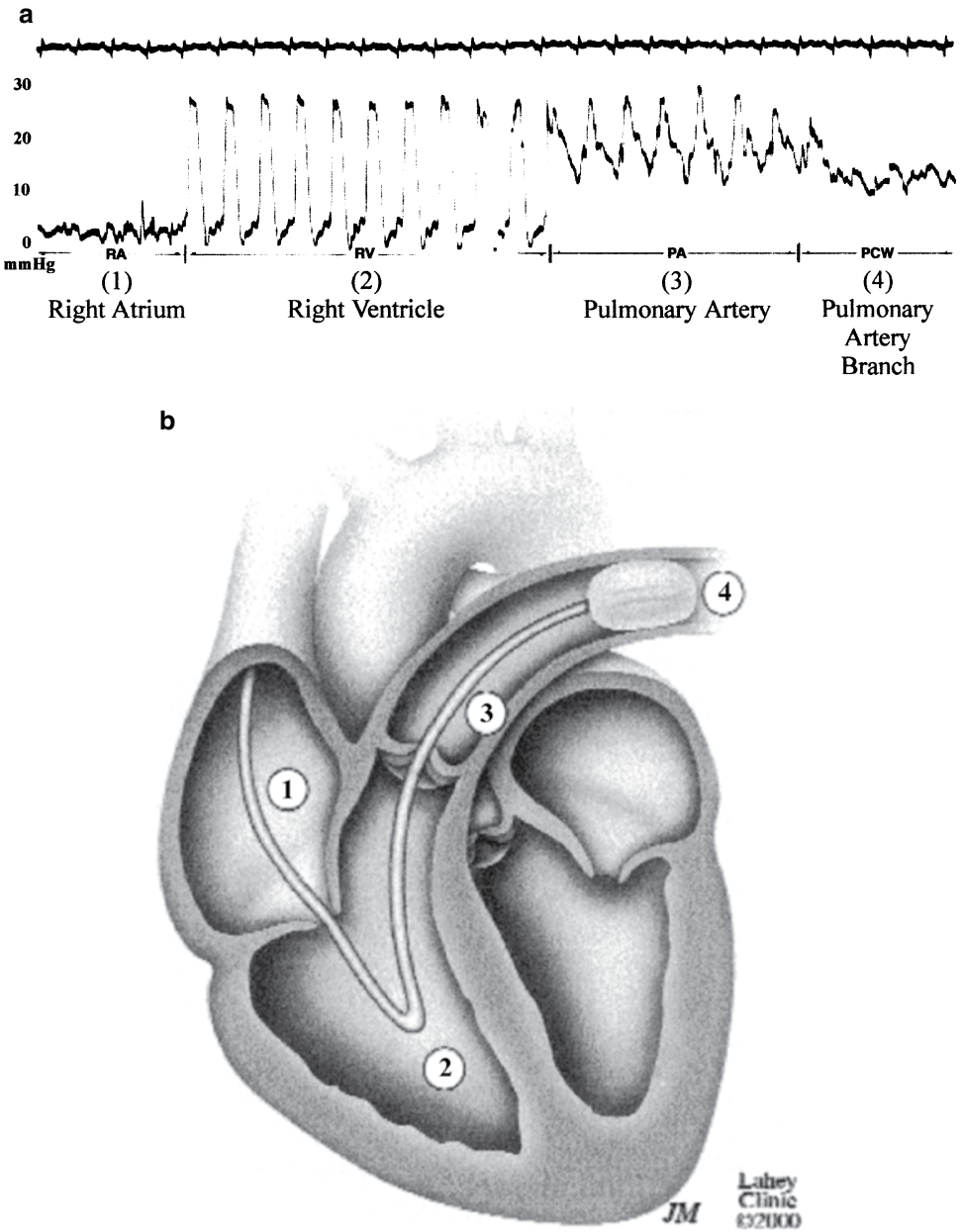

FIG. 3.3. Three approaches for access to the internal jugular vein. (**a**) Anterior to the sternocleidomastoid. (**b**) Central between the clavicular and sternal heads of the sternocleidomastoid. (**c**) Posterior to the sternocleidomastoid.

Shoulder manipulation has been reported to facilitate passage of the guidewire.[30] The vein is identified as it crosses the sternocleidomastoid muscle and cannulated at a 15- to 20-degree angle. Surface location of the vein makes it ideal for central catheterization in patients with coagulopathies, because any significant bleeding can be easily recognized and treated with local pressure. The risk of pneumothorax is also avoided. Because catheters inserted through the neck are more difficult to dress and maintain than those in other sites, this approach is not suitable for prolonged central venous access.

Femoral Vein

Although studies have shown no higher incidence of mechanical complications from femoral cannulation than from other central access sites,[31] concerns regarding the risk of infection and thrombosis continue to limit its general acceptance for long-term use in critically ill patients.[23,32,33] The vein can be located just medial to the femoral artery 2 cm below the inguinal ligament. The needle is directed cephalad at a 45-degree angle. The distal tip should not traverse the inguinal ligament to minimize the risk of retroperitoneal hematoma.

Ultrasound Guided Techniques

Doppler and ultrasound guidance for the cannulation of central veins have been described since the 1970s.[34] B-mode (two-dimensional) ultrasound equipment is becoming increasingly available in many institutions and many ultrasound-guided procedures can now be performed at the point-of-care. The greatest value of ultrasound guidance is for cannulation of the internal jugular veins. It is technically very difficult to catheterize the subclavian veins due to the limitations of imaging the vessels through overlying bone. The two most common techniques involve using the probe for real-time guidance of the needle, or instead, scouting the patients' anatomy and marking the skin with an appropriate needle insertion site. One prospective, randomized trial of central venous cannulation by real-time ultrasound, scout only, and traditional landmark technique demonstrated a significant reduction in the number of needle sticks and time required to successfully cannulate the vein in both ultrasound groups.[35] Success on the first attempt was doubled in the scout-only group compared to landmark technique, and was even higher in the real-time group. Based on existing literature, the Agency for Healthcare Research and Quality identified the use of real-time ultrasound guidance for central venous line placement as one of the practices that should be used to improve patient care.[36]

An assistant should be available during the procedure. The patient is placed in Trendelenburg position with the operator standing at the head of the table. The head is rotated to the right or left to offer greater exposure of the desired insertion site. It may be helpful to perform a preliminary ultrasound examination of the neck prior to preparing a sterile field. At the onset of the procedure, approximately 3–5 mL of ultrasound gel is applied to the tip of the vascular ultrasound probe before placing it inside a sterile plastic sleeve. Sterile ultrasound gel should be applied to the outside of the sleeve. The neck is examined along the anterior border of the sternocleidomastoid muscle in the transverse plane. The carotid artery and internal jugular vein are located 1–3 cm below the skin, with the carotid lying medial to the jugular, then migrating posterior to the vein as it descends the patient's neck. The jugular vein will be easily compressible with the ultrasound probe, whereas the artery will not readily compress. If the ultrasound machine is equipped with a color mode, it may be helpful to assess the blood flow pattern of each vessel to separate arterial and venous pulsations. The probe is then centered directly over the jugular vein. The depth from skin to vein should be measured and used to guide the insertion of the needle. This may prevent through-and-through puncture of the vein when the needle is inserted too deeply. The cannulation needle is advanced through the skin at a 45-degree angle on the center of ultrasound probe's edge. The needle tip is often not visible when viewing the vein in transverse section, so the operator must pay particular attention to the compression of overlying tissues as an indicator of needle tip position. This can be enhanced by gently toggling the needle as it is directed toward the vein. Successful cannulation is verified by the free aspiration of venous blood. The remainder of the procedure follows the steps previously described for the nonultrasound guided technique. After insertion of the guidewire, the operator may choose to further verify correct position by rotating the ultrasound probe 90° into longitudinal alignment with the vein. The wire should be visible on the monitor with its long axis parallel to that of the probe.

Complications

Complications occurring during catheter placement include catheter malposition; arrhythmias; embolization; and vascular, cardiac, pleural, mediastinal, and neurologic injury. Pneumothorax is the most frequently reported immediate complication of subclavian vein catheterization, and arterial puncture is the most common immediate complication of internal jugular vein cannulation. Long-term complications related to the length of time that the catheter remains in place include infection and thrombosis. Surface-modified central venous catheters have been developed to reduce catheter-related infection. One meta-analysis of available data concerning central venous catheters impregnated with chlorhexidine-silver sulfadiazine demonstrated a significant reduction in both catheter colonization and catheter-related bloodstream infections as compared to standard catheters.[37] Catheters coated with minocycline and rifampin have also been reported to reduce the risk of catheter-related colonization and bloodstream infections.[38,39]

Pulmonary Artery Catheterization

Indications

Use of a pulmonary artery catheter is indicated whenever the data it provides improve therapeutic decision-making, although significant debate as to whether this improves morbidity and mortality or not is ongoing. In the mid 1990s, one trial indicated that mortality might be increased by the use of pulmonary artery catheters,[40] leading some to propose a moratorium on the use of these devices.[41] However, clinical use of the pulmonary artery catheter persisted, and larger randomized controlled trials (RCT) on outcomes have been conducted.

The most recent multicenter RCT of 433 patients with congestive heart failure demonstrated no significant difference in overall mortality or hospitalization time for those managed with pulmonary artery catheters vs. those managed with clinical assessment alone.[42] This study was also included in a simultaneously published meta-analysis of all sufficiently powered RCTs from 1985 to 2005. The analysis encompassed 13 trials representing 5,051 medical and surgical patients, including those with sepsis, acute respiratory distress syndrome, or advanced heart failure. Again, there was no evidence that the pulmonary artery catheter had a positive or negative influence on mortality or length of hospitalization.[43] Table 3.1 shows the

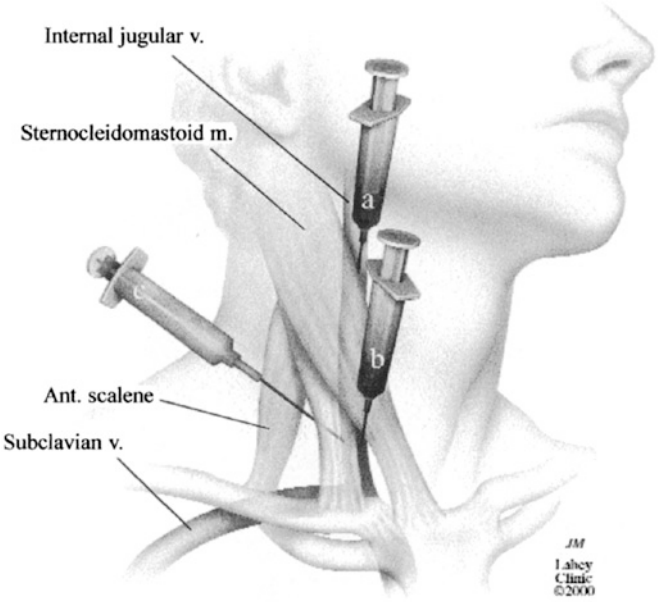

FIG. 3.4. Pressure tracing recordings with corresponding locations as the pulmonary artery catheter is passed into the "wedge" position.

TABLE 3.1. Conditions for which pulmonary artery catheterization have been recommended.

Surgical
Perioperative management of high-risk patients undergoing extensive surgical procedures
Postoperative cardiovascular complications
Multisystem trauma
Severe burns
Shock despite perceived adequate fluid therapy
Oliguria despite perceived adequate fluid therapy
Cardiac
Myocardial infarction complicated with pump failure
Congestive heart failure unresponsive to conventional therapy
Pulmonary hypertension (for diagnosis and monitoring during acute drug therapy)
Pulmonary
To differentiate noncardiogenic (adult respiratory distress syndrome) from cardiogenic pulmonary edema
To evaluate effects of high levels of ventilatory support on cardiovascular status

indications for pulmonary catheterization most often noted in the literature.

Contraindications

There are no specific contraindications to pulmonary artery catheterization, but the same cautions apply as those attached to central venous access.

Clinical Utility

The pulmonary artery catheter provides a significant amount of physiologic information that can guide therapy in critically ill patients. This information includes central venous pressure, pulmonary artery diastolic, systolic, and mean pressures, pulmonary artery occlusion "wedge" pressure, cardiac output by bolus or continuous thermodilution techniques, mixed venous blood gasses by intermittent sampling, and continuous mixed venous oximetry. A multitude of derived parameters can also be obtained.[44]

Technique

A conventional pulmonary artery catheter contains a distal lumen, a proximal lumen, a lumen for inflation of the balloon located at the catheter tip, and a thermistor for measurement of cardiac output by the thermodilution method. Preparation of the electronic monitoring equipment and testing of the catheter components before insertion are essential. Access to the central venous circulation for insertion of a pulmonary artery catheter is the same as for placement of a central venous catheter. The procedure has been facilitated by the use of introducer assemblies. Once an introducer sheath is in place, the pulmonary artery catheter is inserted and advanced until the tip reaches an intrathoracic vein (as evidenced by respiratory variations on the pressure tracing). The balloon is then inflated with 1.5 mL of air and the catheter advanced while the pressure waveform and the ECG tracing are being monitored. The catheter is advanced through the right atrium and into the right ventricle where a sudden increase in the systolic pressure appears on the tracing. The catheter is subsequently advanced through the pulmonic valve and into the pulmonary artery where a sudden increase in the diastolic pressure is recorded. The catheter is gently advanced until a pulmonary artery occlusion or "wedge" tracing is obtained[11] (see Fig. 3.4). The balloon is deflated, a pulmonary artery tracing is confirmed, the catheter is secured and a chest radiograph is obtained.

Complications

The most common complication during passage of the pulmonary artery catheter is the development of arrhythmias. During catheter insertion, coiling, looping, or knotting in the right ventricle can occur This can be avoided if no more than 10 cm of catheter is inserted after a ventricular tracing is visualized and before a pulmonary artery tracing appears. Aberrant catheter locations, such as pleural, pericardial, peritoneal, aortic, vertebral artery, renal vein, and inferior vena cava, have also been reported. After catheter insertion, the complications include infection,[45] thromboembolism, pulmonary infarction, pulmonary artery rupture, hemorrhage, pseudoaneurysm formation,[46,47] thrombocytopenia, cardiac valve injuries, catheter fracture, and balloon rupture. Finally, complications can result from delays in treatment because of time-consuming insertion problems and from inappropriate treatment based on erroneous information or erroneous data interpretation.[48]

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4
Fluid Resuscitation

Joachim Boldt

Hypovolemia is common among trauma, surgical, and intensive care unit (ICU) patients. Fluid deficits can occur in the absence of obvious blood or fluid loss secondary to either vasodilation or alterations of the endothelial barrier resulting in diffuse capillary leak (e.g., in septic patients). Sepsis is characterized by a panendothelial injury with subsequent development of increased endothelial permeability, loss of proteins, and interstitial edema leading to fluid shift from the intravascular to the interstitial compartment. In the critically ill intensive care patient, adequate volume restoration for treating noncompensatory, irreversible shock is essential. Prolonged under-resuscitation of the hypovolemic patient can have fatal consequences for organ function – lengthy uncorrected hypovolemia will even jeopardize survival secondary to continuous release of various vasoactive substances and stimulation of cytokine cascades. Vigorous optimization of the circulating volume is a prerequisite to avoid development of Multiple Organ Dysfunction Syndrome (MODS) in the hypovolemic patient.[1] In a prospective review of 111 consecutive patients who died in hospital after admission for treatment of injuries, the most common defects in patient management were related to inadequate fluid resuscitation.[2] In approximately 50% of septic patients, only adequate volume replacement may reverse hypotension and restore hemodynamics.[2]

The increasing awareness of the risk of transmitting viral diseases by blood transfusion has resulted in more aggressive use of nonsanguinous volume replacement. A reduction in hematocrit and arterial oxygen content is not deleterious even in "high-risk patients" since compensating mechanisms are able to guarantee tissue oxygenation and systemic oxygen transport. Careful attention is necessary to evaluate the patient's oxygen-carrying capacity. Although extensive information is available on the use of hemodilution, the "safe" hemoglobin level is still not definitely known. In the elderly and the critically ill surgical patient, limitations of cardiac and pulmonary function will influence the components of oxygen delivery. Nevertheless, blood/blood component therapy should be restricted to those cases presenting severe anemia or coagulation disorders. Non-blood alternatives for volume replacement in these patients should be used as much as possible.

Pathophysiology of Fluid/Volume Deficits

The primary goal of volume administration is to guarantee stable systemic hemodynamics and microcirculation by rapidly restoring the volume of the intravascular compartment. Excessive fluid accumulation, particularly in the interstitial tissue, should be avoided. Infused fluid may stay in the intravascular compartment or equilibrate with the interstitial/intracellular fluid compartments (Fig. 4.1). Composition and volume of each body compartment are controlled through a complex mechanism including antidiuretic hormone (ADH) system, renin-aldosterone-angiotensin (RAA), and the sympathetic nervous system (SNS). The principal actions of these systems are to restore intravascular volume deficit, retain sodium, and increase the hydrostatic perfusion pressure through vasoconstriction. The control of ADH secretion depends on osmolality, whereas the most important stimulus for the activation of the RAA system is depletion of the intravascular volume.

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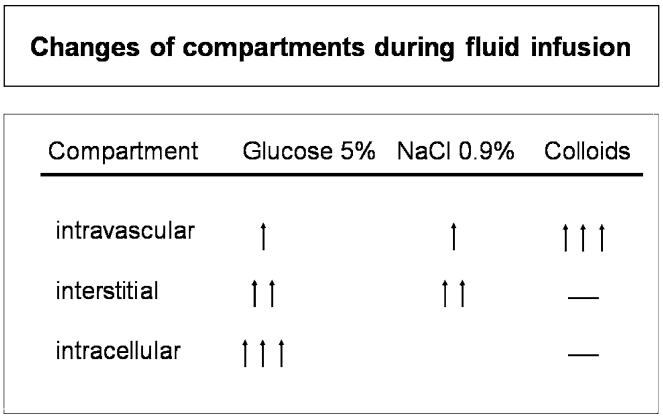

FIG. 4.1. Influence of different fluid replacement strategies on fluid compartments.

Enhanced activity of ADH, RAA, and SNS is known to occur in stress situations, for example, during trauma or surgery. Although the normal response to surgery and starvation results in improved metabolic activity, it can be expected that a preexisting deficit of water/intravascular volume further increases this activity. If the stimulus of water or intravascular volume deficit and the stress-related stimulus of ADH, RAA, and SNS are additive, fluid management could inhibit them through a counter-regulatory mechanism. Attempts to inhibit or attenuate the activity of ADH and RAA systems by administering different volumes of isotonic crystalloid solutions have been studied. ADH production is subordinate to the maintenance of the extracellular volume and, in particular, the intravascular compartment. Administration of a restricted volume of crystalloid solutions could possibly replace a previous deficit of water, but the replacement of an intravascular volume deficit would require much more volume to inhibit the secretory stimulus of all the hormones committed to maintain it. It can be expected that the replacement of water alone is unable to inhibit the normal response of ADH, RAA, and SNS; whereas administration of a combination of a crystalloid and colloid (replacement of water deficit simultaneous with restoration of intravascular volume) may achieve this goal. Subsequently, "fluid therapy" (replacement of interstitial fluid deficit) and "volume therapy" (replacement of intravascular volume deficit) have principally to be distinguished.

Armamentarium to Correct Fluid/Volume Deficits

Crystalloids

Crystalloid solutions can be divided into hypotonic (e.g., dextrose in water), isotonic (e.g., lactated Ringer's solution [RL]), and hypertonic solutions (e.g., 7.5% saline solution). The underlying electrolyte status of the patient must be kept in mind when selecting the fluid for volume replacement; solutions containing potassium should be avoided in patients with hyperkalemia. Crystalloids are freely permeable across the vascular membrane and are therefore distributed in the plasma and interstitial fluid compartment. After a 1,000 ml saline infusion, plasma volume expands by only 180 ml[3]; that is, only about 25% of the infused saline remains in the intravascular compartment, while the remaining 75% extravasates into the interstitial space.[4] Thus, large volumes of crystalloids are required for restoring sufficient hemodynamics: Crystalloid solutions have to be given in a four- to fivefold amount compared to colloids in order to exert similar circulatory effects. Infusion of such high volumes of unbuffered saline is associated with the development of hyperchloremic acidosis.

Additionally, dilution of plasma protein concentration by high amounts of crystalloids is accompanied by an unwanted reduction in plasma colloids oncotic pressure (COP). Thus crystalloids alone seem to be less qualified for volume replacement in the critically ill because of the large amount that is necessary to guarantee hemodynamic stability. In elderly patients, there is an increased risk of worsening pulmonary function by infusion of large amounts of crystalloids.[5,6] Use of crystalloids is also less likely to restore altered microcirculation. In an animal (hemorrhage) experiment, Wang et al.[7] investigated the quality of fluid resuscitation by laser Doppler flowmetry (LDF): RL did not restore microvascular perfusion sufficiently in this situation.

Hypertonic Crystalloids

Great enthusiasm has been expressed for hypertonic saline solution (HS) in the treatment of (refractory) hypovolemic shock. The concentration of sodium ranged from 3% to 7.5%. HS may improve cardiovascular function on multiple levels: displacement of tissue fluid into the blood compartment, direct vasodilatory effects, reduction in venous capacitance, and positive inotropic effects through direct actions on the myocardial cells. Additionally, HS is able to improve organ blood flow and microcirculation. The main mechanism of action of HS is rapid mobilization of endogenous fluid and subsequent plasma volume expansion. Due to the hypertonicity of the solution, only a small volume of fluid (approximately 4 mL/kg) is necessary to effectively restore cardiovascular function ("small volume resuscitation"). The initial improvement in cardiovascular function (e.g., increase in cardiac output) seems to be mediated by the hypertonicity of the solution and subsequently by the increase in ventricular preload, whereas the solute composition does not seem to be important. Beneficial effects of HS were reported to be rather transient. Thus, HS was often mixed with colloids (prepared in hypertonic-dextran [HS/HDS] or prepared in hydroxyethylstarch solution [HS/HES]) and these mixtures showed significant prolongation of the efficacy.[8] The use of extreme HS (up to 2,400 mosmol/L) has been studied only in some clinical trials, mostly for burns and patients with severe hypovolemia secondary to surgery.[9,10]

Colloids

The available colloids widely differ in their physico-chemical characteristics, their clinical effects, and their unwanted side effects.

Albumin

Albumin is a naturally occurring plasma protein and has long been judged to be the kind of solution by which the patients would profit most ("gold-standard"). Although albumin is derived from pooled human plasma, there appears to be no risk of disease transmission because albumin is heated and sterilized by ultrafiltration. In terms of transmission of infectious diseases, albumin is generally considered to be safe. The molecular weight of albumin is 69,000 dalton. Four percent albumin is hypo-oncotic and 5% albumin is iso-oncotic, whereas 20 and 25% solutions are hyperoncotic. In more recent studies, the oncotic force of concentrated human albumin (e.g., 20%) has been shown to reduce pulmonary edema. This effect of albumin depends on its movement between the intravascular and extravascular compartments and greatly varies with regard to the patient's disease. In patients with altered vascular endothelial integrity (e.g., after cardiac surgery, septic patients), however, albumin may pass into the interstitial space, promoting fluid shifts from the intravascular compartment to the interstitial space substantially inducing interstitial edema[11] and deteriorating tissue perfusion. The value of albumin for volume replacement in the critically ill has often been doubted.[12–14] People have been born without albumin (congenital analbuminemia) and these people are remarkably asymptomatic.[15] Thus, what is the role of albumin in the intensive care patient: vital component or place-holder, hero or poseur?

"Synthetic" Colloids

The term "synthetic" colloids is somewhat misleading because all of them are of biological origin – albumin is also "synthetized" (from pooled plasma). Thus the term "nonprotein" colloids appears to be more precise and less "negative." In contrast to the natural colloid albumin, which is a monomer (all molecules have the same size and weight), synthetic colloids are polydispersed; that is, they are a combination of many differently sized molecules. Large molecules only contribute minimally to the volume expansion effects; they reflect viscosity and persistance in the circulation. Smaller molecules of these solutions are quickly lost by renal filtration or diffusion into the interstitial space.

Dextrans

Dextrans are a polydispersed mixture of glucose polymers. Six percent dextran 70 (average molecular weight 70,000 dalton) and 10% dextran 40 (average molecular weight 40,000 dalton) are the two available dextran preparations. Increase of plasma volume after infusion of 1,000 ml of dextran 70 ranged from 600 to 800 ml. The main differences between the two solutions concern their influence on microcirculation. Infusion of dextran 40 has been described to increase microcirculatory flow because of a reduced red cell and platelet sludging, volume expansion, and hemodilution-induced reduction in whole blood viscosity. Dextrans, however, are associated with severe side effects (e.g., anaphylactic reactions, coagulation abnormalities) and impaired blood cross-matching, so that they have been replaced by other synthetic colloids in several countries.

Gelatins

Gelatins are modified beef collagens. In the USA, gelatin preparations were abandoned in 1978 due to their high incidence of hypersensitivity reactions. Gelatin exists in three different modifications: crosslinked gelatin (e.g., Gelofundiol®), urea-linked gelatin (e.g., Haemaccel®), and succinylated gelatin (e.g., Gelofusine®). The only major differences between these preparations consist in different electrolyte concentrations: Urea-linked gelatin includes high calcium and potassium contents, while succinylated preparations have low calcium and potassium contents. The increase of blood volume is approximately the same as that of the infused volume of gelatin. Due to the low molecular weight average (approximately 35,000 dalton), the plasma half-life is short (maximum 2 h) and reinfusion of gelatins are necessary to sufficiently maintain blood volume.

Hydroxyethylstarch (HES)

HES is a derivative of amylopectin, which is a highly branched compound of starch. In humans and animals, amylopectin is rapidly hydrolyzed by alpha-amylase and renally excreted. In order to slow down the metabolic degradation, anhydroglucose residues of the amylopectin are substituted with hydroxyethyl groups. The hydroxyethyl groups can be introduced mainly at positions C2 and C6 of the anhydroglucose residues. HES preparations are characterized by the following:

1. Concentration (3, 6, 10%)
2. Weight average molecular weight (Mw: the sum of each molecule's weight divided by the total mixture's weight times the weight of the molecule)
   (a) Low molecular weight [LMW]-HES: 70 kD
   (b) Medium molecular weight [MMW]-HES: 130 to 260 kD
   (c) High molecular weight [HMW]-HES: >450 kD
3. Molar substitution (MS: the molar ratio of the total number of hydroxyethyl groups to the total number of glucose units)
   (a) Low MS: 0.4, 0.42, and 0.5
   (b) Moderate MS: 0.62
   (c) High MS: 0.7

4. The C2/C6 ratio. The ratio of the C2:C6 hydroxyethylation is important for pharmacokinetic behavior of HES and also for its side effects (e.g., accumulation)

In the USA, high molecular weight (concentration: 6%; Mw: 450 kD; MS: 0.7) and low molecular weight (concentration 6%; Mw 130 kD; MS: 0.4) are available for volume replacement. Pentastarch (concentration: 10%; Mw: 260 kD; MS: 0.45) is FDA approved only for plasmapheresis. Pentafraction, a diafiltered solution of hydrolyzed amylopectin similar to pentastarch, possesses a narrower molecular weight range (Mw: 280 kD; MS: 0.5) and is not commercially available at this time. In Europe, many more HES solutions with different concentrations, Mw, and MS are available. The extent and duration of plasma expansion is extremely dependent on the physico-chemical characteristics of the HES solution. Maintenance of hemodynamic stability seems to be highly dependent on the kind of HES-preparation used. The different HES preparations cause different effects on rheology, coagulation, oncotic pressure, intravascular half-lives, and also different adverse effects.

Risks of Fluid Resuscitation

Coagulation Problems

Imbalances in the normal hemostatic mechanisms can commonly be seen in the intensive care patient either due to large blood loss, hypothermia, or activation of inflammatory pathways with subsequent activation of procoagulatory mechanisms and down-regulation of anticoagulant pathways. All plasma substitutes lower the concentration of clotting proteins by means of hemodilution. *Crystalloids* appear to have no major deleterious effects on coagulation, although in vivo and in vitro experiments have shown that hemodilution per se (also with crystalloids) compromised blood coagulation (e.g., inducing hypercoagulopathy).[16] *Albumin* is widely considered to have no significant negative effects on blood clotting aside from hemodilution. *Dextrans* negatively influence hemostasis either by reducing von Willebrand factor or by impairing platelet function.[17] When administering dextran, both VIIIR:Ag and VIIIR:RCo levels decrease significantly. Reduced VIIIR-RCo is associated with reduced binding to platelet membrane receptor proteins GPIb and GPIIb/IIIa, which results in decreased platelet adhesion. *Gelatins* are considered to be without relevant influence on hemostatic competence. In an in vitro study, however, significant inhibition of platelet aggregation was demonstrated by two gelatin preparations (polygeline and succinylated gelatin).[18] In another in vitro study using 3.5% polygeline and 4% succinylated gelatin, a significant reduction in clot quality was documented.[19] In six healthy men, an infusion of 1 L of gelatin resulted in a 1.7-fold increase in bleeding time, a substantial decrease in vWg:ag (−32%) and ristocetin cofactor (−29%), and a significant impairment of ristocetin-induced platelet aggregation.[20]

Hydroxyethyl starch is the substance with most reports on negative effects on hemostasis and increased bleeding tendency. The majority of the studies used the old ("first-generation") HMW-HES (Mw: 450,000 dalton, MS of 0.7 [Hetastarch]). This HES preparation may induce a type I von Willebrand-like syndrome with decreased factor VIII coagulant activity, and decreased von Willebrand's factor antigen and factor VIII-related ristocitin cofactor. HMW-HES diminished the concentrations of VIIIR:Ag and VIIIR:RCo more pronouncedly than HES with lower molecular weight (LMW-HES). HMW-HES resulted also in the overall most pronounced impaired platelet aggregation. Modern HES preparations, especially ("third-generation") HES (HES 130/0.4), did not show the same negative effects on platelet function as seen after HMW-HES administration.[21] Low- and medium-weight HES preparations (Mw ranging from 70,000 to 260,000 dalton) with a lower MS (ranging from 0.4 to 0.5) do not have such negative effects on coagulation outside of hemodilution and can be safely used in the critically ill.[22,23]

Kidney Function

Albumin and gelatins appear to be without relevant negative effects on renal function. Dextrans may initiate kidney dysfunction by inducing "hyperoncotic acute renal failure," especially in those patients in whom not enough crystalloids have been given along with the dextrans. HES solutions with a high MS have been shown to be associated with considerable negative effects on renal function.[24] Some histological studies have documented reversible swelling of renal tubular cells after the administration of certain HES preparations, most likely related to reabsorption of macromolecules. Swelling of tubular cells causes tubular obstruction and medullary ischemia, two important risk factors for the development of acute renal failure. Use of HES 2000/0.62 in brain-dead donors was associated with "osmotic nephrosis-like lesions" (vacuolization of the proximal tubular cells) in the transplanted kidneys. These lesions, however, had no adverse effects on graft function or serum creatinine and can be seen also after the use of other drugs (e.g., mannitol, dextrans). The most likely mechanism for causing renal dysfunction is the induction of hyperviscosity of the urine by infusion of hyperoncotic colloids (e.g., 10% HES) in dehydrated patients. Glomerular filtration of hyperoncotic molecules from colloids causes a hyperviscous urine and stasis of tubular flow, resulting in obstruction of the tubular lumen. Considering this pathogenesis, it can be hypothesized that all hyperoncotic colloid solutions can induce renal impairment ("hyperoncotic acute renal failure"). Adequate hydration by giving sufficient amounts of crystalloids is able to prevent these adverse effects on renal function. Large amounts (>2,000 mL) of HES preparations with a low or medium molecular weight (e.g., 6% HES 130/0.4 or 6% HES 200/0.5) with a low MS (0.4; 0.5) have been used safely in patients without altered kidney function.[25,26] The "critical" creatinine plasma level when HES should be avoided is not

definitely known. New light on this problem is shed by the last (third) generation of HES: In volunteers showing mild-to-severe renal dysfunction (mean creatinine clearance of 50 mL/min/1.73 m^2), 6% HES 130/0.4 was used.[27] After 500 ml of 6% HES 130/0.4, kidney function was not affected, indicating there were no negative effects of this new preparation with regard to kidney function, suggesting that this kind of HES preparation can be used safely even in patients with impaired kidney function.

Fluid Resuscitation and Additional Effects

The ideal plasma substitute for treating hypovolemia in the critically ill goes beyond the simple hemodynamic effects[28] – influences on organ perfusion and microcirculation also have to be taken into account when considering the best volume replacement strategy in this situation. Improving hemodynamics by optimization of the patient's intravascular volume status may have an important impact on immune response.[29] When treating the hypovolemic septic patient, the quantity of fluid administered rather than its composition is assumed to be the main determinant.[30] There is increasing evidence, however, that certain plasma substitutes possess more than just volume replacing properties. In vitro, in vivo, and human studies have assessed the effects of different plasma substitutes on microperfusion, capillary integrity, inflammatory response, and endothelial activation/integrity. Although the results are far from being uniform some "trends" are summarized[31]:

- *Crystalloids* are often recommended for treating hypovolemia in the critically ill because they are inexpensive and they are believed to have only a few side effects. Delayed and inadequate restoration of intravascular circulating volume by crystalloids, however, has been shown to worsen microvascular flow, endothelial integrity, and tissue oxygenation. A direct, substance-specific beneficial effect on the immune system or endothelial integrity has not been demonstrated. Experimental, animal, and human studies documented even some negative effects of crystalloids on inflammation, endothelial activation, and capillary leakage. Consequently, the Institute of Medicine raised concern with a Ringer's lactate-based volume replacement strategy due to aggravating the inflammatory process following resuscitation.[32]
- *Human albumin* is the most expensive plasma substitute. Non-oncotic, additional effects of albumin (e.g., anti-inflammatory properties) have been shown in some experimental/animal studies; however, negative effects on inflammatory response/endothelial activation as well as aggravation of tissue edema have also been described. At present, no convincing beneficial effects on perfusion, inflammation, tissue edema, or organ function have been demonstrated in humans justifying the use of this expensive plasma substitute.
- Only a few studies using *dextrans* have been published and dextrans have been more or less replaced by other colloidal plasma substitutes. Data on beneficial effects on microcirculation, inflammatory response, or organ perfusion with dextrans are rare.
- *Gelatins* are the least intensively studied class of plasma substitutes. Additional effects other than treating volume deficits have been reported very rarely.
- *Hydroxyethyl starch (HES)* appears to have considerable effects in addition to its volume replacement properties. The reasons for the beneficial effects of HES on the inflammatory response, endothelial injury/activation, and capillary leakage can only be speculated upon at present. The HES molecule may exert direct, substance-specific effects on endothelial cells. Certain HES preparations are improving organ perfusion (e.g., splanchnic circulation) and microcirculation that may also be responsible for some of the beneficial effects of HES in the critically ill.
- *Hypertonic saline (HS) or hypertonic/colloid solutions (HCS)* may improve cardiovascular function on multiple levels – displacement of tissue fluid into the blood compartment; direct vasodilatory effects, both in the systemic and pulmonary circulation; reduction in venous capacitance; and positive inotropic effects through direct actions on the myocardial cells. While shock-associated microvascular failure is often unresolved after conventional resuscitation, HS/HCS appear to reduce microvascular collapse, restoring vital nutritional blood flow. HS tends to blunt the upregulation of leukocyte and endothelial adhesion molecules that occur with isotonic resuscitation of shock. In animal studies, convincing data showing improved microcirculation/organ perfusion, inflammatory response, endothelial integrity, and tissue edema have been demonstrated with HS and HCS. The combination with a hyperoncotic HES appears to be most promising, because combinations with dextrans may be associated with unwanted negative effects.

A New Debate: "Dry or Wet"

Aside from the controversy on the "ideal" volume replacement strategy, a "wet versus dry" philosophy has become a subject of substantial debate. It has been suggested that restricting fluid input resulted in significantly reduced complications and improved outcome.[33] Keeping the patients "dry" may be a two-edged sword because maintaining patients as hypovolemic may result in compromised organ perfusion and tissue oxygenation. Most of the "dry"-supporting studies used fixed amounts of volume instead of adapting fluids to the patients' need ("goal-directed" fluid resuscitation). No generally accepted definition of "restricted," "dry," or "overload" is available. One fundamental problem with this issue is how to define: (1) inadequate fluid therapy, (2) adequate fluid therapy, and (3) excessive fluid therapy. Most institutions have defined their individual protocols for fluid therapy

and definitions such as "standard," "aggressive," "restrictive," or "liberal" fluid regimen are far from being clearly defined or generally accepted. In this context, not only the amount of the administered fluid, but also the kind of fluid appears to be important. Current evidence indicates that using crystalloids in excess may result in overloading the interstitial compartment with considerable negative sequelae; whereas using colloids may improve microperfusion and tissue oxygenation. At present, there exists only meager literature on a restricted volume replacement strategy and a "dry" approach cannot be generally recommended at this point of time.

How Is Fluid Therapy Guided?

Evaluation of volume deficit and guiding adequate volume therapy remain a challenge. The aim of appropriate monitoring is to avoid insufficient fluid infusion as well as fluid overload. Standard hemodynamic monitoring such as measuring blood pressure and heart rate (HR) are often inaccurate to detect volume deficits or to guide volume therapy. Despite some negative data on the value of pulmonary artery catheters (PAC) in the critically ill, they are still widely used for hemodynamic monitoring in the critically ill. However, cardiac filling pressures (e.g., central venous pressure [CVP] and pulmonary artery occlusion pressure [PAOP]) are often misleading surrogates for assessing optimal left ventricular loading conditions. Cardiac filling pressures are influenced by several factors other than blood volume, including alterations in vascular or ventricular compliance and intrathoracic pressure.

Measurement of intrathoracic blood volume (ITBV) has been reported to be a more reliable method to monitor volume therapy in this setting.[34] Studies have shown a reduction in ICU and hospital stay and mortality utilizing this technique.[34,35]

Echocardiography, especially transesophageal echocardiography (TEE), appears to be the most specific instrument to evaluate cardiac filling. Due to its high costs it is not available in every ICU. Moreover, TEE is an intermittent diagnostic tool rather than a continuous monitoring device and thus appears to be impractical as a guide to volume therapy.

Perturbation of organ perfusion is thought to be of fundamental importance in the pathogenesis of organ dysfunction in the critically ill.[36] Even occult hypovolemia may be associated with the development of organ perfusion deficits and organ dysfunction.[37] There still does not exist an ideal monitoring tool to detect perfusion deficits. Cardiac output, VO_2, and DO_2 are not believed to be ideal measures for assessing the adequacy of regional or microcircular perfusion.[38] The hypovolemic patient is at risk of experiencing splanchnic hypoperfusion with subsequent development of translocation and systemic inflammatory response syndrome (SIRS).[39] Abnormalities of splanchnic perfusion may coexist with normal systemic hemodynamic and metabolic parameters. Noninvasive, continuous tonometry measuring gastric mucosal partial pressure of carbon dioxide (gastric pCO_2) may be an attractive option for diagnosis and monitoring of splanchnic hypoperfusion. Although this monitoring instrument has produced some promising results, it is far from being the new "gold standard" for guiding volume management of the critically ill.[40]

Fluid Resuscitation in the Mirror of Meta-Analyses

- The Cochrane Injuries Group published in 1998 a meta-analysis comparing the use of albumin with other regimens of volume replacement (crystalloids, synthetic colloids).[41] The analysis included 30 studies with a total of 1,419 patients. The pooled results showed an overall excess mortality of 6.8% (or about 6 additional deaths for every 100 patients treated with albumin).
- In a Cochrane Review from 2002, a systematic review was made on colloids versus crystalloids for fluid resuscitation in critically ill patients.[42] No actual study (2000 and earlier) was included in this analysis comparing mortality of colloids versus crystalloids for fluid resuscitation in humans. Twenty-six trials comparing crystalloids with different kinds of colloids, nine trials comparing colloids prepared in hypertonic crystalloids with isotonic crystalloids, and three trials comparing hypertonic crystalloids with colloids were included. There was no evidence that resuscitation with colloids reduces the risk of death in patients with trauma, burns, and following surgery.
- In another systematic review from the Cochrane Group from 2002, hypertonic-based volume replacement regimen was compared with crystalloid-based volume replacement in critically ill patients.[43] Although a mass of studies has been published on this topic, only 12 studies were included in the analysis. The authors concluded that there is no evidence that one strategy of volume therapy is superior to the other in patients with trauma (five studies included), burns (three studies included), or those undergoing surgery (four studies included).
- Another meta-analysis on hypertonic volume replacement from 1997 comparing hypertonic saline-based volume therapy with dextran-based volume replacement[44] suggests a favorable survival benefit for hypertonic saline treatment of traumatic hypotension.
- The influence of an albumin-based volume therapy on mortality compared to other volume replacement strategies was compared in a meta-analysis of randomized controlled trials from 2001.[45] No actual study was included (2000 and earlier). Trials involving surgery and trauma (27 studies), burns (4 studies), hypoalbuminemia (5 studies), high-risk neonates (6 studies), ascites (5 studies), and other indications (8 studies) were included. None of the analyzed factors (outcome, mortality) were significantly influenced by either of the volume replacement regimens. There was overall no beneficial effect of albumin on

mortality in these 55 studies including 3,504 patients compared to other plasma substitutes.

- One meta-analysis focused on the effects of plasma substitutes on blood coagulation and on postoperative bleeding in cardiac surgery patients in whom either albumin or different HES preparations had been given.[46] Both solutions had been used either before or after cardiopulmonary bypass (CPB) or as an addition to the priming solution. When high-molecular weight (HMW) HES (Hetastarch) was compared to albumin (9 studies with 354 patients), postoperative bleeding was significantly higher in the HMW-HES patients than in the albumin-treated group. When HES with a lower Mw (200 kD) was compared with albumin (8 studies with 299 patients), there was no statistical difference in postoperative bleeding.
- Some have questioned whether meta-analyses focusing on outcome are appropriate instruments to examine the value of different fluids therapy in the critically ill, because mortality has never been an endpoint in any of the studies. New concepts about critical care, for example, the role of inflammation, immunological aspects, and organ function, may shed new light on this problem.

Conclusions

Adequate fluid resuscitation in the critically ill intensive care patient should not aim only at restoring systemic hemodynamics (Fig. 4.2). The ideal fluid resuscitation strategy in the critically ill continues to be debated. Beside the natural colloid albumin, several non-protein ("synthetic") colloids are increasingly being used as plasma substitutes. The results concerning the ideal strategy in this situation is far from being uniform:

- Allogeneic blood should be avoided if at all possible. It cannot, however, be completely eliminated from our strategy to manage the patient in hemorrhagic shock (Fig. 4.3).
- Although there is convincing evidence that blood volume is restored more rapidly with colloids than with crystalloids – colloids are more efficient resuscitative fluids than crystalloids, and colloids are also a more efficient regimen to guarantee microcirculatory flow than crystalloids – crystalloids have been often recommended as the first choice to treat hemorrhage. The *American College of Surgeons Classes of Acute Hemorrhage* specified four classes of acute hemorrhage using a blood loss ranging from up to 750 to >2,000 ml[47] (Fig. 4.4). Fluid replacement should be performed with crystalloids exclusively (3:1 rule). There is no place for administrating (synthetic) colloids because the patients are at risk for fluid overload.
- Certain colloids (e.g., HES) are associated with beneficial effects on microperfusion, capillary integrity, inflammatory response, and endothelial activation/integrity, but they still seem to be underutilized in the hypovolemic patient.
- What endpoints should be chosen when guiding volume replacement? Although often used, "clinical signs" of hypovolemia

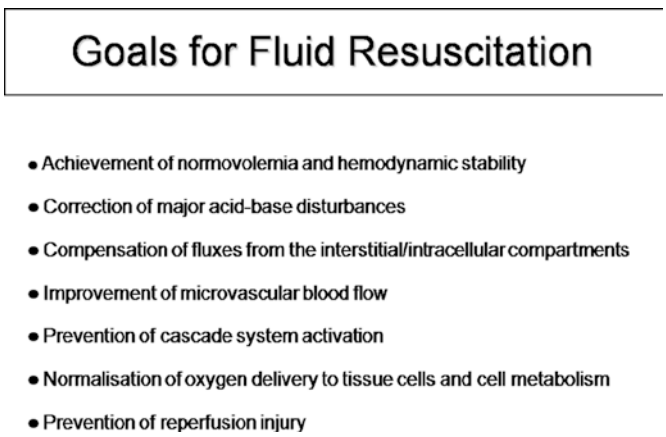

Fig. 4.2. Goals of fluid resuscitation.

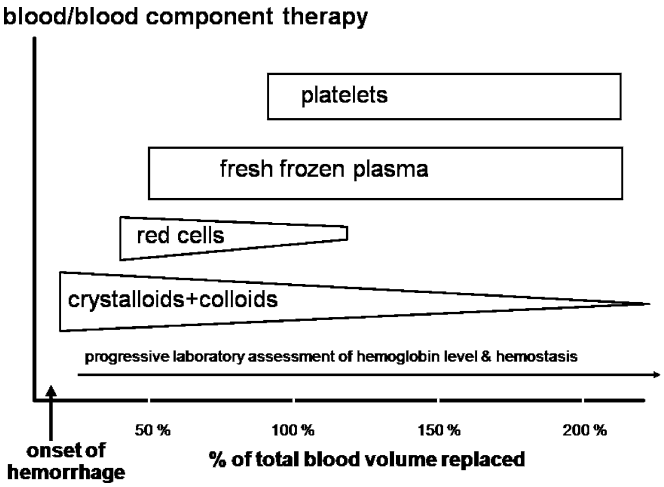

Fig. 4.3. Stepwise approach of the use of blood and/or blood components.

American College of Surgeons Classes of Acute Hemorrhage

Factors	I	II	III	IV
Blood loss,ml	< 750	750-1500	1500-2000	> 2000
Blood loss, %BV	< 15	15-30	30-40	> 40
Puls, BPM	> 100	> 100	> 120	> 140
Blood pressure	Normal	Normal	Decreased	Decreased
Puls pressure (mmHg)	Normal/increased	Decreased	Decreased	Decreased
Capillary refill test	Normal	Positive	Positive	Positive
Respiration per min	14-20	20-30	30-40	>35
Urine output, ml/hr	30 or more	20-30	5-10	Negligible
CNS (metal status)	Slightly anxious	Mildly anxious	Anxious confused	Confused lethargic
Fluid replacement	**Crystalloid**	**Crystalloid**	**Crystalloid+blood**	**Crystalloid+blood (3:1 rule)**

Fig. 4.4. Fluid resuscitation with regard to recommendation of the American College of Surgeons Classes of Acute Hemorrhage.[47]

are nonspecific and insensitive. Most studies on volume replacement were not focused on outcome. It remains unclear whether mortality is an appropriate endpoint when assessing the benefit of different volume replacement strategies. New concepts on treating hypovolemia such as development of systemic inflammatory response syndrome (SIRS) and posthemorrhagic organ dysfunction (e.g., renal or pulmonary insufficiency) should change this point of view. We need improved monitoring technologies that will help us better guide volume therapy as well as improved "point-of-care" markers that will help us better assess whether volume therapy is appropriate to sufficiently restore hypovolemia-associated alterations.

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5
Vasoactive Amines and Inotropic Agents

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One of the central goals of the clinician caring for critically ill patients is to maintain hemodynamic stability. This requires knowledge of the anatomy and physiology of the autonomic nervous system, the cardiovascular system, and their interaction. This chapter reviews the autonomic innervation of the heart and peripheral circulation and the cardiovascular effects of the vasoactive amines and various inotropes.

Autonomic Innervation of the Heart

The autonomic nervous system affects the heart by changing the rate (chronotropism), augmenting contractibility (inotropism), and regulating coronary blood flow.[1]

The principal effect of the parasympathetic nervous system (PNS) on the heart is chronotropic. PNS fibers are distributed mainly to the supraventricular portion of the heart. Sympathetic nervous system (SNS) fibers have supraventricular and ventricular distribution, therefore affecting chronotropy and inotropy. Denervated hearts (i.e., cardiac transplantation) are capable of maintaining effective circulation.[1]

Coronary blood flow is primarily autoregulated and depends on local myocardial metabolic requirements and occurs at the level of small intramyocardial precapillary vessels (resistance vessels). The large epicardial vessels (conductance vessels) respond to neurogenic stimulation from the interaction of the SNS and PNS systems.[1]

Autonomic Innervation of the Peripheral Circulation

The peripheral circulation is regulated by the SNS-producing vasodilatation or vasoconstriction. Basal vasomotor tone consists of a state of intermediate arterial constriction, which is maintained by impulses from the lateral portion of the medulla oblongata and circulating epinephrine from the adrenal medulla.[1] The SNS also alters the capacitance of the venous system, significantly changing venous return to the heart (preload).

Neurotransmitters

Acetylcholine is the preganglionic neurotransmitter in both the SNS and PNS, as well as the postsynaptic neurotransmitter in the PNS. The postsynaptic transmitter in the SNS is norepinephrine excluding the sweat glands.[1]

The sympathetic fibers reaching the adrenal medulla are preganglionic. They interact with the chromaffin cells of the medulla (second order neuron) resulting in the release of epinephrine (80–85%) and norepinephrine (15–20%) into the circulation where they act as hormones with a ten times longer duration than with direct SNS stimulation.[1]

The catecholamine chemical structure includes a catechol group (a benzene ring and two adjacent hydroxyl groups) and

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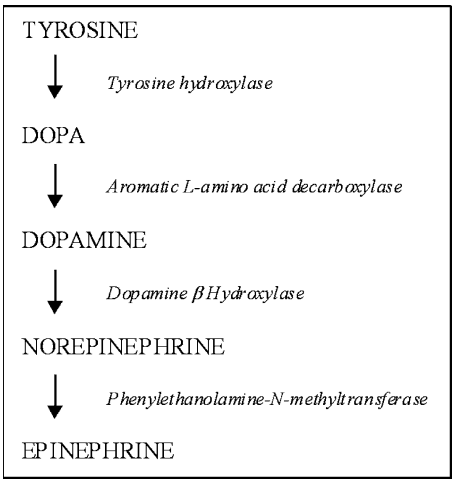

FIG. 5.1. Synthesis of catecholamines.

an amine containing side chain. Figure 5.1 summarizes the formation of the three endogenous catecholamines (epinephrine, norepinephrine, and dopamine) and the corresponding enzymes.[1] Dopamine is the precursor of norepinephrine, and norepinephrine is the precursor of epinephrine in the adrenal medulla. Endogenous or systemically administered catecholamines do not cross the blood-brain barrier. Dopamine and norepinephrine in the Central Nervous System (CNS) are synthesized and metabolized in situ.

Catecholamines are removed from their site of action by three separate mechanisms. Endogenous catecholamines are removed primarily by reuptake into the presynaptic terminals (uptake 1). A minor mechanism for endogenous catecholamines removal includes breakdown by monoamine oxidase (MAO) and catechol-o-methyltransferase yielding vanillyl mandelic acid (uptake 2). The final pathway results from diffusion into the circulation followed by metabolism in liver and kidneys (uptake 3). Uptake 3 is an important mechanism for exogenous administered catecholamines.[1]

Adrenergic Receptors

Receptors are best described as target structures – usually macromolecules located on the cell membrane – that is, when stimulated by an agonist, provoke a response of the effector cell.

SNS stimulation is either α or β receptor mediated. Both the α and β receptors are further divided into two subtypes. Recently, a β3 receptor has been described. It is activated by catecholamines but at higher concentration than a β1 or β2 receptor. In blood vessels, stimulation of a β3 receptor produces a vasodilation.[2] In visceral adipose tissue these receptors play a role in lipolysis, thermogenesis, and weight control.[3,4]

Chronic receptor stimulation by agonists or antagonists can affect the concentration of receptors producing either down regulation or up regulation, respectively. Table 5.1 summarizes the adrenoreceptors and their effects on various target organs. Individual effector organ response depends on the type and concentration of receptors present, the SNS innervation, and the vascular supply.[1]

Vasoactive Amines and Inotropes

Oliver and Schäfer in 1895 were the first to describe the cardiovascular effects of injected adrenal extracts.[5] Synthetic amines related to epinephrine are referred to as sympathomimetics and act by either directly interacting with the receptors or indirectly by promoting the release of endogenous catecholamines.[6] Certain sympathomimetics have both direct and indirect activity (mixed).

Sympathomimetics, as their name indicates, evoke responses at the target organs similar to those produced by the activity of the sympathetic nervous system: (1) vasoconstriction in the cutaneous and renal circulation, (2) vasodilation in the skeletal muscle vasculature, (3) bronchodilation, (4) inotropism, (5) chronotropism, (6) arrhythmogenesis, (7) release of free fatty acids from tissues, (8) glycogenolysis, (9) endocrine effects (primarily insulin, renin, and pituitary hormones), (10) immunological effects (on T-cells), and (11) CNS effects. These effects depend on the distribution (α vs. β), concentration, and selectivity (chemical structure) of the particular agent. Sympathomimetics are traditionally classified based on their origin: endogenous catecholamines, synthetic catecholamines, or synthetic non-catecholamines.

Endogenous Catecholamines

Epinephrine

Epinephrine is considered the prototype sympathomimetic with both α and β effects.[7] Exogenous epinephrine must be administered intravenously or subcutaneously since oral administration is ineffective. MAO and COMT rapidly metabolize epinephrine, principally in the liver.[6] It lacks CNS effects as a result of poor lipid solubility.[6,7]

Cardiovascular Effects

The cardiovascular effects of epinephrine are dose dependent. At lower doses (2 μg/min) β2 activation results. Intermediate doses (4 μg/min) produce β1 stimulation while α effects predominate at larger doses (10–20 μg/min).

Stimulation of the β1 receptor produces an increase in systolic blood pressure, heart rate, and cardiac output.[7,8] Diastolic blood pressure decreases secondary to β2 effects in the skeletal muscle vasculature. Although there is an increase in pulse pressure, mean arterial pressure shows minimal or no change and this may account for the lack of baroreceptor reflexes (bradycardia) in response to epinephrine.[6,7]

Epinephrine produces vasoconstriction in skin, splanchnic, and renal vasculature as a result of α1 stimulation. As mentioned

Table 5.1. Adrenoreceptors and effects on target organs.

	α1	α2	β1	β2
CNS	N/A	↓ CNS activity Insulin release ADH Bowel motility Analgesia Sedation	N/A	N/A
Eye	Mydriasis ↑	N/A	N/A	Ciliary muscle relaxation
Salivary glands	Secretion	N/A	N/A	N/A
Heart	↑ Coronary constriction Inotropy	Coronary constriction	↑ Chronotropy Inotropy Dromotropy Conduction Coronary relaxation	↑ NE release Inotropy Chronotropy
Peripheral vascular Smooth muscle	Constriction	N/A	N/A	Relaxation
Airway smooth muscle	Constriction	N/A	N/A	Relaxation
Pancreas	↓ Insulin secretion	N/A	N/A	↑ Insulin Glucagon secretion
Upper GI tract	Sphincter contraction	N/A	N/A	↓ Tone Motility
Liver	Glycogenolysis	N/A	N/A	Gluconeogenesis
Splanchnic bed Smooth muscle	Constriction	N/A ↑	N/A	Relaxation
Kidney	Vasoconstriction Antidiuresis	Natriuresis Diuresis	Renin release	Vasodilation
Bladder	Sphincter and trigone contraction	N/A	N/A	Detrusor relaxation

N/A not applicable.

previously, it causes vasodilation in skeletal muscle via β2 activation. The net result is a preferential distribution of cardiac output to skeletal muscles, with a decrease in systemic vascular resistance.[6,7] In the kidney there is a decrease in renal blood flow and increased renin release.[7]

Epinephrine increases coronary blood flow even at doses that do not produce changes in blood pressure.[7] It also increases the work of the heart and myocardial oxygen consumption. Non-selective β-blockade (i.e., propranolol) results in a marked hypertensive response to epinephrine.[8] This is not observed with selective β-blockade (i.e., atenolol).

Effects on the Airway

Epinephrine affects respiration primarily by stimulating β2 receptors and relaxing bronchial muscle. It has a powerful bronchodilator action, most evident when bronchial muscle is contracted because of disease such as asthma, or in response to drugs or various autacoids. Its beneficial action in asthma is also attributed to β2-receptors inhibition of mast cells as well as to reduction of congestion within the mucosa mediated by α receptors.[6]

Metabolic Effects

Epinephrine plays an important role in the metabolic response to stress. β stimulation results in liver glycogenolysis and tissue lipolysis.[7] Alpha stimulation inhibits the release of insulin.[7] β receptor stimulation of the α cells of the pancreas causes release of glucagon.[6] Epinephrine also impairs the uptake of glucose by skeletal muscle in part due to its action on insulin.[6,8] Increased levels of lactate may reflect the enhancement of glycogenolysis induced by epinephrine in the skeletal muscles. These mechanisms are at least in part responsible for the hyperglycemia associated with trauma in the perioperative period. Epinephrine increases oxygen consumption by 20 to 30%.[6]

Effects on Electrolytes

Hypokalemia has been reported in patients receiving epinephrine infusions. The likely mechanism appears to be β2 agonist effects on the sodium–potassium pump leading to a transfer of potassium ions into skeletal muscle.[7,9] However, transient increases in serum potassium with epinephrine administration have been reported, apparently due to release of the ion by the liver.[7,8]

Miscellaneous Effects

Ocular administration of epinephrine causes contraction of the radial muscle of the iris producing mydriasis[7] and lowers intraocular pressure.[6] β adrenergic agonism stimulation of the bladder produces detrusor relaxation, while α adrenergic stimulation causes contraction of the trigone and sphincter muscles.[7] Epinephrine may be a contributing factor in the

hypercoagulable state seen during the perioperative period due to an increase in factor V activity.[7] Hematologic effects include leukocytosis and eosinopenia.[6,7]

Adverse Effects and Contraindications

There is a vast array of side effects following the parenteral administration of epinephrine. Anxiety, restlessness, tremor, and headaches have been described. Severe hypertension and fatal ventricular arrhythmias have been reported with intravenous epinephrine. In patients with coronary artery disease, angina can occur. Epinephrine is contraindicated in patients who are receiving non-cardioselective β blockers since unopposed α1 stimulation can produce severe hypertension and possible CNS hemorrhage.[6]

Norepinephrine

Norepinephrine is a potent α1 agonist and also has β1 activity. It is less potent than epinephrine and lacks β2 activity.[6,7] Norepinephrine is ineffective when administered orally and poorly absorbed subcutaneously.[6] It is metabolized by MAO and COMT.

The administration of norepinephrine at doses ranging from 0.5 to 30.0 μg/min results in intense vasoconstriction in the renal, hepatic, skeletal muscle, skin, and vascular beds. The end result is a significant increase in the systemic vascular resistance, and an increase in systolic, diastolic, and mean arterial pressures.[6,7] Experiments using selective receptor antagonists have demonstrated that norepinephrine produces increase in venous return due to both α- and β-adrenergic receptor stimulation.[10] A baroreceptor response usually overcomes β1 stimulation resulting in a decrease in heart rate. The increase in systemic vascular resistance and the decrease in heart rate can decrease cardiac output.[6,7] Peripheral vasoconstriction may lower tissue perfusion, producing metabolic acidosis.[7] Norepinephrine also increases coronary blood flow, possibly by the increase in blood pressure and direct coronary vasodilation.[6] Glomerular filtration rate is usually preserved unless renal blood flow is greatly impaired.[6]

Norepinephrine is the vasopressor agent of choice in management of hypotension in hyperdynamic septic shock, as recently recommended by a subcommittee of Surviving Sepsis Campaign.[11] It can increase oxygen delivery and, frequently, can correct refractory hypotension, although large doses may be required to achieve these effects due to α-receptor down regulation. In the setting of sepsis, norepinephrine also improves renal blood flow and urine output,[12] and its use has been associated with improved survival.[13]

Norepinephrine does not have an impact on the metabolic milieu. Hyperglycemia is unlikely to occur as a result of norepinephrine. Unlike epinephrine, norepinephrine does not produce bronchodilatation. Local extravasation of norepinephrine can result in vasoconstriction and tissue necrosis, which may be attenuated by infiltration with the α receptor antagonist phentolamine.[6]

Dopamine

Dopamine is the immediate metabolic precursor of norepinephrine and is a neurotransmitter in both the peripheral and central nervous systems.[6,7] Similar to the other two naturally occurring catecholamines, dopamine is a substrate for MAO and COMT, and, thus, is inactive when given orally. As much as 21% of a clinical dose of dopamine appears to be cleared by the lungs.[14]

There are two identified dopaminergic receptors: DA1 and DA2.[6,7,15] DA1 is postsynaptic and mediates vasodilatation in renal, mesenteric, coronary, and vascular beds.[6,15] Activation of DA1 stimulates adenylate cyclase, resulting in an intracellular increase of cAMP and vasodilation.[6,15] DA2 receptors are located on postganglionic sympathetic nerves and autonomic ganglia,[15] and their activation inhibits norepinephrine release from the sympathetic nerve endings. DA2 receptors are also found in the emetic center of the CNS and the anterior lobe of the pituitary gland.[15]

Dopamine activates different kinds of adrenoreceptors preferentially in a dose-related manner. At lower doses (0.5–3 μg/kg/min), dopamine activates primarily DA1 receptors in the renal, coronary, and mesenteric circuits[6,16] and, to a lesser extent, DA2 receptors. This results in an increase in renal blood flow with a diuresis and natriuresis, and is most evident in normovolemic patients. In one study, Hilberman et al.[17] compared dopamine against dobutamine, which has no renal vasodilatory effects. Both drugs were titrated to obtain equal cardiac outputs to offset the possible effect of improved hemodynamics on renal function. They failed to demonstrate a selective renal vasodilator effect of dopamine, but did show diuretic, natriuretic, and kaliuretic properties that are possibly best explained by a direct tubular inhibition of substrate reabsorption.

Since renal protective properties of dopamine were suggested by the work of Goldberg in 1972,[18] significant controversy has ensued and multiple efforts have been made to clarify this matter. Despite the diuretic effect of dopamine, several researchers have failed to demonstrate a significant increase in creatinine clearance or improvement in renal outcomes in patients at risk for renal failure.[7,16] Even at low doses, dopamine can cause intestinal mucosa ischemia, resulting in bacterial translocation, which appears to be a critical event leading to multiple organ-system failure. Other side effects include tachyarrhythmias, myocardial ischemia, decreased respiratory drive, and increased intrapulmonary shunting.[7] The use of dopamine for renal protection cannot be recommended at this time.[19]

Dopamine-induced increases in mesenteric blood flow have been associated with decreases in oxygen extraction, nutritive blood flow, and capillary density in the intestines. Therefore, dopamine may divert blood flow away from intestinal mucosa and predispose to mucosal ischemia.[20]

At intermediate doses (3–10 μg/kg/min), dopamine activates β1 receptors in the myocardium and promotes the release of norepinephrine, producing an increase in cardiac output, heart rate, systolic blood pressure, and widening of pulse pressure.

However, it also increases the pulmonary capillary wedge pressure.[8] Part of the effects of dopamine on the myocardium are secondary to conversion to norepinephrine and may account for the attenuation of effects (tachyphylaxis) seen with prolonged infusion.[8] This makes it an unreliable inotrope in patients with maximized sympathetic tone (i.e., chronic heart failure).[7]

At high doses (greater than 10 μg/kg/min), α1 activation prevails, leading to increased systemic vascular resistance and blood pressure. Higher doses are associated with increased risk of arrhythmias due to enhanced β1 stimulation.

Dopamine has been found to decrease the plasma concentration of all anterior pituitary hormones except cortisol.[21,22] It also appears to impair the activity of T-lymphocytes, which can perpetuate the anergic state of critically ill patients.[22,23]

Synthetic Catecholamines

Dobutamine

Dobutamine is a synthetic catecholamine that acts mainly as a selective β1 agonist. The principal use of dobutamine is to increase cardiac output in patients with heart failure. It is associated with no change or a minimal decrease in systemic and pulmonary vascular resistance and blood pressure. For this reason it may not be useful in patients requiring a pressor effect in addition to inotropic support (i.e., sepsis). On the contrary, this combination of effects and the decrease in atrial filling pressures[7,8] are most advantageous in a volume-loaded failing heart in which afterload reduction is of great benefit.[24] Heart rate can increase slightly with dobutamine administration. In the absence of a significant increase in heart rate, dobutamine may decrease myocardial oxygen consumption. Patients are less prone to arrhythmias than with dopamine since dobutamine does not convert to norepinephrine.[7] Dobutamine does facilitate atrio-ventricular conduction, which puts patients in atrial fibrillation at risk for rapid ventricular responses.[6,7] The effects of dobutamine on the heart may be attenuated with prolonged infusion.[6,8]

Dobutamine is generally initiated at an infusion rate of 2 μg/kg/min, and can be titrated up to 15 μg/kg/min or higher to achieve the desired hemodynamic or clinical effect.

Isoproterenol

Isoproterenol is a non-selective synthetic β-agonist catecholamine. Inotropic and chronotropic effects occur via β1 stimulation of the heart, while β2 agonism produces vasodilatation principally in the skeletal muscle, renal, hepatic, and mesenteric beds.[6] As a result, isoproterenol increases cardiac output and heart rate and decreases systemic vascular resistance, diastolic blood pressure, and mean arterial pressure. Isoproterenol facilitates the occurrence of cardiac arrhythmias.[6–8] The decrease in diastolic and mean arterial pressure can decrease coronary perfusion pressure. This later coupled with the increased inotropism and chronotropism may result in an unfavorable myocardial oxygen supply demand ratio, which can be detrimental to patients with coronary artery disease. Isoproterenol also decreases pulmonary vascular resistance.[6–8] Giving the likelihood of its toxicity, the clinical use of isoproterenol is limited to the bradycardia in the denervated heart (status post heart transplant),[6] and to hemodynamically significant bradycardia not responding to anticholinergic agents until a pacemaker is inserted. The starting infusion rate for isoproterenol is 1 μg/min, which can be titrated up to 10 μg/min to achieve the desired response. Isoproterenol is also a potent bronchodilator, but it has been largely replaced as such by more selective β2 agonists.

Synthetic Non-Catecholamines

Ephedrine and phenylephrine are two sympathomimetics chemically unrelated to catecholamines.

Ephedrine

Ephedrine is a mixed acting sympathomimetic that stimulates both α and β adrenoreceptors (direct acting) and causes release of norepinephrine from storage sites (indirect acting). It is not metabolized by gastrointestinal MAO, and, therefore, can be administered orally as well as intramuscularly and intravenously. Forty percent of the drug is excreted unchanged in the urine. It is 250 times less potent than epinephrine, but its effects last 10 times longer.[6,7]

Ephedrine increases the heart rate, cardiac output, systolic and diastolic blood pressure, and coronary and skeletal muscle blood flow. Ephedrine produces minimal changes in systemic vascular resistance due to opposing α and β effects on different vascular beds. It does not significantly alter uterine blood flow, making it useful to treat anesthesia-related hypotension in the parturient.[7] Unlike phenylephrine, ephedrine increases venous return to the heart.[25] Tachyphylaxis has been reported and it may result from prolonged binding of ephedrine to adrenoreceptors or depletion of norepinephrine stores.[7] Adverse effects include myocardial ischemia, hypertension, and tachyarrhythmias.[6] It is frequently used in the treatment of hypotension induced by both general and regional anesthesia, but it has a limited role in intensive care patients.

Phenylephrine

Phenylephrine is primarily a direct acting synthetic sympathomimetic with a high affinity for α1 adrenoreceptors. At much larger doses, it stimulates β adrenoreceptors.[5] Phenylephrine increases systemic blood pressure as well as systemic and pulmonary vascular resistance, and can decrease heart rate and cardiac output. This decrease in cardiac output is probably

due to the added effects of baroreceptor-mediated bradycardia and increased afterload. Coronary blood flow is increased as opposed to renal, splanchnic, and cutaneous blood flows, which are decreased.[7] The absence of β-agonist activity at usual doses makes phenylephrine an attractive agent for the management of hypotension in clinical situations where tachycardia limits the use of other agents. Phenylephrine, infused at 30–180 μg/min, is commonly used in the treatment of hypotension secondary to regional and general anesthesia. It has also been used in hyperdynamic septic shock, although there are concerns about its potential to reduce cardiac output, splanchnic blood flow, and oxygen delivery in these patients.[11] It can be used in conjunction with nitric oxide to improve oxygenation in patients with ARDS[7] and as a nasal decongestant and eye drops.

Phosphodiesterase Inhibitors

Selective phosphodiesterase (PDE) III inhibitors (i.e., amrinone and milrinone) represent a heterogeneous group of non-catecholamines, non-glycoside compounds that antagonize PDE III, resulting in an increase of intracellular cAMP.[26–29] Inhibiting PDE III is an effective way of bypassing the β-receptor-adenylate cyclase system to activate cAMP,[29] which makes these drugs useful in the treatment of patients with decreased adrenoreceptor density (down regulation). These compounds also have an action on the slow calcium channels that may contribute to their inotropic effect.[8] The hemodynamic effects of PDE III inhibitors include an increase in cardiac index and a decrease in SVR, PVR, and pulmonary capillary wedge pressure (PCWP).[26–28,30] This occurs at minimal expense of heart rate, systolic blood pressure, and myocardial oxygen consumption.[27] For their positive inotropic and vasodilatory properties, PDE III inhibitors have also been called "inodilators".[27,28] Renal blood flow and glomerular filtration also increase with PDE III inhibitors.[28] Hypotension can follow rapid injection of both amrinone and milrinone. Thrombocytopenia has been associated with chronic administration of amrinone. Long-term use of PDE III inhibitors has been associated with the development of tolerance and with increased cardiac mortality. This has not been observed with short-term use.

PDE III inhibitors may be useful in the treatment of low cardiac output syndrome of multiple etiologies with concomitant high afterload and filling pressures. They may also be of value in the treatment of pulmonary hypertension associated with mitral valve stenosis.[8] The fact that they are adrenoreceptor independent for activation of cAMP and that they are non-glycosides probably account for the additive effects seen with combination therapy with catecholamines such as epinephrine. Milrinone is generally administered as an intravenous loading dose 50 μg/kg, followed by a continuous infusion at dose range from 0.25 to 1 μg/kg/min. As it is renally excreted, milrinone dose should be adjusted in patients with renal failure.

Vasopressin

8-Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is a nonapeptide synthesized in the hypothalamus and serving as an important backup system for blood pressure control and cardiovascular sympathetic modulation. Three subtypes of vasopressin receptors, V1, V2, and V3, have been identified. V1 receptors are found on various cells including vascular smooth muscle, platelets, and hepatocytes. V1 receptor stimulation causes vasoconstriction of blood vessels in the skin, skeletal muscle, and mesentery. Renal collecting duct cells express V2 receptors, which mediate water retention. V3 receptors are primarily located within the adenohypophysis of the central nervous system. Their stimulation modulates corticotropin secretion.[31]

A relative vasopressin deficiency in patients with vasodilatory shock and sepsis has been reported in several studies.[32,33] This deficiency may be caused by early depletion of hypothalamic AVP stores as shown by Sharshar et al.[34] Vasopressin restores vascular tone in vasoplegic shock states by at least four known mechanisms; through activation of V1 receptors, modulation of Katp channels, modulation of nitric oxide, and potentiation of adrenergic and other vasoconstrictor agents.[35] AVP infusion (0.01–0.04 U/min) has been shown to increase peripheral vascular resistance and arterial blood pressure in patients with septic shock within minutes of application.[36] AVP should be used as a continuous infusion in conjunction with other agents, and not titrated as a single vasopressor agent. Administration of the AVP decreases catecholamine requirements in the majority of patients, including children[37] with septic shock. Apart from sepsis, vasopressin has also been used to increase arterial blood pressure in several other vasodilatory conditions, such as hypotension after cardiopulmonary bypass[38] and hemodynamically unstable organ donors.[39]

Vasopressin achieved level IIb status as a vasoconstrictor to improve myocardial and cerebral blood flow in adults with ventricular fibrillation unresponsive to defibrillation. The 2005 American Heart Association Guidelines on CPR recommend one dose of 40 U vasopressin as an alternative to repeated boluses of epinephrine.[40]

Terlipressin, long-acting selective V1 receptor agonist, is currently undergoing clinical investigation for the treatment of hypotension not responsive to conventional vasopressor therapy. The half-life of terlipressin is 6 h, and the duration of action is 2–10 h.

Conclusions

Table 5.2 summarizes the hemodynamic effects of the vasoactive amines and the phosphodiesterase inhibitors. By understanding the hemodynamic differences in this group of drugs, the clinician can correctly select an agent that best meets the needs of each uniquely different critically ill patient.

TABLE 5.2. Hemodynamic effect of vasoactive amines and PDE III inhibitors.

	Receptor	CO/CI	HR	MAP	SVR	PVR	PCWP	RBF
Epinephrine	α, β	↑	↑	↑↓	↑↓	↑	□	↓
Norepinephrine	α, β1	↓	↓	↑	↑	↑	↑↓	↓
Dopamine	α, β1, β2, D	↑	↑	↑	↑	□↑	↑	↑
Isoproterenol	β1, β2	↑	↑	↑↓	↓	↓	↓	↓
Dobutamine	β1	↑	↑	↑↓	□↓	□↓	↓	↑
Phenylephrine	α	↓	↓	↑	↑	↑	□↑	↓
Ephedrine	α, β1, β2	↑	↑	↑	↑	□↑	↑↓	□
Vasopressin	V1	↓	□	↑	↑	↓	□	↑
PDE III inhibitors	None	↑	□↑	□↓	↓	↓	↓	↑

□ without change.

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6
Shock

Kyle J. Gunnerson and Emanuel P. Rivers

Introduction

Evolving knowledge of critical illness has greatly influenced our understanding of shock and how we define it. The first century Roman savant Aulus Cornelius Celsus made the following observation, "When much blood is lost, the pulse becomes feeble, the skin extremely pale, the body covered with a malodorous sweat, the extremities frigid, and death occurs speedily." In 1737, French surgeon, Le Dran, introduced the term "choc" to describe a severe impact or jolt, which was later adapted by Clarke, an English physician who used the term "shock" to describe the rapid physiological deterioration of a badly injured trauma victim. Historic advances in medicine, specifically the ability to measure blood pressure, changed the meaning of the term "shock" to denote arterial hypotension associated with hemorrhage. Later in the first part of the twentieth century, great physiologists such as Keith, Cannon, Blalock, and Cournard introduced the notion that tissue hypoperfusion, rather than isolated arterial hypotension, was the key feature of hemorrhagic shock. The contemporary understanding of shock is generally regarded as a syndrome precipitated by a systemic derangement of perfusion (global tissue hypoperfusion) that leads to widespread cellular dysoxia and vital organ dysfunction. Furthermore, by acknowledging that acquired derangements in mitochondrial function can impair cellular energetics, shock can be even more broadly defined as an acute physiological derangement resulting from the inadequate production of adenosine triphosphate (ATP) by cells in many organs of the body.

Determinants of Oxygen Delivery

With the exception of selected cases (e.g., subtypes of septic shock), a common feature of all forms of shock is a decrease in the delivery of oxygen (DO_2) to tissues such that the transport of oxygen into the cells is inadequate to meet their metabolic demands. Under these conditions, oxygen utilization (VO_2) is determined by its availability rather than the intrinsic demand associated with cellular metabolic requirements. This condition is called "delivery-dependent oxygen uptake" (see Fig. 6.1). Systemic DO_2 (i.e., the amount of oxygen delivered to tissues in arterial blood per unit time) is determined by four factors: the concentration of hemoglobin in the blood, hemoglobin oxygen saturation, the amount of oxygen dissolved (PaO_2) in the arterial blood (minor contribution), and the cardiac output (see Fig. 6.2). This relationship is represented by the following formula:

> Systemic DO_2 (mL O_2/min) = cardiac output (mL blood/min) × arterial oxygen content (ml O_2/mL blood) = cardiac output (L/min) × 10 (dL/L) × {[arterial hemoglobin concentration (g/dL) × 1.36 mL O_2/g hemoglobin × arterial hemoglobin saturation] + [arterial partial pressure of oxygen (mmHg) × 0.003 (mL O_2/dL blood)]}.

In the absence of regurgitant flow, cardiac output is determined by left ventricular stroke volume (LVSV) times heart rate. LVSV is determined by ventricular preload, afterload, and contractility.

The term "preload," in its strict sense, is a parameter used in in vitro studies to specify the degree of stretch imposed on a strip of myocardial tissue prior to a contraction. End-diastolic volume (EDV) is the in vivo correlate of preload. Clinicians frequently use end-diastolic pressure (EDP) as a surrogate for EDV. However, EDP is determined not only by volume, but also by the diastolic compliance of the ventricular chamber. Ventricular compliance is altered by various pharmacological agents and pathological conditions. For example, diastolic compliance decreases when the ventricle is ischemic or hypertrophied. This pressure-volume relationship is important to appreciate, so when one measures a "normal" central

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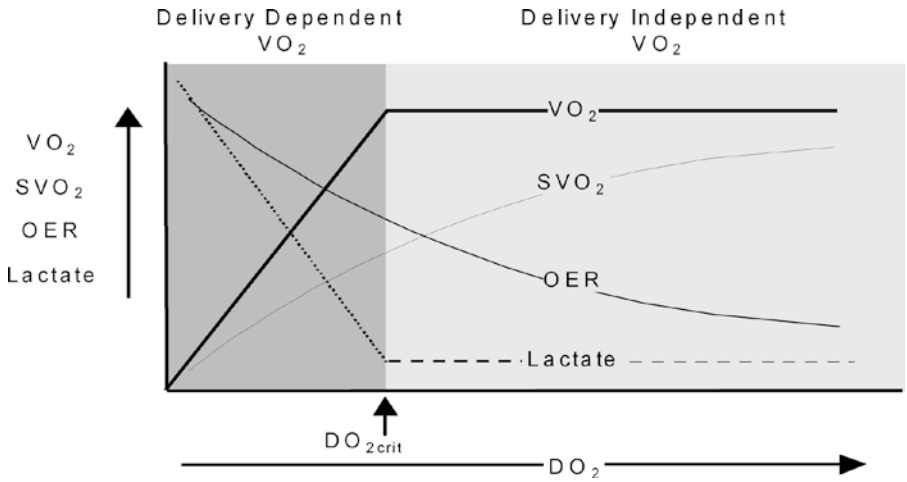

FIG. 6.1. The relationship between oxygen delivery and oxygen consumption in shock. When DO_2 decreases to less than the value for critical delivery (DO_{2crit}), oxygen consumption (VO_2) is linearly dependent on the delivery of oxygen to the tissues (DO_2). In the delivery-dependent region, oxygen extraction ratio is maximal and anaerobic metabolism increases with an associated increase in lactate and decrease in SVO_2. This region to the left of DO_{2crit} is where oxygen debt starts to accumulate. $DO_2 = CaO_2 \times CO$ (normal range: 460–650 ml/min/m^2); $VO_2 = CO \times (CaO_2 - CVO_2)$ (normal range: 96–170 ml/min/m^2); CaO_2 (arterial oxygen content) = $(Hb \times 1.39 \times SaO_2) + (0.003 \times PaO_2)$; $CVO_2 = (Hb \times 1.39 \times SVO_2) + (0.003 \times PVO_2)$. CO = Cardiac output; PaO_2 = arterial oxygen tension; Hb = hemoglobin. SVO_2 normal range: 70% (±5%). (From Neumar and Ward[98] by permission of Rosen's Emergency Medicine: Concepts and Clinical Practice, 5th edition, 2002, Mosby, Elsevier).

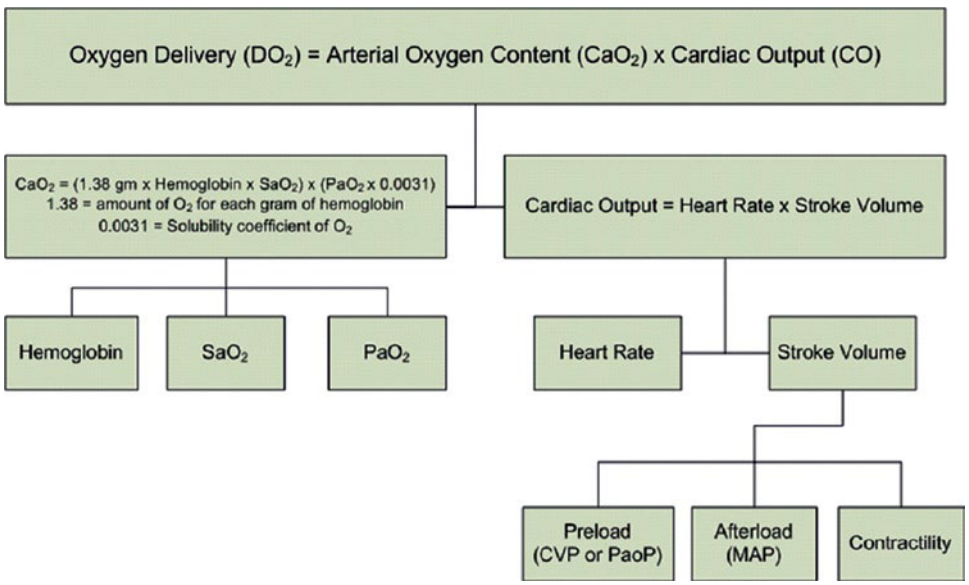

FIG. 6.2. Determinants of oxygen delivery (DO_2).

venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP), inadequate preload is not uniformly ruled out as a cause of shock.

Heart-lung interactions are also very important when evaluating pressure-volume relationships in various shock states.[1] Increased intrathoracic pressure decreases venous return. This phenomenon is the primary mechanism responsible for the development of shock in patients with tension pneumothorax. Increased intrathoracic pressure also can decrease cardiac output in patients receiving positive pressure ventilation, especially when intravascular volume is low or positive end-expiratory pressure (PEEP) is applied. The magnitude

of the effect of positive pressure mechanical ventilation on cardiac output is determined, in part, by pulmonary compliance. Thus, when the lungs are relatively noncompliant, as is typically the case in patients with the acute respiratory distress syndrome (ARDS), high airway pressures may not be transmitted to the pleural and mediastinal spaces. Even if extrinsic PEEP is not applied, positive pressure mechanical ventilation can still generate PEEP if air is trapped within the lung at end-expiration because of high airway resistance, short expiratory times, or both. This phenomenon is sometimes called intrinsic PEEP or auto-PEEP. Intrinsic PEEP can further impede venous return and, thereby, compromise cardiac output.[2]

Just like the term "preload," the term "afterload" is also borrowed from in vitro studies using isolated muscle strips. Afterload is the force resisting contraction. The in vivo correlate of afterload is the input impedance of the arterial tree. Since vascular input impedance is difficult to measure, systemic vascular resistance (SVR), calculated as MAP/cardiac output, is often used by clinicians as a surrogate for afterload. SVR is primarily determined by the degree of vasomotor tone in the precapillary smooth muscle sphincters.

Contractility refers to the ability of the myocardial fibers to shorten at constant preload and afterload. Numerous factors can compromise myocardial contractility. These factors include: ischemia or ischemia/reperfusion injury, loss of ventricular mass due to infarction, certain proinflammatory mediators, and various pharmaceuticals.

Compensatory Responses to Shock

Stages of Shock

The progression of shock can be either rapid or insidious. The shock transition can be divided into three indistinct stages. The first stage has been called early, reversible, or compensated shock. This stage is characterized by compensatory responses that help to minimize tissue injury. If the etiology of shock is recognized and treated early in this stage, full recovery with minimal morbidity is the likely outcome. The second stage of shock is the beginning of cellular and microvascular injury. In this stage, shock can be treated, but recovery can be prolonged and complicated by organ failure. The third stage is late, irreversible, or decompensated shock. When shock reaches this point, cellular and tissue injury is extensive and largely irreversible. Progression to death is inevitable, regardless of therapy. The physiologic basis of these stages is based on the theory of "oxygen debt."

Oxygen Debt

Critical to the relationship between oxygen supply, demand, and mismatch (shock) is the concept of oxygen debt. Oxygen debt occurs when VO_2 becomes directly dependent on DO_2. It is determined by both the magnitude of the drop in VO_2 and the length of time VO_2 is below baseline (see Fig. 6.3). This relationship was first demonstrated in the early 1960s where death, survival with organ failure, and survival without organ failure relate directly to the level of oxygen debt incurred.[3,4] This is not surprising if one views oxygen debt as degrees of ischemia. The severity and duration of ischemia results in more organ system involvement and irreversible damage will eventually occur. It is notable, however, that short of catastrophic injury or illness, it does not seem possible to predict the accumulation of a lethal oxygen debt. In animal models and clinical studies of trauma and hemorrhage, development of lethal oxygen debts (measured directly or by surrogates of lactate and base deficit) cannot be predicted by cumulative hemorrhage volume, time, systemic, or central hemodynamic variables such as blood pressure, hematocrit, or cardiac output prior to definitive hemostasis or after the initial resuscitation.[5–9] These studies also indicate that simple restoration of blood volume and return of systemic and central hemodynamic variables to within normal ranges (blood pressure, cardiac filling pressures, and cardiac output) are incapable of improving survival after accumulation of lethal oxygen debts and cannot be used to uniformly predict or prevent such accumulation despite achieving hemostasis. In fact, these same studies indicate that oxygen debt may continue to accumulate during the period of resuscitation if resuscitation is inadequate. The use of vital signs to judge the severity of the insult as well as the adequacy of treatment will become more fraught with uncertainty given the general aging of the population, chronic and complex disease states, and polypharmacy. Thus it is imperative that resuscitation strategies incorporate endpoints that adequately represent the restoration of tissue oxygen utilization rather than focus on isolated normalization of systemic hemodynamic variables.

Autonomic Nervous System

The vasomotor center of the medulla regulates afferent impulses from various receptors in the body (baroreceptors, stretch receptors, chemoreceptors, and osmoreceptors). The neuronal compensation of shock orchestrates a series of physiologic responses based on hypotension, hypovolemia, acidosis, and hypoxia.

Activation of the baroreceptor reflex via stretch receptors located in the carotid sinus, splanchnic vasculature, and aortic arch is extremely sensitive to even small decreases in arterial blood pressure. Hypovolemia can also activate stretch receptors located in the right atrium. Activation of these receptors increases outflow through the sympathetic nervous system resulting in compensatory responses. The compensatory responses mediated by the sympathetic nervous system include: (1) redistribution of blood flow away from skeletal muscle beds and the splanchnic viscera[10,11]; (2) augmentation of myocardial contractility and heart rate[11]; (3) increased venous return by the constriction of venous capacitance vessels, particularly in the splanchnic bed[10,11]; (4) activation of

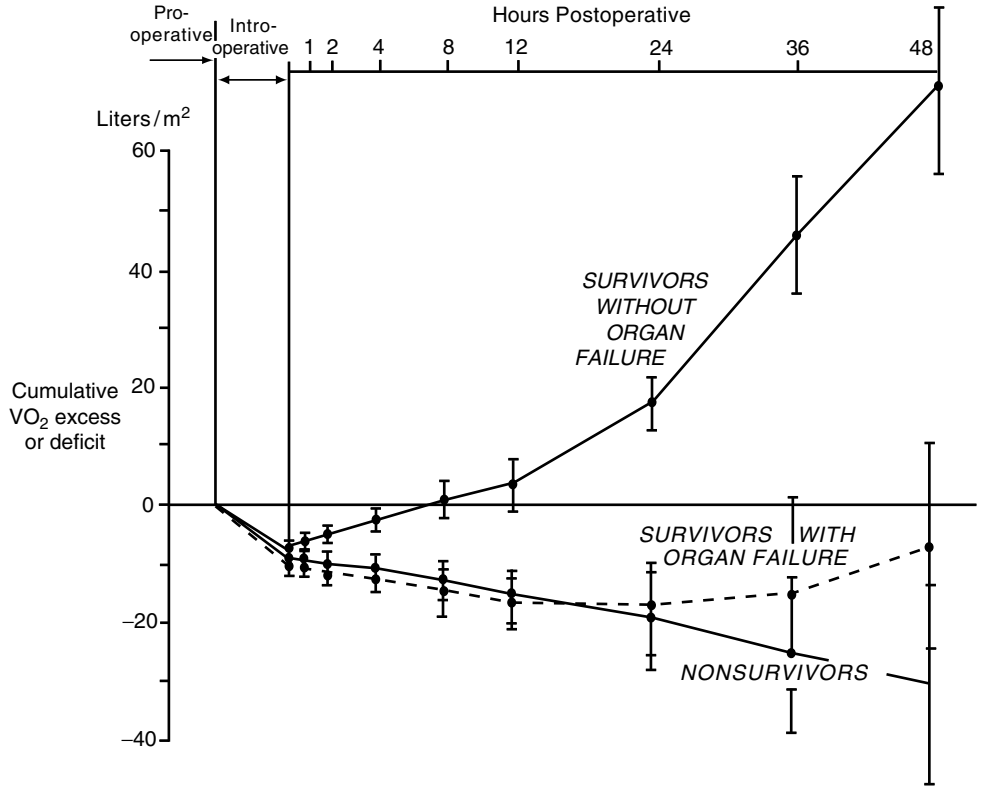

FIG. 6.3. Oxygen debt. Net cumulative VO_2 deficit for survivors without organ failure (*solid line*), survivors with organ failure (*dashed line*), and nonsurvivors (*solid line*) calculated for each successive time period postoperatively. A more protracted and severe oxygen debt was associated with increased organ failure and death. (By permission of Shoemaker WC, Appel PL, Kram HB. Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. Crit Care Med 1988;16:1117–1120, Lippincott).[9]

the renin-angiotensin, vasopressin axis[12]; and (5) release of adrenocortical and adrenomedullary hormones, including cortisol and epinephrine.[13]

Renin-Angiotensin System

Renin is released by the juxtaglomerular cells in the nephron when the kidney senses decreased blood flow. Renin is also released in response to decreased renal distal tubular sodium delivery and sympathetic activation.[14] Angiotensinogen, which is produced by the liver, is cleaved by renin to yield the inactive decapeptide angiotensin I. Angiotensin-converting enzyme (ACE) then converts circulating angiotensin I into angiotensin II (AII). ACE-dependent formation of AII occurs primarily in the lungs. ACE also converts the vasodilator bradykinin into an inactive peptide. AII is also generated locally at its site of action; thus, it can function as a paracrine mediator.[15]

In shock, AII stimulates the release of aldosterone from adrenal cortex, and thereby promotes renal retention of sodium and water. AII also acts to restore systemic arterial blood pressure by increasing arteriolar vasomotor tone, primarily in the mesenteric bed.[10] In addition, AII stimulates the secretion of epinephrine from the adrenal medulla, increases myocardial contractility, and promotes the release of arginine vasopressin from the posterior pituitary.[14]

Arginine Vasopressin

Arginine vasopressin (AVP), a nonapeptide secreted by the posterior pituitary gland, is also known as antidiuretic hormone. AVP is released in response to either hypovolemia or hyperosmolality in response to stretch and baroreceptors in the atria, carotid bodies, and osmoreceptors in the hypothalamus. In its role as an antidiuretic factor, AVP increases the permeability of the renal collecting ducts to water, thereby promoting the reabsorption of water driven by the osmotic gradient in the renal medulla. AVP also regulates gastrointestinal and uterine smooth muscle activity, platelet aggregation, hepatic glycogenolysis, and the secretion of adrenocorticotrophic hormone (ACTH) and aldosterone.[16,17] AVP, of course, is also a vasoconstrictor, albeit not a very potent one, under normal conditions. Whereas plasma AVP concentrations of 1–7 pg/mL are sufficient to increase renal reabsorption of free water, circulating AVP levels of 10–200 pg/ml are necessary to promote arteriolar vasoconstriction.[18] Although AVP plays at most a

minor role in the normal minute-to-minute regulation of arteriolar vasomotor tone, during episodes of severe hypotension due to hypovolemia or sepsis, plasma concentrations of this hormone increase considerably.[18]

Transcapillary Refill

The Starling equation describes the movement of fluid into or out of the intravascular compartment as a function of several parameters as shown in Fig. 6.4. The rate and direction of net fluid movement across the capillary wall is determined by the hydrostatic pressure gradient between the microvascular and the interstitial spaces. In the compensatory response to shock, precapillary vasoconstriction decreases microvascular blood pressure, thereby promoting the net movement of fluid from the interstitial compartment into the vascular compartment.[19]

Decompensatory Mechanisms in Shock

As shock states progress for a period of time without appropriate resuscitation, the syndrome eventually becomes refractory to treatment and multiorgan dysfunction ensues. Eventually every organ succumbs and death is inevitable.

Vasomotor Decompensation

The transition into an irreversible stage of hemorrhagic shock, in animal models, is signaled by the vasodilatation of precapillary sphincters despite persistent activation of the sympathetic nervous systems and high circulating levels of the vasoconstricting autacoids, AII and AVP.[20] This loss of vasomotor responsiveness to endogenous constrictors in irreversible shock may include: (1) excessive production of the potent vasodilator nitric oxide, secondary to induction of the enzyme inducible nitric oxide synthase (iNOS)[21]; (2) energetic failure (i.e., inadequate ATP synthesis) in vascular smooth muscle cells as a result of activation of the enzyme poly (ADP ribosyl) polymerase (PARP)-1[21]; (3) deleterious effects of lipid mediators[22]; and (4) opening of ATP-sensitive potassium channels in vascular smooth muscle cells.[23,24]

Inappropriate vasodilation and vasoplegia (i.e., reduced responsiveness to vasopressors) is a key feature of septic shock. Although the pathophysiology of this phenomenon remains incompletely understood, several important mechanisms have been implicated, namely: (1) activation of ATP-sensitive potassium channels in the plasma membranes of vascular smooth muscle cells[25]; (2) induction of iNOS expression in vascular smooth muscle cells, leading to excessive release of nitric oxide[26,27]; (3) insufficient release of AVP[18];

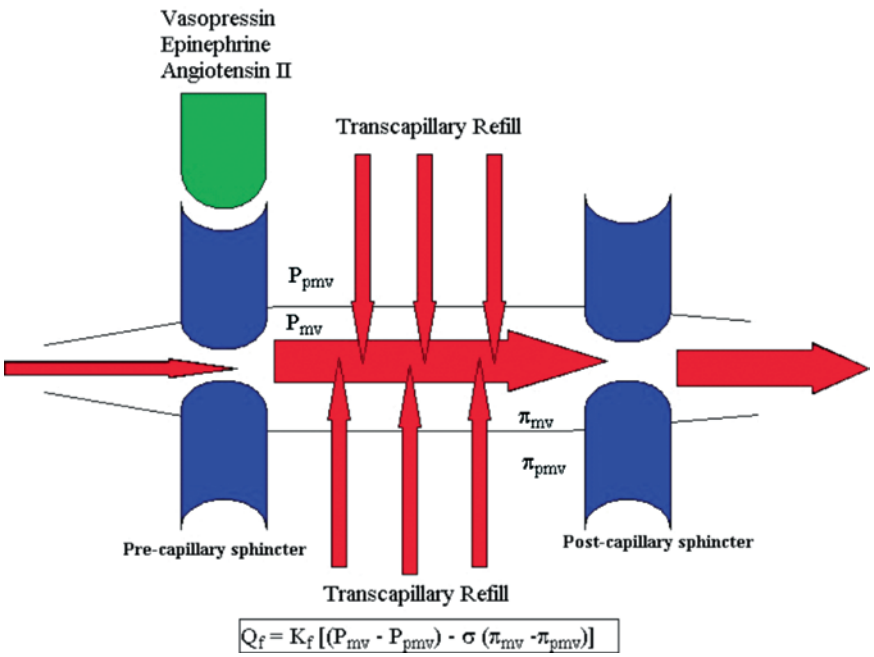

FIG. 6.4. Transcapillary refill. Several parameters affect the movement of fluid into and out of the intravascular space across the capillary walls. In the compensatory response to shock, precapillary sphincters contract more than postcapillary ones, causing a decreased P_{mv}. As a result, P_{pmv} decreases promoting the net influx of fluid into the intravascular space. Q_f = flow across the capillary wall (volume/unit time), K_f = filtration coefficient, P_{mv} = microvascular (i.e., capillary hydrostatic) pressure, P_{pmv} = perimicrovascular (interstitial) fluid hydrostatic pressure, σ = osmotic reflection coefficient, π_{mv} = capillary colloid osmotic pressure, π_{pmv} = perimicrovascular (interstitial) colloid osmotic pressure. (From Fink and Gunnerson,[99] by permission of Sabiston and Spencer. Surgery of the Chest, 7th edition, Elsevier).

and (4) energetic failure in vascular smooth muscle cells due to PARP-1 activation.[28]

Microvascular Alterations

The microcirculation is a vital organ of the cardiovascular system. The main function of this lattice-like network is the final conduit in the delivery of oxygen to the tissues. It is lined with endothelial cells that can be injured during inflammatory insults. The microcirculation is also a complex network of resistance and exchange vessels, where perfusion is dependent on several factors: (1) blood viscosity; (2) red and white blood cell deformity and flow; (3) arterial oxygen saturation; (4) oxygen consumption; (5) vascular shunting; (6) vasodilatation; (7) vasoconstriction; (8) stasis in arterioles and capillaries; (9) diffusion constants of gases and nutrients; and (10) distances from cells nearest the blood vessels.[29] The microcirculation has been evaluated more extensively in septic shock, while multiple organ failure often develops despite improvement in hemodynamic variables, regardless of the etiology. Indeed, even after aggressive resuscitative interventions, the microvasculature continues to have significant alterations and thus contributes to the development of multiple organ failure.[30] Until recently, the window into the microvasculature was limited to techniques applying intravital microscopy (first described by Wagner and Cohenheim in the 1800s) requiring sizeable equipment rendering it impractical for bedside clinical use. With the introduction of orthogonal polarization spectral imaging (OPSI) in the 1990s, investigators are now able to evaluate the microcirculation of human mucosal surfaces at the bedside[31](see Figs. 6.5 and 6.6). Although microvascular assessment is a promising, novel resuscitative adjunct, this technology is still in its clinical infancy.[32]

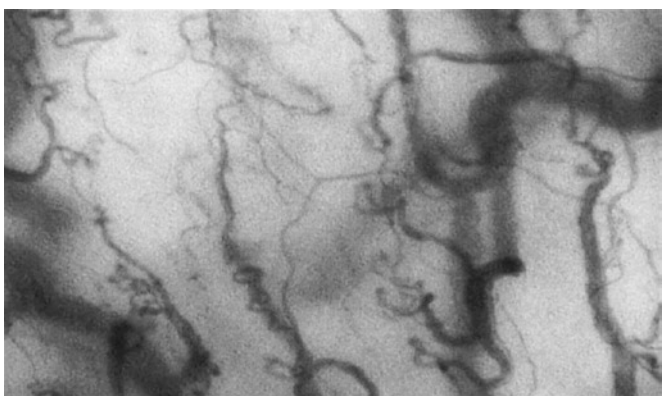

Fig. 6.5. Orthogonal polarization spectral imaging of the sublingual area of a healthy volunteer. Note the dense venular (larger vessels) and capillary (small lace-like vessels) network.

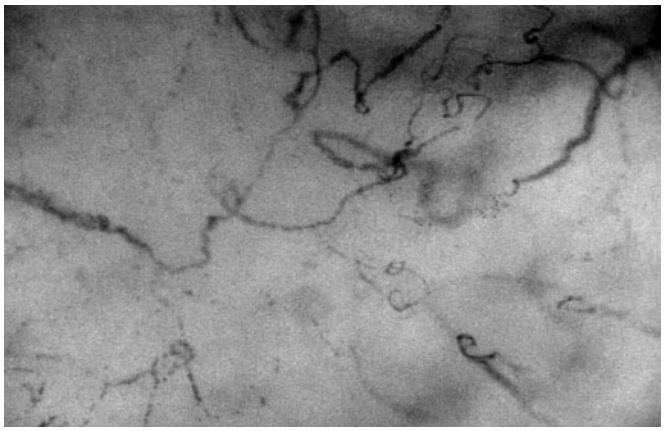

Fig. 6.6. Orthogonal polarization spectral imaging of the sublingual area of a patient in shock. Note the heterogeneous flow with a marked decrease in capillary density and stagnant flow when compared to Fig. 6.5.

Endothelial Activation and Leukosequestration

Endothelial cell activation occurs in shock. This leads to a progressive increase in the expression of adhesion molecules, such as E-selectin and intracellular adhesion molecule (ICAM)-1, on the cells' surface. The adhesion molecules first promote rolling, then adhesion, and finally transudation of circulating polymorphonuclear neutrophils (PMNs). Sequestration of activated PMNs in the lungs, liver, and other organs has been implicated as being an important factor leading to the development of organ system dysfunction as a consequence of hemorrhage, resuscitation, and sepsis.[33,34]

Decreased Erythrocyte Deformability

The mean diameter of capillaries is 4.5 microns. Normal human erythrocytes are seven microns in diameter. Therefore, blood flow through the microcirculation is dependent upon the deformability of erythrocytes, a characteristic that allows these cells to alter their shape and squeeze through small vessels to deliver oxygen. In studies using intravital microscopy during hemorrhagic shock, crenated erythrocytes are seen within the arterioles, venules, and capillaries. Furthermore, during the refractory stage of shock, nearly all erythrocytes become crenated spheres.[35] This impairment of erythrocyte deformability leads to decreased microvascular flow and subsequent local tissue ischemia, potentially resulting in multiorgan failure.[36,37] The mechanism responsible for this phenomenon is not clear, but may involve alterations in the synthesis of prostaglandins or nitric oxide.[37,38] The primary targets are most likely membrane skeletal proteins and the lipid bilayer.

Cellular Depolarization

Septic and hemorrhagic shock states have been associated with decreases in the normal electrochemical potential gradient across the cytosolic membranes of cells. Cellular depolarization is associated with disturbances in the regulation of the concentrations of several intracellular ions, a factor that might contribute to cellular and organ dysfunction in shock. This can be demonstrated by measuring an increase in intracellular Na^+ and Cl^- with a concomitant decrease in intracellular K^+.[39] The molecular basis for cellular depolarization in shock is poorly understood, although diminished aerobic production of ATP is undoubtedly important.[40] Another factor contributing to attenuation of the transmembrane electrochemical potential gradient may be the release of a circulating depolarizing factor during shock.[41, 42]

Mitochondrial Dysfunction

Mitochondria continually monitor intracellular calcium ions, protons, reactive oxygen species, redox state, pH, and nitric oxide in order to regulate electron transfer function.[43] Therefore it is easy to understand why the mitochondria are in the "front lines" of the breakdown between homeostasis and dysfunction in the cellular compensatory response to shock. One manifestation of mitochondrial dysfunction is the inability of cells to utilize available O_2 during shock. This is most evident during septic shock and has been attributed to acquired derangements in mitochondrial function. This phenomenon has been termed "cytopathic hypoxia."[44] Until recently, the notion that mitochondrial dysfunction occurs in sepsis or shock was mostly derived from studies using animals or even cultured cells. Recently, however, clinical data are becoming available that lend credence to the idea that acquired mitochondrial dysfunction is an important determinant of outcome in patients with septic shock.[45, 46]

A number of mechanisms might be responsible for the development of mitochondrial dysfunction as a consequence of shock. Nitric oxide can compete with oxygen for binding to cytochrome oxidase, the terminal enzyme in the mitochondrial electron transport chain. Accordingly, iNOS induction leading to excessive production of nitric oxide might inhibit mitochondrial respiration on this basis. In addition, nitric oxide can react with superoxide radical anion, a reactive oxygen species (ROS) that is produced during and after resuscitation from shock, to form a potent oxidizing and nitrosating agent, peroxynitrite anion. This latter moiety can damage nuclear DNA, leading to activation of PARP-1. Activation of this enzyme depletes cellular levels of nicotinamide adenine dinucleotide (NAD^+), a vital redox-active enzymatic cofactor that is essential for converting fuels, such as glucose, into forms that can be used to support mitochondrial oxidative phosphorylation and ATP synthesis. Potent inhibitors of PARP-1 are being developed as potential therapeutic agents for treating patients with shock and sepsis.

The failing mitochondrion is responsible for a number of pathological processes:[47] (1) endothelial compromise, (2) oxidative damage to DNA and proteins, (3) proinflammatory response and WBC infiltration, (4) apoptosis, and (5) Toll-like receptor downregulation. Of all the consequences of the failing mitochondria, the loss of ATP production is the most profound. ATP production is rapidly reduced in traumatic and septic shock. This has been observed in real time with intact patients by using nuclear magnetic resonance and near infrared spectroscopy.[48,49] ATP production decreases in both vital (e.g., liver) and nonvital (e.g., muscle) cells. ATP is produced as the metabolic demands of the cell require. There is no storage or "warehousing" of excess ATP. Once ATP is depleted, production may remain depressed for as long as 48 h, even after adequate resuscitation and with ample substrate (glucose and oxygen).[50,51] This is the cellular condition previously described as cytopathic hypoxia.[44]

Classifications of Shock

Blalock proposed that shock can be categorized into one of four major types: (1) neurogenic, (2) cardiogenic, (3) hypovolemic, or (4) vasogenic.[52] A still simpler classification scheme will be used here (see Table 6.1).

The physiologic, diagnostic, and therapeutic approach to shock begins with a hemodynamic-characterization-based preload, afterload, contractility, and metabolic endpoints representing the microcirculation and tissue perfusion.

Hypovolemic Shock

The primary derangement in hypovolemic shock is loss of circulating volume. Blood loss (hemorrhage) is the most common cause of hypovolemic shock, but hemodynamically significant hypovolemia also can result from inadequate replacement of asanguineous fluids. The diagnosis of hemorrhagic shock is fairly straightforward when the site of bleeding is identified. Common causes of hemorrhagic shock include trauma, gastrointestinal bleeding, bleeding during or after surgical procedures, rupture of aortic or other arterial aneurysms, and peripartum catastrophes (e.g., placental abruption or postpartum uterine bleeding). When bleeding is visible, making the diagnosis is usually not difficult. When bleeding is internal, the diagnosis may be less obvious. In these cases, the history is often helpful. Special studies including abdominal computed tomography, angiography, and abdominal ultrasonography can be helpful. However, time-consuming diagnostic studies (e.g., computed tomography) should not be performed if the patient is unstable. In any case, diagnostic studies should not delay treatment with intravenous asanguineous fluids, packed red blood cells, and (if indicated) platelet transfusions and coagulation factors. Prompt surgical intervention, when indicated, is crucial.

Table 6.1. Comparison between classes of shock states.

	MAP	CVP	$ScvO_2$	Lactate	CI	SVR	Comment
Hypovolemic	↓	↓	↓	↑	↓	↑	Hemorrhagic or nonhemorrhagic
Cardiogenic	↓	↑	↓	↑	↓	↑	Myocardial infarction or decompensated heart failure
Obstructive	↓	↑	↓	↑	↓	↑	Cardiac tamponade or massive pulmonary embolus
Distributive	↓	↓	↓	↑	↓	↓	Anaphylaxis, neurogenic shock, adrenal insufficiency
Septic							
Stage 1	↓ or Normal	↓	↓	↑	↓	↑	Early sepsis, hypovolemia
Stage 2	↓	Normal	↑	↑	↑ or Normal	↓ or Normal	Compensated
Stage 3	Normal	↑	↓	↑	↓ or Normal	Normal	Myocardial suppression
Stage 4	↓	Normal	↑	↑	↑	↓	Impaired tissue oxygen utilization or cytopathic hypoxia

MAP mean arterial pressure, *CVP* central venous pressure, *$ScvO_2$* central venous saturation, *CI* cardiac index, *SVR* systemic vascular resistance.

Nonhemorrhagic hypovolemic shock can be caused by severe dehydration secondary to massive urinary or gastrointestinal fluid losses. Such losses are common in conditions such as diabetic ketoacidosis or cholera. Massive insensible losses of water or perspiration can precipitate shock in patients with major burn injuries or heat stroke. Another form of nonhemorrhagic hypovolemic shock is caused by the sequestration of asanguineous fluid in the extravascular compartment as a result of surgery, bowel obstruction, hepatic failure (severe ascites), systemic inflammation, acute pancreatitis, or thermal injuries. This phenomenon is often referred to as "third spacing."

Cardiogenic Shock

Cardiogenic shock is a hypoperfused state due to acute cardiac failure. The definition still relies upon classic hemodynamic parameters: hypotension (systolic blood pressure: <90 mmHg) or a mean arterial blood pressure 30 mmHg lower than baseline, markedly reduced cardiac index (<1.8 L/min m^2) without support or <2.0 L/min m^2 with support, and normal or high filling pressures. Common etiologies include acute myocardial ischemia or infarction, impaired myocardial contractility due to toxins or medications, valvular heart disease, dysrhythmias, myocardial contusion, and myocarditis. The incidence of cardiogenic shock complicating the spectrum acute coronary syndrome appears to be declining, approximately 5 to 8% for ST segment elevation myocardial infarction (STEMI) and 2% for non-STEMI events. This mortality decrease parallels the increased use of primary percutaneous coronary intervention for acute myocardial infarction (AMI).[53,54] Two large randomized trials showed up to a 13% absolute increase in 1-year survival in patients assigned to early revascularization who present with cardiogenic shock complicating AMI.[55,56]

Underlying causes for acute mitral insufficiency leading to cardiogenic shock include papillary muscle rupture secondary to acute myocardial infarction, endocarditis, blunt chest trauma, or sudden failure of a previously implanted mechanical valve. Without surgical correction, shock associated with acute mitral insufficiency carries a very high mortality.[57] Acute aortic insufficiency is usually a complication of endocarditis, but also can be related to acute aortic dissection or mechanical valve failure. Acute ventricular septal defects typically lead to cardiogenic shock a few days after an acute myocardial infarction.

The clinical picture in cases of cardiogenic shock secondary to right ventricular (RV) infarction is somewhat different from other forms of cardiogenic shock, being characterized by increased right atrial pressure and normal or low PAOP. The mortality is similar to left ventricular (LV) dysfunction with shock and has a similar outcome after revascularization.[55] Completely isolated RV infarction is uncommon, occurring in approximately 5% of all cases of cardiogenic shock complicating AMI. RV failure may limit adequate LV filling due to the decreased RV cardiac output, ventricular interdependence or both. Traditional treatments of RV dysfunction with shock revolve around achieving adequate filling pressure to maintain an adequate cardiac output and LV preload.[58] However, it is not uncommon for these patients to have RV end-diastolic pressures >20 mmHg. This elevated RV pressure can shift the interventricular septum toward the LV, ultimately impairing LV filling. This geometric alteration also impairs LV systolic function.[59] Therefore, the common practice of aggressive volume resuscitation may be counterproductive in RV failure with shock.

Obstructive Shock

Extracardiac obstructive shock is caused by a lesion or a process interfering with the forward flow of blood. In some cases, the major problem is impaired diastolic filling. Conditions in this category include cardiac tamponade, tension pneumothorax, obstruction of the large veins by a mediastinal mass, and constrictive pericarditis. In other cases, the main problem is

impaired ventricular ejection as a result of an acute increase in right or left ventricular afterload. A classic example of this process is a massive pulmonary embolus.[60]

Special consideration is warranted when dealing with a suspected cardiac tamponade in the postcardiac surgery patient. Unlike most other instances of cardiac tamponade, where fluid is uniformly distributed between the pericardium and epicardium, in the postcardiac surgery patient, fluid (blood) is commonly loculated. Blood may collect posteriorly, behind the right atrium, slowly compressing the right-sided cardiac chambers. This is usually not detected by a transthoracic echo and the diagnosis typically is made by transesophageal echo or at reoperation, depending on the stability of the patient.[61] Postcardiac surgery tamponade, although rare (1–2%), can be life threatening, and a high index of suspicion must be maintained in the event of an unexplained decrease in cardiac output with rising filling pressures.[62]

Distributive, Hormonal, and Dissociative Shock

This category includes shock due to anaphylaxis, spinal cord injury, sepsis, and adrenal insufficiency. Dissociative shock includes disorders than inhibit effective utilization of oxygen by cellular biochemical machinery, such as cyanide poisoning and cytopathic tissue hypoxia.

Anaphylactic reactions are commonly triggered by insect stings, food antigens, and medications and can be mediated by both IgE-dependent and IgE-independent pathways.[63] In addition to arterial hypotension, other common features of anaphylaxis include airway obstruction due to angioedema and generalized urticaria. Contrary to popular belief, the pathology of anaphylactic shock is not purely an isolated vasodilatory response. Cardiac output typically decreases dramatically and calculated vascular resistance increases during anaphylactic shock.[64] The primary pathophysiological problems in this condition are functional hypovolemia secondary to increased microvascular permeability combined with decreased myocardial contractility. The treatment of severe anaphylaxis and shock begins with removing the offending agent if possible. The next step, often carried out simultaneously, is to protect the airway. Intravenous epinephrine and intravenous fluids should be administered to support blood pressure and cardiac output. Supplemental oxygen should also be provided. Antihistamines, corticosteroids, glucagon, albuterol, and aminophylline are all secondary medications that are mostly useful as prophylactic interventions to decrease the risk of a recurrence.[65]

Neurogenic shock is characterized by hypotension with or without paradoxical bradycardia. It is associated with an acute injury to the spinal cord that disrupts sympathetic outflow leaving unopposed vagal tone.[66] The term "neurogenic shock" should not be confused with the term "spinal shock"; the latter term is used to denote a temporary loss of spinal reflex activity below the level of a spinal cord injury. Blunt trauma accounts for more than 85% of all spinal cord injuries.[66, 67] In addition to the standard management of any trauma victim, neurogenic shock is managed by infusing intravenous crystalloid or colloid volume expanders and vasopressors as needed. A mean arterial pressure (MAP) between 85 and 90 mmHg for the first week after a spinal cord injury is a reasonable target to minimize the risk of secondary injury to the cord on the basis of inadequate perfusion.[68] The value of administering methylprednisolone in cases of acute spinal cord injury is debatable, but data are lacking to support the notion that intervention is of particular value in cases of neurogenic shock.[69, 70]

Sepsis is a clinical syndrome defined by the presence of both *infection* and a *systemic inflammatory response*.[71] Infection is defined as a pathologic process caused by the invasion of a normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms. Sepsis includes hypovolemia, vasodilatory, cardiogenic, and dissociative shock as single or multiple components. The pathogenesis, diagnosis, and treatment of sepsis will be discussed in Chap. 27.

Although very high doses of corticosteroids were previously advocated for the treatment of septic shock, the results from several large multicenter randomized clinical trials led clinicians to abandon this therapeutic approach.[72–74] Subsequent findings from two small single-center randomized trials suggested that prolonged administration of physiologic "stress doses" of hydrocortisone can improve hemodynamics and promote resolution of shock in patients with severe sepsis.[75,76] These findings were confirmed and extended by Annane and colleagues, who demonstrated a 10% absolute reduction in mortality when vasopressor-dependent septic shock patients with evidence of adrenal insufficiency were treated with hydrocortisone and a mineralocorticoid.[77] However, a recent study, CORTICUS, showed no mortality improvement between patients randomized to receive stress dose steroids and those receiving placebo.[78] Current guidelines reflect this ongoing steroid-replacement-in-septic-shock controversy. Indeed, there appears to be enough evidence for the Surviving Sepsis Guidelines to continue to recommend stress dose hydrocortisone for patients who are hypotensive and are not responding to adequate intravenous fluid resuscitation and vasopressor support. However, ACTH stimulation is no longer recommended in establishing the diagnosis of adrenal insufficiency.[79]

Diagnosing Shock

When the clinician is confronted with a profoundly hypotensive patient with an obvious source of bleeding, making the diagnosis of hemorrhagic shock is fairly straightforward. However, identifying other forms of shock can be challenging, especially when the etiology is not clear as in an occult source of sepsis or when blood pressure is "normal" due to intact compensatory mechanisms. Despite the difficulties inherent in diagnosing these occult forms of shock, it is of

utmost importance to identify these patients as early as possible. In patients with sepsis, early institution of therapy with appropriate antibiotics improves survival.[80] In patients with septic shock, very prompt "goal-directed" resuscitation aimed at resolving global tissue hypoxia also clearly improves survival.[81]

Making an early diagnosis starts by obtaining a thorough problem-directed history and performing a careful physical examination. Obtaining an accurate list of current medications is important, because many drugs (e.g., β-adrenergic antagonists or diuretics) can alter physiologic responses to shock. Physical examination may reveal an obvious source of infection or bleeding. In the absence of arterial hypotension, other findings on physical examination, such as tachycardia, tachypnea, diaphoresis, mental status changes, poor capillary refill, or cutaneous mottling, can suggest the presence of a hypoperfused state. However, even if these signs are absent, the clinician cannot rule out occult shock on the basis of clinical findings alone, especially in certain patient populations such as those with trauma, gastrointestinal bleeding, or infection. Accordingly, other adjunctive diagnostic studies are needed to aid in identifying tissue hypoperfusion. Many of these (e.g., measurement of blood lactate concentration) are also useful for assessing the adequacy of resuscitation.

Treatment of Shock

Treatment begins during the initial assessment and primary survey. Resuscitation starts with "the ABCDE's of shock." This includes establishing an *A*irway, providing and controlling the work of *B*reathing, optimizing the *C*irculation, assuring adequate oxygen *D*elivery, and achieving *E*ndpoints of resuscitation. If any doubt exists about the patency of the airway or the adequacy of ventilation, endotracheal intubation should be performed and mechanical ventilation initiated. Respiratory muscles are significant consumers of oxygen during shock and contribute to lactate production. Mechanical ventilation and sedation to decrease the work of breathing has been shown to improve survival in shock. Mechanical ventilation also may prevent damage to the respiratory muscles during shock or sepsis.[82]

Circulatory or hemodynamic stabilization begins with intravascular access through large-bore peripheral venous lines. Trendelenburg positioning, historically considered necessary for maintaining perfusion in the hypotensive patient, does not improve cardiopulmonary performance compared with the supine position. It may worsen pulmonary gas exchange and predispose to aspiration.[83] If a volume challenge is urgently required, rather than using the Trendelenburg position, an alternative is to raise the patient's legs above the level of the heart with the patient supine.[84] Central venous access will aid in assessing volume status (preload) and monitoring central venous oxygen saturation ($ScvO_2$). It is the preferred route for the long-term administration of vasopressor therapy and provides rapid access to the heart if a transvenous pacemaker is required.

Fluid resuscitation begins with isotonic crystalloid. The amount and the rate are determined by an estimate of the hemodynamic abnormality. Most patients in shock have either an absolute or relative volume deficit, except the patient in cardiogenic shock with pulmonary edema. Fluid is given rapidly, in set quantities (e.g., 500 or 1,000 mL), with reassessment of the patient after each amount. Patients with modest degrees of hypovolemia usually require an initial 20 mL/kg of isotonic crystalloid. More fluids may be necessary with profound volume deficits. Controversy still exists regarding the role of colloids. The recent multicenter Saline versus Albumin Fluid Evaluation (SAFE) study found that after enrolling almost 7,000 ICU subjects requiring volume resuscitation, there was no significant mortality difference observed between subjects receiving either 4% albumin or normal saline.[85]

Vasopressor agents are used when there has been an inadequate response to volume resuscitation or when a patient has contraindications to volume infusion. Other than vasopressin, vasopressors act primarily on the α- and β-adrenergic receptors.[86] They are most effective when the vascular space is "full" and least effective when the vascular space is depleted. Nevertheless, vasopressors may be necessary early in the treatment of shock, before volume resuscitation is complete. This temporary use is to prevent potentially lethal consequences of prolonged systemic arterial hypotension and is especially important in elderly patients with significant coronary and cerebrovascular disease. Rapidly restoring the MAP to 60 mmHg or systolic pressure to 90 mmHg may avoid the coronary and cerebral complications of decreased blood flow.

Assuring Adequate Oxygen Delivery

Once blood pressure is stabilized through optimization of preload and afterload, DO_2 can be assessed and further manipulated. Arterial saturation should be returned to physiologic levels (93–95%) and hemoglobin maintained above 10 g/dL. If cardiac output can be assessed, it should be increased using volume infusion and inotropic agents in incremental amounts until mixed venous oxygen saturation (SvO_2) or $ScvO_2$ lactate are normalized, and the base deficit is corrected.

The control of VO_2 is important in restoring the balance of oxygen supply and demand to tissues. A hyperadrenergic state results from the compensatory response to shock, physiologic stress, pain, and anxiety. Shivering is not uncommon after large volumes of cool fluids are infused and pain can increase myocardial oxygen demand. Collectively, these physiologic responses can greatly increase systemic oxygen consumption. Providing analgesia, muscle relaxation, anxiolytics, and even paralytic agents, when appropriate, can decrease VO_2 substantially.

Global tissue oxygen extraction indices (e.g., SvO_2 or $ScvO_2$ and lactate) can roughly assess the adequacy of resuscitation by estimating if tissue oxygen requirements are being met. These indices are measured by obtaining frequent, serial

samples from the appropriate anatomic location (e.g., pulmonary artery or superior vena cava). Continuous measurement of SvO_2 or $ScvO_2$ through fiber-optic technology can be used to avoid frequent phlebotomy.[87] Although SvO_2 and $ScvO_2$ are not identical, in shock, the trend of their response to global tissue hypoperfusion makes them interchangeable.[88] A variety of other technologies are in various stages of development. These have potential for identifying, more precisely, tissue perfusion during resuscitation and recovery. Some of these technologies include (not all inclusive) near-infrared spectroscopy,[89] Raman spectroscopy,[90] OPSI,[91] and Sidestream Dark Field imaging.[92]

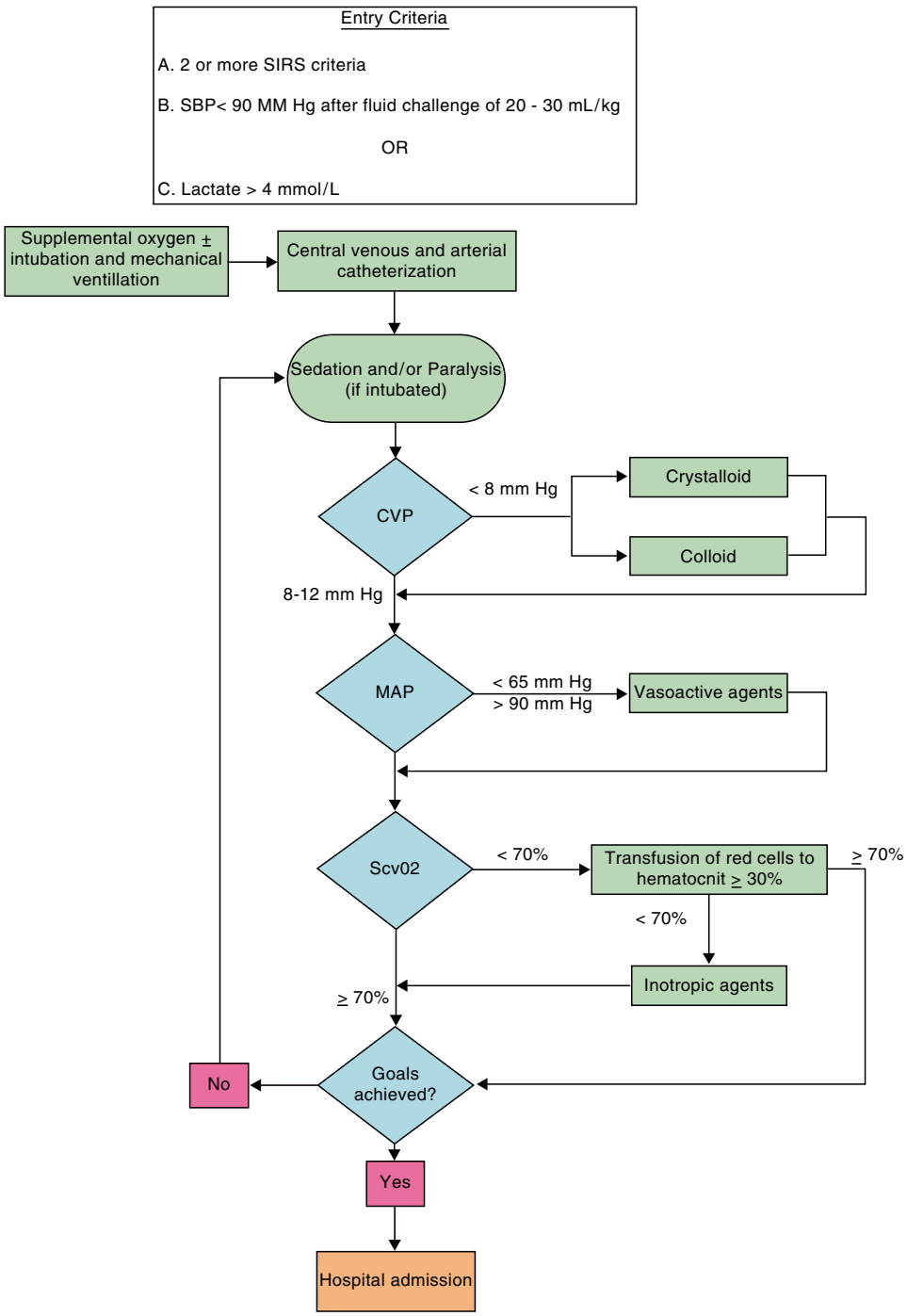

FIG. 6.7. Protocol for early goal-directed therapy in septic shock. (By permission from Rivers, Nguyen, Havstad, et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. NEMJ, 2001;345;1368 1377).[81]

Achieving End Points of Resuscitation

Traditional resuscitation end points have included the normalization of blood pressure, heart rate, and urine output. Clinical observations have revealed that global tissue hypoxia can still persist in patients resuscitated from shock even with normalization of vital signs and urine output.[93,94] Since traditional endpoints underestimate the degree of remaining tissue hypoperfusion and oxygen debt, other physiologic end points have been investigated.[95] No therapeutic end point is universally effective, and only a few have been tested in prospective trials, with mixed results. The goal of resuscitation is to maximize survival and minimize morbidity using objective hemodynamic and physiologic values to guide therapy. A goal-directed approach at achieving urine output ≥0.5 mL/kg/hour, CVP 8–12 mmHg, MAP 65–90 mmHg, and $ScvO_2 \geq 70\%$ during resuscitation has been shown to significantly decrease mortality in septic shock[81] (see Fig. 6.7). This strategy of restoring adequate oxygen delivery and resolving global tissue hypoxia has recently been adapted to resuscitate intraoperative and postoperative patients. This goal-directed strategy has shown the ability to decrease postoperative complications and reduce the duration time in the hospital.[96,97]

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7
Hemodynamic Monitoring

Flávio E. Nácul and John M. O'Donnell

The art of critical care medicine has greatly changed in the last 30 years with a better understanding of physiology, advances in technology, and the development of more sophisticated monitoring systems. Hemodynamic monitoring now plays a major role in assessing and managing critically ill patients and includes the pulmonary artery flotation catheter, echocardiography, pulse contour analysis, transesophageal Doppler, and microcirculation monitoring.

Pulmonary Artery Catheter

The use of the balloon-tipped, flow-directed thermodilution pulmonary-artery catheter (PAC) or Swan-Ganz catheter has been a mainstay of invasive monitoring in critically ill patients since 1970.[1] On the assumption that measuring and manipulating cardiac output and deriving hemodynamic parameters at the bedside improved outcome, this device became widely used in intensive care units.

The Standard 7-Fr gauge PAC is 110-cm long and made of radiopaque, flexible plastic with a 1.5-cc inflatable balloon just proximal to the tip and a thermistor port 4 cm from the end of the catheter. At the proximal end, there are four ports: proximal, distal (both used for pressure measurements), one for balloon inflation, and another for external connection to the thermistor. Some catheters have an additional venous infusion port (VIP) for the infusion of crystalloids, colloids, blood products, and various medications. Pulmonary artery catheterization is achieved by inserting the PAC through an existing central line introducer sheath. The flow-directed catheter is advanced with the balloon inflated. The position of the catheter in the various cardiac chambers is confirmed by recognition of the characteristic waveforms (see Chap. 3).

Hemodynamic Parameters

The Pulmonary Artery Occlusion Pressure

The temporary inflation of the balloon results in the occluding of a branch of pulmonary artery and is signaled by a characteristic pulmonary artery occlusion pressure (PAOP) tracing. It has traditionally been considered to be an indirect estimate of left atrial pressure, left ventricular diastolic pressure, and hence, left ventricular end- diastolic volume. For PAOP values to be valid, the catheter tip must be situated in West zone III of the lungs (i.e., a dependent region of high blood flow). A catheter positioned in zone I or II (high ventilation, lower perfusion) may show marked respiratory variation, especially in patients receiving mechanical ventilation with high levels of positive end-expiratory pressure (PEEP). Pressures measured in these zones might reflect alveolar pressure rather than left ventricular pressure. A careful evaluation of a (PAOP) curve can show if the catheter is correctly positioned at zone III. A portable lateral chest X-ray may show that the catheter tip is positioned other than below the level of the left atrium in a supine patient (i.e., zone I or II) and require repositioning. Because PACs are flow directed, most often they migrate to zone III.[2–5]

No aspect of pulmonary artery catheterization has undergone more scrutiny than the utility of the PAOP.[6] The relationship between the left ventricular intracavitary pressure and volume is curvilinear and may change depending on alterations in ventricular compliance.[7,8] Some of the cardiopulmonary variables that have been identified as affecting this

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pressure-volume relationship include patient position, mean airway pressure, acute and chronic pulmonary disease, and pulmonary venous pressure.[9,10] Ventricular compliance can be affected by intrathoracic pressure, myocardial ischemia, myocardial edema, hypertrophy, inotropic agents and vasoactive amines affecting afterload.[9] When compliance is decreased, a minimal addition of fluid can cause a marked increase in pressure. Conversely, when the compliance is increased (e.g., dilated cardiomyopathy, afterload reduction), the same amount of fluid might cause only a small increase in pressure.[10,11] The usefulness of the PAOP as an indicator of preload is further complicated by the well-documented inability of many practitioners to accurately interpret pressure wave forms.[12,13] Spurious data coupled with an inadequate knowledge base sets the stage for flawed assumptions and poor therapeutic decision making, so while the PAC provides a reasonably accurate estimation of cardiac index and oxygen delivery (see later), a wave form or digital value reflecting PAOP should be interpreted and employed very cautiously.

Pulmonary Artery Pressure

The finding of pulmonary hypertension, defined as mean pulmonary pressure greater than 20 mmHg, is common in critically ill patients. Etiologies include heart failure, hypoxia, chronic pulmonary hypertension, poor pulmonary compliance and chest wall compliance, pulmonary thromboembolism, acute respiratory distress syndrome, chronic obstructive pulmonary disease, and interstitial lung disease. A gradient between the pulmonary artery diastolic pressure (PAD) far in excess of PAOP (the normal difference is ≤5 mmHg) suggests the presence of a pulmonary disorder as the cause of pulmonary hypertension. Conversely, when the PAD is elevated as well as the PAOP and the normal gradient is preserved, pulmonary hypertension is the result of the rise in left ventricle end diastolic pressure (e.g., heart failure).[14]

Cardiac Output

The PAC allows measurement of cardiac output by the thermodilution method, requiring the injection of a solution into the proximal or right atrial port of the catheter. The resultant change in temperature in the liquid is measured by the thermistor mounted 4 cm from the pulmonary artery catheter tip. The cardiac output is then calculated using an equation that considers the temperature and specific gravity of the injectate and the temperature and specific gravity of the blood along with the injectate volume.[15–17] The cardiac index (CI) is the cardiac output indexed to the patient's body surface area (BSA).

A CI less than 2.2 L/min/M^2 reflects threat to tissue oxygenation. However, it may be normal despite a low systolic index if a compensatory tachycardia is present. If the CI is abnormally low, the central venous pressure (CVP) and PAOP should be evaluated to determine the cause. In the presence of a low CI, a low CVP and PAOP suggest hypovolemia. In the presence of a low CI, a high CVP and PAOP suggest left ventricular failure.

Derived Hemodynamic Parameters

The PAC is able to provide a comprehensive overview of the circulatory status by measuring the pressures within the pulmonary circulation, right heart, and superior vena cava (Table 7.1). From the direct measurements obtained, derived parameters can be calculated to further assess cardiac performance. These derived parameters include systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and left ventricle stroke work (LVSW). SVR measures the afterload for the left ventricle, PVR estimates the right ventricle afterload, and LVSW is another way to measure ventricular function.

Changes in these parameters are subject to changes in cardiac output, mean arterial pressure, right atrial pressure, and pulmonary arterial pressure. Therefore, before accepting a low or high SVR (or another derived parameter), one should make certain that they were measured correctly.

Decreased SVR indicates a low afterload and is usually associated with distributive shock states or patients receiving vasodilators, such as sodium nitroprusside, nitroglycerin, and calcium-channel-blocking agents. On the other hand, an increased SVR is commonly seen in hypovolemic, cardiogenic, and obstructive shock.

Oxygenation Parameters

Additionally, oxygenation parameters can be measured and calculated. From a blood sample collected at the distal lumen in the PAC, one can measure mixed venous blood saturation

Table 7.1. Measured and calculated hemodynamic data by the PAC.

Hemodynamic variables	Normal value
CVP	2–6 mmHg
MAP = (PAS + 2PAD)/3	60–100 mmHg
RAP	2–6 mmHg
PASP	15–30 mmHg
PADP	6–15 mmHg
meanPAP	9–17 mmHg
PAOP	6–12 mmHg
CI = CO/BSA	2.5–4 L/min/m^2
SVI = CI/HR	35–60 mL/beat/m^2
SVRi = 80 × (MAP − RAP)/CI	2,000 – 2,400 dyne s/cm^5/m^2
PVRi = 80 × (mean PAP − PAOP)/CI	250 – 280 dyne s/cm^5/m^2
LVSWi = SVI × (MAP − PAOP) − 0.0136	50 – 62 gm-m/m^2/beat

CVP central venous pressure, *MAP* mean arterial pressure, *RAP* right atrial pressure, *PASP* pulmonary artery systolic pressure, *PADP* pulmonary artery diastolic pressure, *PAP* pulmonary artery pressure, *PAOP* pulmonary artery occlusion pressure or wedge pressure, *CI* cardiac index, *BSA* body surface area, *SVI* stroke volume index, *SVRi* systemic vascular resistance index, *PVRi* pulmonary vascular resistance index, *LVSWi* left ventricle stroke work index.

(SvO_2) and calculate venous oxygen content (CvO_2). From a blood sample collected from an arterial line, one can measure the arterial blood saturation (SaO_2) and calculate arterial oxygen content (CaO_2). Using these parameters, oxygen delivery (DO_2), oxygen consumption (VO_2), and oxygen extraction ratio (O_2ER) can be calculated.

Calculated Oxygenation Parameters

CaO_2 is defined as the amount of oxygen carried bound to hemoglobin plus the amount of oxygen dissolved in the arterial blood, whereas CvO_2 is the amount of oxygen bound to hemoglobin plus the amount of oxygen dissolved in the venous blood. DO_2 is the amount of oxygen presented to the tissues each minute, which is normally three to four times greater than is necessary for tissue oxygenation. It is dependent on cardiac output and the CaO_2. VO_2 is the amount of oxygen consumed by the tissues. It is calculated from cardiac output and arteriovenous oxygen difference, which is the difference between CaO_2 and CvO_2. Finally, O_2ER is the percentage of oxygen that is extracted from the tissues and represents the relationship between DO_2 and VO_2 (Table 7.2).

With the exception of high output states, a common feature of all forms of shock is a decrease in DO_2 resulting in an inadequate transport of oxygen into the cells**.** Low DO_2 may be due to alterations in cardiac output, hemoglobin concentration, and arterial oxyhemoglobin saturation. As DO_2 declines, VO_2 can be maintained by a compensatory increase in O_2ER. At this point, VO_2 and DO_2 remain independent. As the DO_2 falls further, a critical point is reached (DO_2 crit) and O_2ER can no longer compensate for the fall in DO_2. At this time, VO_2 becomes DO_2 dependent. When the VO_2 is DO_2 dependent, there is a state of oxygen debt that is associated with the presence of hyperlactatemia and reduction in SVO_2 (Fig. 7.1).

The finding of a low SVO_2 virtually always indicates an unfavorable disturbance in the normal balance between DO_2 and VO_2 and should be addressed by evaluating inadequacies in the components of DO_2 (i.e., cardiac output, hemoglobin, SaO_2) or through attempts to reduce excessive oxidative demands (e.g., work of breathing, agitation, fever, pain).[17]

Table 7.2. Measured and calculated oxygenation variables.

Oxygenation variables	Normal values
$DO_2i = (CI \times CaO_2 \times 10)$	500–600 mL/min/m^2
$VO_2i = [CI \times C(a–v)\ O_2 \times 10]$	120–160 mL/min/m^2
$CaO_2 = 1.34 \times Hb \times SaO_2$	20 mL/min
$CvO_2 = 1.34\ Hb \times SvO_2$	15 mL/min
$O_2ER = VO_2/DO_2$	20–30%
SVO_2	65–80%
$ScVO_2$	70–85%

DO_2i oxygen delivery index, *CI* cardiac index, *CaO_2* arterial blood oxygen content, *VO_2i* oxygen consumption index, *Hb* hemoglobin concentration, *SaO_2* oxygen saturation in the arterial blood, *CvO_2* venous blood oxygen content, *O_2ER* extraction rate of oxygen, *SVO_2* mixed venous hemoglobin saturation, *$ScVO_2$* central venous hemoglobin saturation.

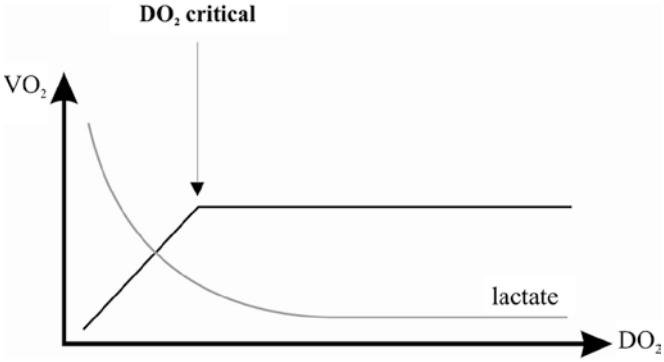

Fig. 7.1. The normal relationship between DO_2 and VO_2 is biphasic. Under normal conditions, as DO_2 decreases, VO_2 remains constant, dependent only on the ability of the tissues to modulate the degree of oxygen extraction. Below the DO_2-critical value, further increases in oxygen extraction are limited and the degree of VO_2 is dependent on the magnitude of DO_2. Pathological supply dependency infers a condition of altered oxygen extraction resulting in tissue dependency for VO_2 on DO_2.

Complications

The use of PAC may be associated with complications such as hemorrhage at the insertion site, pneumothorax, damage to large thoracic vessels, transient arrhythmias, damage to valvular structures, pulmonary artery rupture, and infection.[18] Most of these can be minimized with thorough familiarization of insertion techniques, catheter maintenance, and patient history. With patients who are elderly, hypothermic, anticoagulated, or have a history of pulmonary hypertension, extreme care should be taken during insertion of PACs. Most believe that these comorbid states are risk factors for pulmonary artery rupture and hence, wedging of the catheter should be performed very carefully, if at all.[19]

Electrocardiographic monitoring during catheter insertion should be maintained for all patients, with careful attention to those with complete left bundle branch block, Wolff-Parkinson-White syndrome, and Ebstein's malformation.

Controversy

Over the recent years the PAC has become a controversial tool with many authors advocating that it should be abolished. The concern increased in 1996 after the publication by Connors et al.[20] of an observational study of 5,735 critically ill patients showing that the use of the PAC was associated with an increased mortality and increased use of resources. In 2003, Sandham et al.[21] did not find any benefit to therapy directed by PAC over standard care in elderly, high-risk surgical patients requiring intensive care. For the past decade, investigators have studied various patient populations to elucidate the safety and efficacy of the PAC. Rhodes et al.[22] randomized 201 patients with shock, oliguria, vasoactive drugs infusion, or acute respiratory failure to either receive PAC or not. They demonstrated

that there was no difference in overall mortality between the groups. Patients who had PAC placement received significantly more fluids in the first 24 h and also had a greater incidence of renal failure and thrombocytopenia. In 2005 Harvey et al.[23] studied 1041 patients and found no clear evidence of benefit or harm by managing critically ill patients with a PAC. In 2006 Harvey et al.[24] published a meta-analysis on the use of PAC in critically ill patients. They identified 12 studies, 8 on high-risk surgery patients, and 8 on general intensive care patients. They found that PAC did not affect mortality and intensive care unit or hospital length of stay. Four studies, conducted in the United States, measured costs based on hospital charges billed to patients, which on average were higher in the PAC groups.

When looking carefully at these studies, one can see that they are poorly comparable. The patient populations are very different, the time after the onset of hemodynamic instability when the patients are monitored is also different, and the interventions are almost never controlled. In this scenario, it is not wise to conclude that PAC is associated with a better or worst outcome.

The use of the PAC in acute care management has reduced markedly over the past 10 years. The reasons usually cited for the decision not to use the PAC include the following: (a) increased risk to the patient; (b) the ability to measure similar variables via central venous catheterization, echocardiography, or other less invasive techniques; (c) increased cost; (d) misuse of the PAC-derived variables by their inaccurate measurement; (e) incorrect interpretation and application of the PAC-derived data to clinical care; and (f) lack of proven benefit of PAC use in the overall management of patients.[25–27]

Some clinicians feel that the lack of improved outcome demonstrated in the PAC studies can be directly linked to the study participants' lack of knowledge of cardiopulmonary pathophysiology, their unfamiliarity with PAC and its derived hemodynamic variables, a misunderstanding of the decision-making tree based on these variables, and inappropriate patient selection. Iberti et al.[28] and Gnaegi et al.[29] administered multiple choice questions to critical care physicians to assess their knowledge and understanding of the use of the PAC and interpretation of the data derived from it. They found that the proportion of incorrect answers to some basic questions was disturbingly high and that physicians' knowledge varied considerably. To this end, numerous programs have been developed to improve the clinicians' general knowledge of pulmonary artery catheterization and hemodynamic monitoring. Two such study guides and self-assessment programs can be found on the Internet at http://www.thoracic.org and http://www.pacep.org.

Echocardiography

Echocardiography has been found to be very useful in the management of the critically ill patient as a noninvasive diagnostic and monitoring tool. It is commonly employed for assessing cardiac output, pulmonary artery pressure, left atrial pressure, transvalvular pressure, and the presence of underlying myocardial ischemia. It can also be utilized for the diagnosis of infectious endocarditis, pulmonary embolism, thoracic aorta dissection, pericardial tamponade, intracardiac thrombi, and intracardiac shunt.[30]

Cardiac ultrasound is increasingly used to assess volume status and fluid responsiveness in the critically ill patient. A systolic obliteration of the left ventricle in the two-dimensional (2D) echocardiography is a good indication of hypovolemia. Two other 2D methods have been validated to estimate the volume status of a mechanically ventilated ICU patient. One uses respiratory changes and the distensibility index of the inferior vena cava by transthoracic echocardiogram (TTE), and the other utilizes the collapsibility index of the superior vena cava by transesophageal echocardiography (TEE).[31–35]

Both TTE and TEE provide real-time bedside information about a variety of structural and functional abnormalities of the heart. Although TTE is less invasive, suboptimal acoustic windows lead to low-quality images in some patients. These are generally the result of obesity, pulmonary disease, chest tubes, drains, wound dressings, and patient positioning. In spite of recent advances in technology such as harmonic imaging, digital image acquisition, and contrast echocardiography resulting in improvements on image quality, TEE remains the procedure of choice. It is indicated in patients with suspected aortic dissection, aortic injury, and endocarditis, and in the evaluation of the heart or aorta as a source of arterial emboli.

Pulse Contour Analysis

Concerns regarding the use of PAC have stimulated research into less invasive methods of hemodynamic monitoring. Arterial pulse contour analysis as a continuous measurement of cardiac output has been introduced into critical practice as an alternative to the PAC. It is based on the principle of predicting vascular flow by means of the arterial pressure wave form.[36] This technology encompasses a variety of techniques that allow cardiac output and stroke volume to be derived from the contour of the arterial tracing. The ability to monitor cardiac output from the arterial pressure line has a number of benefits, including the fact that the technique is minimally invasive and the data are continuous, providing clinicians with real-time information that allows interventions to be appropriately tracked and targeted.[37] Currently, there are three commercially available systems using pulse wave analysis to determine cardiac output: PiCCO-plus™ (Pulsion Medical Systems, Munich, Germany), PulseCO™ (LiDCO Ltd., London, UK), and Flo Trac/Vigileo™ (Edwards LifeSciences, Irvine, California, USA).

Using the PiCCO-plus system, aortic pressure wave forms are recorded via femoral, brachial, or radial access by a thermistor-tipped arterial catheter. Cardiac output is calculated on a beat-to-beat basis from the area under the systolic part of the pressure wave tracing after calibration by transpulmonary thermodilution.[38,39] LiDCO uses lithium as the indicator for

the dilution technique for the estimation of cardiac output. The system is based on an arterial pulse power analysis, which is calibrated every eight hours with a small nonpharmacological dose of lithium injected as a bolus via the central or peripheral route. Cardiac output is derived from the amount of lithium administered and the area under the curve based on the dilution curve generated by a lithium-sensitive electrode attached to the arterial line.[40] The recent introduction of FloTrac/Vigileo that relies on pulse contour analysis with no calibration and the need for just an arterial line has gained widespread interest. The FloTrac sensor provides the arterial pressure signal required by the Vigileo monitor to calculate the stroke volume.[41] The Vigileo monitor can also measure SVO_2 and $ScVO_2$ when used with appropriate oximetry catheters.

Esophageal Doppler

Esophageal Doppler monitoring has emerged as an alternative to the PAC for noninvasive monitoring of critically ill patients in the intensive care unit. This technique is based on the measurement of blood flow velocity in the descending aorta by means of a Doppler transducer at the tip of a flexible probe placed in the esophagus. The probe can be introduced orally and advanced gently until its tip is located approximately at the midthoracic level, and then rotated so that the transducer faces the aorta and a characteristic aortic velocity signal is obtained.[42] The close proximity of the descending aorta to the esophagus provides an excellent window for obtaining Doppler signals, but accurate measurements require good alignment between the Doppler beam and the blood flow. Because esophageal Doppler continuously measures aortic flow and provides a real-time, beat-to-beat estimation of cardiac output, the method is particularly attractive to follow the immediate effects of a therapeutic challenge with volume or vasoactive amines. One of the major inconveniences of the method is the need to reposition the probe each time it has moved from its correct position facing the aorta.[43]

Microcirculation Monitoring

It is now well documented that microvascular blood flow alterations are common in the critically ill and that these alterations can have important pathophysiological implications. Several investigators have reported that the microcirculation is markedly altered in sepsis.[44] The changes that are typically seen include a decrease in the vascular density and an increase in the proportion of nonperfused or intermittently perfused capillaries. The alterations are more severe in nonsurvivors than in survivors,[45] and the persistence of these microvascular abnormalities is associated with development of multiple organ failure and death.[46–48]

Orthogonal Polarization Spectral (OPS) imaging and Sidestream Dark Field (SDF) imaging techniques have recently been introduced to allow direct visualization of the microcirculation. Both devices are based on the principle that green light illuminates the depth of tissue (up to 3 mm) and that the scattered green light is absorbed by hemoglobin of red blood cells contained in superficial vessels. With technical advances, microcirculatory monitoring is more available for application in clinical practice, but measurements within the microcirculation are mostly limited to easily accessible surfaces such as the sublingual and rectal mucosa.

It has now become clear that a poor correlation may exist between systemic hemodynamic parameters and the microcirculatory alterations in the critically ill patient. As a result, optimization of these same hemodynamic and oxygen-derived parameters may not serve as an accurate marker for adequacy of resuscitation. This discrepancy opens the door for the monitoring of microcirculatory function, which is expected to play a pivotal role in the diagnosis and management of the critically ill in the near future.[49]

Tissue Oxygenation Monitoring

Tissue delivery and utilization of oxygen are dependent on cardiac output, hemoglobin concentration, arterial oxygen saturation, and cell function. In many patients, adequate tissue oxygenation can be assumed based on the normalization of our standard endpoints of resuscitation that include arterial pressure, heart rate, central venous pressure, urine output, and mental status. However, in other patients, tissue hypoxia can exist despite normal values of these standard markers (cryptic shock). The finding of low venous oxygen saturation and hyperlactatemia could help to identify patients with normal arterial pressure, central venous pressure, and urine output who are in shock and need more aggressive monitoring and resuscitation.[50,51]

Venous Oxygen Saturation

The oxygen content of the venous blood can be measured either at the level of the pulmonary artery (SVO_2) or superior vena cava or right atria ($ScVO_2$). The SVO_2 is a reflection of venous oxygenation in the entire body, whereas $ScVO_2$ indicates venous oxygenation of the brain and the upper extremities. Although there has been a considerable debate regarding whether $ScVO_2$ is a satisfactory substitute for SVO_2, most of the studies that have analyzed the relationship between SVO_2 and $ScVO_2$ in critically ill patients have shown that the changes in these two parameters usually occur in a parallel manner and that $ScVO_2$ is an average of 5% higher than SVO_2. The finding of low SVO_2 or $ScVO_2$ may identify global tissue hypoxia, whereas the finding of normal or elevated SVO_2 or $ScVO_2$ does not preclude tissue hypoxia, because derangements of cellular oxygen utilization (i.e., cytopathic hypoxia) may be playing a significant role (especially in the late-phase of sepsis). In this context, an SVO_2 lower than 65% or an $ScVO_2$ under 70%

reflect a threat to tissue oxygenation. As the levels get lower, the chance that tissue hypoxia exists increases. On the other hand, an SVO_2 greater than 75% or an $ScVO_2$ higher than 80% may indicate adequate oxygen delivery but inadequate oxygen utilization at the tissue as seen in hyperdynamic shock states (e.g., sepsis, ischemia reperfusion, hepatic failure). In critically ill patients, SVO_2 and $ScvO_2$ have been shown to be a better indicator of tissue oxygenation and derangement of cellular oxygen utilization than vital signs.[52–54] Figure 7.2 shows a suggested protocol for resuscitation of the critically ill using SVO_2.

Lactate

The measurement of lactate levels is easy to perform at the bedside and represents a useful indicator of global tissue oxygenation. In states of hypoperfusion, lactate production exceeds its rate of metabolism and the blood lactate concentrations rise. Elevated blood lactate and the persistence of hyperlactatemia have been correlated strongly with severity and mortality of shock. Causes of hyperlactatemia other than shock are uncommon in the critically ill patients, but they must be excluded. They include hepatic failure, the administration of high doses of catecholamines, and inborn errors of metabolism.[55–58]

Other Techniques

Additional techniques to assess tissue oxygenation include near-infrared spectroscopy (NIRS), reflectance spectroscopy, and tissue CO_2 measurements, but they are not widely available.[59,60]

Conclusions

Hemodynamic monitoring and tissue oxygenation assessment are regarded as essential tools for the management of the critically ill patient and require a physician who is properly trained to employ the techniques and interpret the data accurately. These techniques are only useful when they have the capacity to detect abnormalities and direct management. The information obtained from bedside monitoring should be interpreted in the context of other relevant investigations and clinical findings. Integrating hemodynamic variables with the clinical presentation increases the accuracy of assessment. Hemodynamic trends are generally more useful than interpreting isolated variables at a single point in time.

Despite widespread use of these technologies, there are limited data showing clinical benefit and thus their use should be weighted against their potential harm and costs. Regardless of what equipment is used, the physiology remains the

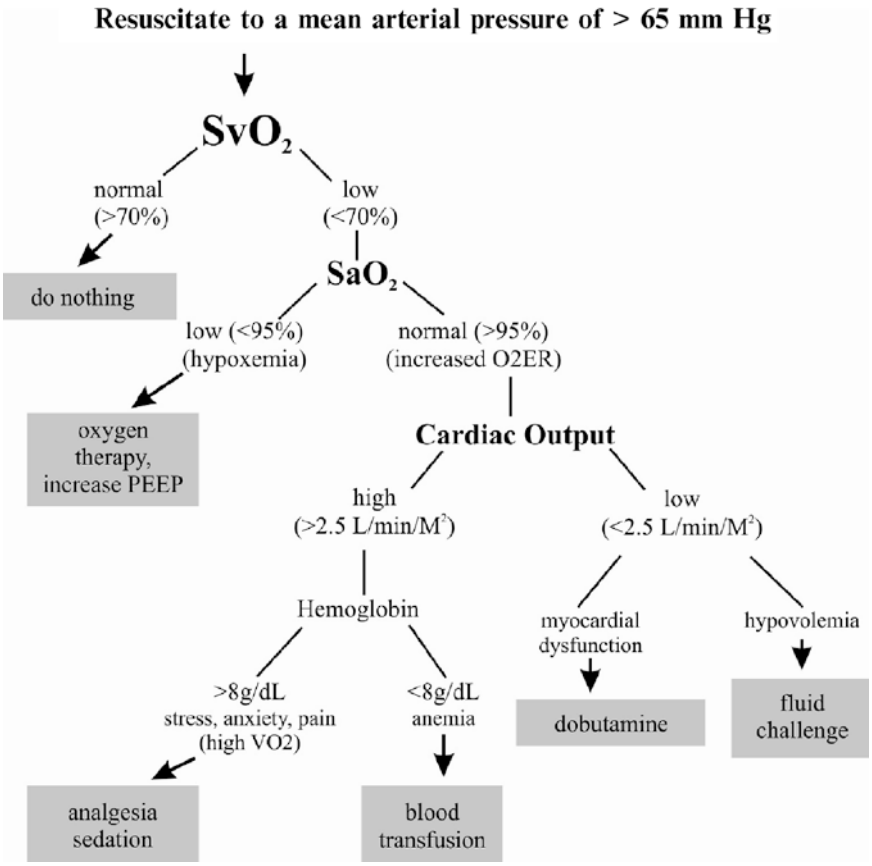

FIG. 7.2. Suggested protocol for resuscitation using PAC-derived data. O_2ER, oxygen extraction ratio; PAC, pulmonary artery catheter; PAOP, pulmonary artery occlusion pressure; PEEP, positive end-expiratory pressure; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation; VO_2, oxygen consumption. Reprinted from Vincent JL. A reappraisal for use of pulmonary artery catheters. *Critical Care* 2006 10(Suppl 3):S1 with permission of BioMed Central.

same. Hemodynamic monitoring will always measure or calculate flow, pressure, and resistance. To "monitor" is to make repeated or continuous observations or measurements of a patient's physiology. Besides installing monitoring equipment, it is very important to make as many observations as possible. Otherwise, the data will be insufficient. More studies are needed to determine optimal management protocols and patient groups who can benefit from the vast array of monitoring tools now at our disposal.

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8
Acid–Base Disorders

Philip M. Alapat and Janice L. Zimmerman

Acid–base disorders present some of the most challenging problems in the care of critically ill patients. They alter physiologic function and contribute to morbidity and mortality. Proper management of these disorders is not possible without the understanding of blood gas interpretation and basic acid–base balance physiology.

The relationship between acids and bases is of great significance to the functioning of all metabolic processes in the organism. This balance is important to the structure and function of proteins, the permeability of membranes, the distribution of electrolytes, and the function of the cells (Fig. 8.1).

The body's balance between acidity and alkalinity is referred to as acid–base balance. Acid–base balance is maintained by changes in alveolar ventilation and the renal excretion of bicarbonate. Pulmonary compensation is rapid, whereas alterations in renal excretion take several days. Other mechanisms for controlling blood pH involve the use of buffers. Buffers are acid–base pairs that minimize changes in pH when either acid or base is added. The most important buffers include bicarbonate, hemoglobin, plasma proteins, phosphate, and ammonia (Table 8.1).

According to the widely accepted "bicarbonate-based" approach to acid–base interpretation, respiratory acidosis or alkalosis is due to a primary abnormality of pCO_2, and metabolic acidosis or alkalosis is due to a primary abnormality of HCO_3^-.

Henderson–Hasselbalch Equation

The tools necessary for accurate interpretation of the acid–base status of a patient include a thorough understanding of the patient's clinical condition, arterial blood gas, and electrolyte results. The pH and pCO_2 levels are able to be measured directly in an arterial blood gas sample. However, the $[HCO_3^-]$ obtained from an arterial blood gas is a calculated value based on the Henderson-Hasselbalch equation:

$$pH = pK + \log [HCO_3^-] / S \times PCO_2$$

pK = apparent dissociation constant = 6.1
S = solubility of CO_2 = 0.03

Henderson Equation

Although blood acidity is generally measured and expressed in pH, the use of logarithms is cumbersome and impractical. The Henderson equation, an approximation of the Henderson-Hasselbalch equation, expresses hydrogen ion concentration in terms of CO_2 tension and bicarbonate ion concentration:

$$[H^+] = 24 \times PaCO_2 / [HCO_3^-]$$

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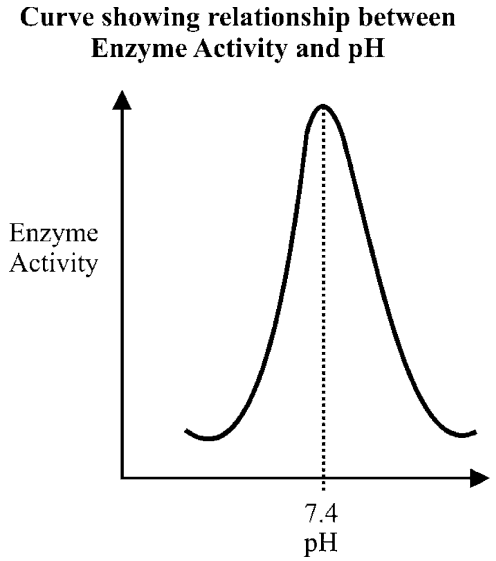

FIG. 8.1. The activity of enzymes is strongly affected by changes in pH. Most cellular enzymes have their best activity around a pH of 7.4 (optimum pH).

TABLE 8.1. Basic concepts on acid–base physiology.

- pH is the negative log of the hydrogen concentration; i.e., hydrogen ion concentration and pH are inversely related.
- Acid–base balance is important for the function of the cells.
- Normal blood pH is 7.38–7.42.
- A buffer is a molecule that can accept or donate hydrogen ions, thereby, maintaining a stable pH. Important buffers include the following: bicarbonates ($HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$); proteins (protein$^-$ + $H^+ \leftrightarrow$ H-protein); hemoglobin (Hb$^-$ + $H^+ \leftrightarrow$ H-Hb); and phosphates ($HPO_4^{2-} + H^+ \leftrightarrow H_2PO_4^-$).
- A blood pH less than normal is referred to as acidemia, and a blood pH greater than normal is referred to as alkalemia. The underlying processes associated with acidemia and alkalemia are termed acidosis and alkalosis, respectively.

TABLE 8.2. Relationship between hydrogen concentration and pH.

[H^+] (nanomol/L)	pH
26	7.60
32	7.50
40	7.40
50	7.30
63	7.20
80	7.10

If the normal PCO_2 is 40 mmHg and bicarbonate concentration is 24 mEq/L, then the hydrogen ion concentration is 40 nanomol/L and the pH will be 7.40. To use this formula and solve for PCO_2, [HCO_3^-], or pH, one only needs to know how to convert hydrogen ion concentration into the pH (Table 8.2).

The plasma biochemical analysis of "total CO_2," as reported in most basic electrolyte panels, is also used to obtain an indirect measure of [HCO_3^-] with 95% of the reported value being due to HCO_3^-. Dissolved CO_2 and carbamino compounds make up the remaining 5%.[1] The laboratory normal ranges are listed in Table 8.3.

Acid–Base Disturbances

Disturbances in acid–base balance are traditionally classified as respiratory or nonrespiratory, according to whether the primary abnormality is caused by an excess or a deficiency of carbon dioxide (respiratory) or of bicarbonate (nonrespiratory). Nonrespiratory disturbances are often referred to as metabolic disturbances. The four primary acid–base disturbances are: (1) metabolic acidosis (decreased bicarbonate); (2) metabolic alkalosis (increased bicarbonate); (3) respiratory acidosis (increased $PaCO_2$); and (4) respiratory alkalosis (decreased $PaCO_2$) (Table 8.4).

Acid–base disorders are usually identified by one or more primary processes. These primary processes initiate predictable secondary compensatory mechanisms that aim to return the pH to normal but do not fully compensate in most cases (Table 8.5).

TABLE 8.3. Laboratory normal ranges.

pH	7.38–7.42
$PaCO_2$	38–42 mmHg
HCO_3^-	22–26 mEq/L
PaO_2	70–100 mmHg[a]

[a] PaO_2 may decrease with aging.

TABLE 8.4. Acid–base disorders.

Condition	pH	PCO_2	HCO_3^-
Metabolic acidosis	↓	↓	↓
Metabolic alkalosis	↑	↑	↑
Respiratory acidosis	↓	↑	↑
Respiratory alkalosis	↑	↓	↓

The term acidosis means a process that tends to increase the concentration of hydrogen ions [H^+]. If the blood [H^+] is elevated, there is an acidemia. The converse is true for alkalosis and alkalemia.

TABLE 8.5. Primary acid–base disturbances and expected compensatory mechanisms.

Disorder	Primary change	Compensatory mechanism
Metabolic acidosis	↓ [HCO_3^-] ↑ [acid]	Alveolar hyperventilation to ↓ pCO_2
Metabolic alkalosis	↑ [HCO_3^-] ↓ [acid]	Alveolar hypoventilation to ↑ pCO_2
Respiratory acidosis	↑pCO_2	↑ renal H^+ secretion resulting in ↑ [HCO_3^-]
Respiratory alkalosis	↓pCO_2	↓ renal H^+ secretion leading to ↓[HCO_3^-]

Metabolic Acidosis

Identification of the etiology of metabolic acidosis is a common and vital part of intensive care practice. The primary defect in metabolic acidosis is an accumulation of acid, which leads to a decreased pH and [HCO_3^-]. The causes include an increase in endogenous acid production that overwhelms renal excretion (e.g., lactic acidosis, ketoacidosis), exogenous acid input (e.g., toxin ingestion), excessive loss of bicarbonate (e.g., diarrhea), and decreased renal excretion of endogenous acids (e.g., chronic renal failure). The normal compensatory mechanism is alveolar hyperventilation causing a decrease in pCO_2.

Expected Compensatory Response

Metabolic acidosis results in a compensatory increase in minute ventilation. The expected $PaCO_2$ for any given degree of metabolic acidosis can be predicted using the following formulas.[2]

$$\text{Expected } PCO_2 = 1.5[HCO_3^-] + 8 \pm 2$$

or

$$\text{Expected} \downarrow PCO_2 = 1.2 \times \downarrow [HCO_3^-])$$

If the $PaCO_2$ is higher than expected, there is a concurrent respiratory acidosis. If the $PaCO_2$ is lower than expected, there is a concurrent respiratory alkalosis.

Example: In a patient with metabolic acidosis and measured HCO_3 of 12 mEql/L, the expected pCO_2 would be: $(1.5 \times 12) + 8 = 26$ mmHg ± 2. If the actual pCO_2 is above 28 mmHg, this indicates the presence of an associated respiratory acidosis (e.g., ketoacidosis and severe pneumonia). Conversely, if the actual pCO_2 is below 24 mmHg, this indicates the presence of an associated respiratory alkalosis (e.g., septic shock and inappropriate mechanical ventilation).

Other physiologic compensatory mechanisms for metabolic acidosis include exchange of intracellular Na+ and K+ for extracellular H+ using ion transport pumps, increased renal H+ excretion with urinary buffers such as ammonia and phosphate, and increased renal bicarbonate reabsorption and formation.

Anion Gap

As metabolic acidosis can have different causes, a further characterization involves the use of the anion gap (AG). In broad view, the AG is the difference between the concentration of measured cations and measured anions in serum (Fig. 8.2).

Unmeasured anions – which include proteins (especially albumin), phosphates, sulfates, and organic acids – normally exceed the unmeasured cations, which include potassium, calcium, and magnesium. The normal AG is 12 ± 4 mEq/L. The AG can be estimated by the following formula:

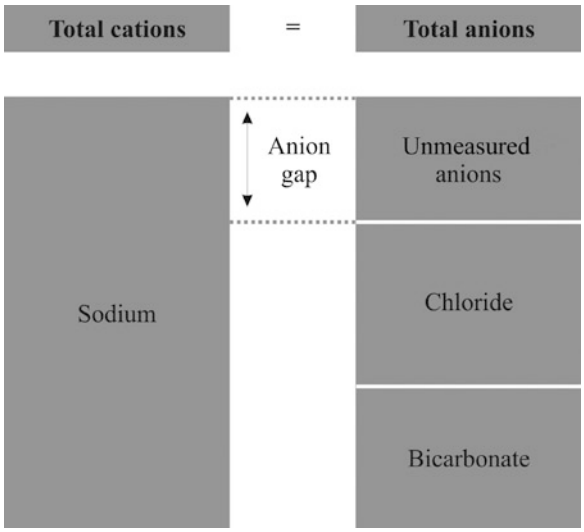

Fig. 8.2. The anion gap.

$$AG = [Na^+] - ([Cl^-] + [HCO_3^-])$$

The classification of metabolic acidoses by the AG is shown in Table 8.6. An increased AG metabolic acidosis is most often due to an increase in unmeasured organic anions (e.g., lactate, ketoacids, uremic organic anions) or exogenous anions (e.g., salicylate, ethylene glycol, methanol), whereas a normal AG metabolic acidosis can be due to a loss in bicarbonate (e.g., diarrhea, renal tubular acidosis).

Elevated AG Acidosis

The AG can be increased because of a decrease in unmeasured cations or an increase in unmeasured anions – or both. Lactic acidosis is the most commonly encountered cause of an elevated AG acidosis in the critically ill. It can occur as a result of either excessive lactate formation or decreased lactate clearance, and can be divided into type A, or hypoxic lactic acidosis, and type B, or nonhypoxic lactic acidosis. Type A lactic acidosis is caused primarily by an increase in lactate formation as a consequence of tissue hypoxia, resulting, for example, from hemorrhagic shock. Type B lactic acidosis occurs during normal oxygen delivery and often occurs secondary to a variety of medications (epinephrine, biguanides, nitroprusside, AZT), metabolic diseases (glucose 6-phosphatase deficiency), and severe liver failure. The pathogenesis of lactic acidosis in sepsis is multifactorial and may include the development of anaerobic glycolysis within tissues, the inhibition of pyruvate dehydrogenase (an enzyme that converts pyruvate into acetyl coenzyme A), and a defective oxygen use at the mitochondrial level.

Other causes of an elevated AG acidosis are easily diagnosed with appropriate laboratory evaluation (i.e., renal function, serum or urine ketones). However, an elevated AG does not always reflect an underlying acidosis. In the case of

Table 8.6. Classification of metabolic acidosis by anion gap.

Increased anion gap
Lactic acidosis
Type A (inadequate oxygen delivery)
Type B (altered cellular metabolism)
Ketoacidosis
Diabetes
Alcohol-induced
Starvation
Renal failure
Toxin ingestion
Salicylates
Methanol
Ethylene glycol
Iron
Isoniazid
Paraldehyde
Normal anion gap (Hyperchloremic)
GI loss of HCO_3
Ureteral diversion
Diarrhea
Ileostomy
Proximal colostomy
Renal loss of HCO_3
Proximal renal tubular acidosis
Carbonic anhydrase inhibitor
Renal tubular disease
Acute tubular necrosis
Chronic tubulointerstitial disease
Distal renal tubular acidosis (types I and IV)
Hypoaldosteronism, aldosterone inhibitors
Pharmacologic
Ammonium chloride
Hyperalimentation
Dilutional acidosis

Because albumin is the major unmeasured anion, a decline in serum albumin of 1 g/dL from the value of 4.0 g/dL decreases the AG by 2.5 mEq/L. This correction should be routinely applied when calculating the AG in hypoalbuminemic patients (normal >3.5 g/dL). Corrected AG = observed AG + 2.5 (4.0 − observed albumin)[4]. For example, a patient with an albumin of 1.8 g/dL would have 2.5 (4.0 − 1.8) = 5.5 mEq/L added to their original AG.

severe alkalemia (pH usually >7.5), albumin and other plasma proteins become more negatively charged, which increases unmeasured anions, thus leading to an elevated anion gap without acidosis.

Delta Gap

In addition to the level of the AG, the relationship between the increase in the AG and the fall in the plasma bicarbonate concentration may be helpful to diagnose an acid–base disorder. In an uncomplicated high AG metabolic acidosis, every increase of 1 mmol/L in the AG should result in a concomitant decrease of 1 mmol/L in $[HCO_3^-]$. Deviation from this relation suggests a mixed acid–base disorder. The difference between these two values has been termed the delta gap (Δgap) and can be expressed as[3]:

$$\Delta\text{Gap} = (\text{Deviation of AG from normal}) - (\text{Deviation of } [HCO_3^-] \text{ from normal})$$

If the normal AG is assumed to be 12 mEq/L and the normal $[HCO_3^-]$ is 24 mEql/L, then the following equation results:

$$\Delta\text{Gap} = (\text{AG} - 12) - (24 - [HCO_3^-])$$

A pure AG metabolic acidosis will yield a Δgap of zero; however, variance in measurements and the changing physiology of the patient can result in a Δgap of 0 ± 6. (If the Δgap is significantly positive, i.e. greater than +6, then a simultaneous metabolic alkalosis exists because the rise in AG is more than the fall in HCO_3. Conversely, if the Δgap is significantly negative, i.e. less than −6, then a concomitant normal AG metabolic acidosis is present because the rise in AG is less than the fall in HCO_3). Another method to diagnose a mixed acid–base disorder is to add the deviation of the AG from normal (AG-12) to the measured $[HCO_3^-]$. If the resulting $[HCO_3^-]$ is greater than normal, a simultaneous metabolic alkalosis exists. If the resulting $[HCO_3^-]$ is less than normal, a normal AG metabolic acidosis coexists.

Osmolar Gap

The osmolar gap is equal to the difference between the measured serum osmolarity ($osmo_m$) and the calculated serum osmolarity ($osmo_c$). A high plasma osmolar gap (>10–15 mOsm/kg) reflects the presence of an unmeasured nonionized compound. It can be mathematically represented by the following formula: osmolar gap = $osmo_m - osmo_c$.

$$\text{Osm}_c = [\text{Na}+] + [\text{Glucose (mg / dL)}] / 18 + [\text{BUN (mg / dL)}] / 2.8$$

Substances that increase the $osmo_m$ and, hence, the osmolar gap are sugars other than glucose, such as mannitol, and all alcohols, such as ethanol, methanol, or ethylene glycol. The most frequent causes of an increased osmolal gap are alcohol, mannitol, ketones, and lactate. Because toxic alcohols also increase the AG, as a general rule, a high AG metabolic acidosis with an elevated osmolar gap is due to a toxic alcohol if lactic acidosis and diabetic ketoacidosis are not present and mannitol has not been administered. The association between a high AG metabolic acidosis with raised serum osmolar gap is known as a double gap acidosis (Table 8.7).

Normal AG Metabolic Acidosis

Also referred to as hyperchloremic acidosis, normal AG metabolic acidosis is frequently noted in the intensive care unit. Most commonly, this acid–base disorder is caused by chloride-rich fluid administration for patients being treated for diabetic ketoacidosis or postoperative patients requiring significant intravenous fluid administration. Other etiologies

Table 8.7. Differential diagnosis of an increased osmolal gap.

With metabolic acidosis	Without metabolic acidosis
Ethylene glycol	Mannitol
Methanol	Ethanol
Diabetic ketoacidosis[a]	Glycine[c]
Lactic acidosis[b]	Severe hyperproteinemia

[a]The osmolal gap in diabetic ketoacidosis is secondary to an increase in acetone, a decrease in the plasma water fraction, and smaller increments in amino acids and glycerol.
[b]The factors responsible for the plasma osmolal gap in lactic acidosis have not been defined.
[c]Glycine may be used during transurethral resection of prostate.

of a normal AG acidosis can be categorized by the potassium level. Hypokalemia (<3.5 mmol/L) is associated with ureteral diversion, diarrhea, proximal colostomy, ileostomy, proximal renal tubular acidosis (RTA), type I distal RTA, and parenteral nutrition. Hyperkalemia (>4.5 mmol/L) can be found in hypoaldosterone states, ammonium chloride administration, and type IV distal RTA.

Urinary Anion Gap

Another useful tool in the evaluation of normal AG metabolic acidosis is the urinary anion gap (UAG). The UAG is the difference between the routinely measured urinary cations and anions and provides a rough index of urinary ammonium excretion:

$$UAG = ([Na^+] + [K^+]) - [Cl^-]$$

Ammonium is positively charged, so a rise in its urinary concentration (i.e., increased unmeasured cations) will increase urinary Cl^-, which will cause a fall in UAG. Hyperchloremic acidosis can be caused by loss of base via the kidney (e.g., renal tubular acidosis) or loss of base via the bowel (e.g., diarrhea). If the acidosis is due to loss of base via the gastrointestinal tract, the kidneys can respond appropriately by increasing ammonium excretion to cause a net loss of H^+. In this case, the urinary chloride will increase resulting in a decreased UAG. If the acidosis is due to loss of base via the kidney, the kidney will not able to increase ammonium excretion and the UAG will remain unchanged.

Thus, the presence of a positive UAG (UAG > 0) in an individual with a normal AG metabolic acidosis suggests that the disorder is due to an impaired H+ secretion by the kidneys (e.g., distal RTA). Conversely, the presence of a negative UAG (UAG < 0) suggests that the normal AG metabolic acidosis is due to loss of base via the gastrointestinal tract (e.g., diarrhea). The urinary values are not reliable in patients with renal insufficiency or in those being treated with diuretics.

Decreased AG

A decreased AG is caused by an increase in unmeasured cations or a decrease in unmeasured anions. Causes of a decreased AG include hypoalbuminemia, hyponatremia, profound hyperkalemia, hypercalcemia, hypermagnesemia, severe hyperlipidemia, lithium toxicity, paraproteinemias, and halide poisoning (Br and I).[4]

Clinical Presentation

The clinical features of metabolic acidosis depend primarily on the underlying disorder. Some effects of acidosis can be related to the change in pH. Rapid, deep respirations (Kussmaul's respirations) are sometimes observed, especially in diabetic ketoacidosis. Various abnormalities such as arrhythmias, abnormal O_2 and CO_2 transport, insulin resistance, hyperkalemia, and coagulopathies have also been noted.

Management

The underlying cause of metabolic acidosis should be corrected. Perfusion, oxygenation, and ventilation must be optimized. Treatment of etiologies of most high AG metabolic acidoses is well established based on the underlying disorder (i.e., insulin for diabetic ketoacidosis or dialysis for renal failure). Therapy for a normal AG metabolic acidosis may require replacing volume losses with a solution that contains low chloride.

Buffers

The buffering agents include sodium bicarbonate, carbicarb, tromethamine, and tribonate. (a) **Sodium bicarbonate** is the most commonly administered agent to alkalinize blood. The use of bicarbonate is appropriate for patients with a normal AG metabolic acidosis or severe acidemia (pH < 7.20), although studies have not shown consistent benefit in patient outcome.[5] Bicarbonate ions combine with hydrogen ions to form carbonic acid, which in turn dissociates into water and CO_2. Potential complications of bicarbonate administration frequently outweigh possible benefits (Table 8.8).[8] (b) **Carbicab** is an equimolar mixture of sodium bicarbonate and sodium carbonate. It does not undergo significant breakdown to CO_2 and H_2O, nor does it increase blood CO_2 concentration to the same extent as does sodium bicarbonate. (c) **Tromethamine** (THAM) is a weak alkali that increases arterial pH without producing CO_2. THAM has potentially serious side effects, including hypoglycemia and hyperkalemia. (d) **Tribonate**

Table 8.8. Potential complications of bicarbonate administration.

Volume overload
Paradoxical cerebrospinal fluid/intracellular acidosis
Respiratory acidosis
Impaired O_2 delivery (tissue hypoxia)
Hypokalemia
Hypocalcemia
Hypernatremia
Hyperosmolality
Overshoot alkalemia

is a buffer solution comprising THAM, sodium bicarbonate, acetate, and phosphate. It has been primarily used in the Scandinavian countries.[6–8]

Metabolic Alkalosis

A net increase in base or decrease in acid in the extracellular fluid will lead to metabolic alkalosis in the critically ill patient. As normally functioning kidneys are able to excrete significant amounts of HCO_3^-, a persistent metabolic alkalosis requires renal contribution by absorption of filtered HCO_3^- due to stimuli such as volume depletion or hypokalemia. Thus, the development of this acid–base disorder is often associated with aggressive diuresis with loop diuretics resulting in a low intravascular volume. Other etiologies are noted in Table 8.9 and are grouped into those that are associated with hypovolemia and hypervolemia.

Measurement of urine chloride (U_{Cl}) is helpful in distinguishing the two categories with U_{Cl} <20 mmol/L in hypovolemia and U_{Cl} >20 mmol/L in hypervolemia. In metabolic alkalosis, the U_{Cl} is a more accurate reflection of intravascular volume than urine sodium because sodium must be excreted with excess HCO_3.

Expected Compensatory Response

The physiologic response to metabolic alkalosis is hypoventilation in spontaneously breathing patients to increase PCO_2. The PCO_2 rise is usually 6–7 mmHg for every 10 mmol/L increase in [HCO_3]. This induced hypoventilation may be detrimental to patients, especially those with comorbid hypoventilatory disorders such as chronic obstructive pulmonary disease (COPD) or obesity hypoventilation syndrome (Table 8.11).

Table 8.9. Etiologies of metabolic alkalosis.

Hypovolemic (saline-responsive)
GI loss of H^+
Vomiting
Gastric suction
Cl^- rich diarrhea
Villous adenoma
Renal loss of H^+
Diuretics
Posthypercapnia
Hypervolemic (saline-resistant)
Renal loss of H^+
Primary hyperaldosteronism
Primary hypercortisolism
Adrenocorticotropic hormone excess
Pharmacologic hydrocortisone/mineralocorticoid excess
Renal artery stenosis with right-ventricular hypertension
Renin-secreting tumor
Hypokalemia
Bicarbonate administration
Pharmacologic overdose of $NaHCO_3$, acetate, citrate, lactate
Milk–alkali syndrome
Exogenous alkali

Effects of Metabolic Alkalosis

The effects of metabolic alkalosis may include the impairment of oxygen delivery to tissues and neuromuscular hyperexcitability (seizures, arrhythmias, paresthesias, carpopedal spasm).

Management

Treatment of metabolic alkalosis requires identifying and addressing the etiology of the acid–base disorder. Care should be taken to identify possible exogenous sources of alkali such as acetate in parenteral nutrition or citrate in blood transfusions. (a) **Saline-responsive alkalosis**: Because hypovolemia increases HCO_3 reabsorption and maintains the alkalosis, saline-responsive alkalosis should be corrected with volume replacement. The therapeutic effectiveness of this regimen can be followed at the bedside by measuring the urine pH, which should increase and exceed 7.0.[9] (b) **Saline-resistant alkalosis**: Acetazolamide (250 mg PO or IV once or twice a day) is a carbonic anhydrase inhibitor that produces diuresis and increases the renal excretion of HCO_3. Acetazolamide should be considered to address the metabolic alkalosis, especially if diuresis is necessary. However, judicious use is paramount as acidemia may result, associated with worsening hypokalemia because of kaliuresis. The efficacy of acetazolamide can be assessed by monitoring the urine pH, which should increase and exceed 7.0 if HCO_3 excretion is substantially enhanced. Refractory or severe alkalemia (ph>7.6) can be treated with isotonic HCl (150 mEq/L) via a central vein over 8–24 h. Potassium deficiencies should be corrected.

Respiratory Acidosis

The defect in respiratory acidosis is ineffective alveolar ventilation and/or an increase in CO_2 production. This acid–base disorder is commonly encountered in the critically ill patient who cannot maintain adequate ventilation. Specific etiologies include airway obstruction, respiratory center depression, neuromuscular disorders, and pulmonary diseases such as COPD. Respiratory acidosis is also induced with intentional hypoventilation (permissive hypercapnia) to aid in the treatment of patients with status asthmaticus or acute respiratory distress syndrome. This "lung protective ventilatory strategy" is well tolerated by the patient and has little impact on hemodynamics.

Expected Compensatory Response

The normal acute physiologic response to respiratory acidosis includes an acute stimulus to increase alveolar ventilation and a slower response to increase renal bicarbonate reabsorption. With acute respiratory acidosis, the rise in PCO_2 is associated

with a linear increase in ventilatory response due to sensing of PCO_2 by carotid body and central medullary chemoreceptors. In acute respiratory acidosis, the $[HCO_3^-]$ increases 1 mEq/L for each increase of 10 mmHg in $PaCO_2$.

The transition from acute to chronic respiratory acidosis is defined by increased renal bicarbonate reabsorption. This process requires several hours to days to effect an adequate response. In chronic respiratory acidosis, the $[HCO_3^-]$ increases 3.5 mEq/L for each increase of 10 mmHg in $PaCO_2$. The limit of renal compensation in chronic respiratory acidosis is $[HCO_3^-]$ ~ 45 mEq/L. Higher values suggest an associated secondary metabolic alkalosis.

Effects of Respiratory Acidosis

The findings on physical examination in patients with respiratory acidosis usually are nonspecific and related to the underlying illness. Patients with obstructive lung disease may have diffuse wheezing, hyperinflation, decreased breath sounds, and prolonged expiration. Rhonchi also may be heard. Cyanosis may be noted if accompanying hypoxemia is present, and the finding of clubbing may indicate the presence of a chronic respiratory disease. Mental status may be depressed in severe elevations of $PaCO_2$. Patients may have asterixis, myoclonus, and seizures. Papilledema may be found during the examination. Conjunctival and superficial facial blood vessels also may be dilated.

Management

Treatment requires the rapid identification of the etiology of respiratory acidosis and implementation of corrective action. In many circumstances, supportive ventilation is necessary with invasive or noninvasive mechanical ventilation. Administration of $NaHCO_3$ for acute respiratory acidosis is not indicated.

A therapeutic pitfall to avoid in the treatment of respiratory acidosis is the creation of a posthypercapnic metabolic alkalosis. This condition most commonly occurs when a patient with compensated chronic respiratory acidosis is overventilated to a normal or near-normal $PaCO_2$. Appropriate ventilator management with adjustments based on the pH and not the PCO_2 should prevent this complication.

Respiratory Alkalosis

This acid–base disorder results from increased alveolar ventilation, expelling more CO_2 than generated. Etiologies are listed in Table 8.10.

Alveolar ventilation is regulated by several factors: chemoreceptors in the medulla (sensitive to $[H^+]$) and great vessels (sensitive to oxygen), cortical input (voluntary control), and pulmonary chemoreceptors and stretch receptors. Any of these factors alone or in combination may lead to hyperventilation.

Table 8.10. Etiologies of respiratory alkalosis.

Hypoxemic drive
Pulmonary disease with arterial-alveolar gradient
Cardiac disease with right-to-left shunt
Cardiac disease with pulmonary edema
High altitude
Pulmonary disease
Emphysema
Pulmonary embolism
Mechanical overventilation
Stimulation of respiratory center
Neurologic disorders
Pain
Psychogenic
Liver failure with encephalopathy
Sepsis/infection
Salicylates
Progesterone
Pregnancy
Fever

Expected Compensatory Response

In acute respiratory alkalosis the $[HCO_3^-]$ decreases 2 mEql/L for each decrease of 10 mmHg in $PaCO_2$. Importantly, chronic respiratory alkalosis is unique among acid–base disorders in that pH may return to normal if the condition is prolonged. The normal physiologic response to persistent hypocapnia is decreased renal H^+ secretion, which results in a decrease of plasma $[HCO_3^-]$ of 5 mEq/L for each 10 mmHg decrease in $PaCO_2$ (Table 8.11).

Effects of Respiratory Alkalosis

The manifestations of the underlying disorder often predominate. In acute hypocapnia, cerebral vasoconstriction reduces cerebral blood flow and syncope and seizures may occur. Cardiovascular changes may include an increase in heart rate, arrhythmias, and angina.

Management

Treatment of respiratory alkalosis requires addressing the underlying disorder. Significant respiratory alkalosis in mechanically ventilated patients may require ventilator adjustments or sedation of the patient after appropriate evaluation of the etiology.

Clinical Approach

Analysis of acid–base disorders in the intensive care unit requires a systematic approach. The following is one such approach that can be utilized at the bedside[4]:

1. Determine the overall acid–base condition by measuring pH. Is acidemia or alkalemia present?
2. Determine if the primary process is metabolic ($[HCO_3^-]$ deviation) or respiratory ($PaCO_2$ deviation).

Table 8.11. Expected compensation for simple acid–base disorders.

Acid–base disorder	Expected compensation
Metabolic acidosis	$\downarrow PaCO_2 = 1.2 \times \downarrow HCO_3^-$ or $PaCO_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$
Metabolic alkalosis	$\uparrow PaCO_2 = 0.6 \times \uparrow HCO_3^-$
Acute respiratory acidosis	$\uparrow HCO_3^- = 0.1 \times \uparrow PaCO_2$
Chronic respiratory acidosis	$\uparrow HCO_3^- = 0.35 \times \uparrow PaCO_2$
Acute respiratory alkalosis	$\downarrow HCO_3^- = 0.2 \times \downarrow PaCO_2$
Chronic respiratory alkalosis	$\downarrow HCO_3^- = 0.5 \times \downarrow PaCO_2$

[a]A positive or negative change represents an increase or decrease, respectively, from the normal value of 40 mmHg for $PaCO_2$ or 24 mEq/L for HCO_3^-.

3. If a respiratory disturbance is present, determine if it is acute or chronic.
4. Determine if the expected compensation is adequate.
5. If a metabolic acidosis is present, calculate the AG.
6. If a high AG metabolic acidosis is present, calculate the Δgap to determine if other metabolic disturbances are present.
7. If a normal AG metabolic acidosis is present, calculate the UAG.

Using this approach, the proper diagnosis of coexisting acid–base disorders is possible. Table 8.11 includes pertinent equations.

Case Examples

Case 8-1

A 24-year-old male is brought to the emergency center with head trauma after a fall at a party. On arrival, vital signs are blood pressure: 110/68 mmHg, pulse: 80/min, respiratory rate: 8/min, and temperature: 97°F (36.1°C). The patient is obtunded and only weakly withdraws to painful stimuli. He is noted to have small pupils.

Laboratory: Na^+ 142 mEql/L, K^+ 4.0 mEql/L, Cl^- 104 mEql/L, albumin 4 g/dL (normal: 3.5–5.0 g/dL) and ABG: pH 7.24, $PaCO_2$ 60 mmHg, PaO_2 64 mmHg, $[HCO_3^-]$ 27 mEql/L.
What is the acid–base disorder and the likely etiology?

Analysis:

1. What is the acid–base condition? Acidemia as evidenced by pH 7.24.
2. What is the primary process? Respiratory, because $PaCO_2$ is increased and $[HCO_3^-]$ is not decreased as would be expected for a metabolic acidosis.
3. Is the respiratory process acute or chronic? Acute, as determined by expected bicarbonate change. In acute respiratory acidosis, an increase of 20 mmHg in the $PaCO_2$ corresponds to an increase in bicarbonate of around 2 mEq/L.
4. Determine if the expected compensation is adequate. The expected compensation for acute respiratory acidosis is about $[HCO_3^-]$ of 26 mmHg

Answer: The acid–base condition is acute respiratory acidosis with a likely etiology of respiratory center depression from acute narcotic and/or alcohol intoxication or head trauma.

Case 8-2

A 58-year-old homeless male with cirrhosis is transferred to the intensive care unit because of hypotension. He had presented to the hospital 12 h earlier with complaints of right groin pain and swelling. Evaluation revealed a febrile patient 102.4°F (39.1°C) with mild right inguinal and scrotal swelling and erythema. Currently, the patient is lethargic but arousable and vital signs are as follows: temperature: 99.4°F (37.4°C), pulse: 134/min, blood pressure: 84/52 mmHg, respiratory rate: 28/min.

Laboratory: Electrolytes: Na^+ 135 mEql/L, Cl^- 106 mEql/L, $[HCO_3^-]$ 16 mEq/L, albumin 1.0 g/dL. Arterial blood gas: pH 7.30, $PaCO_2$ 33 mmHg, PaO_2 68 mmHg, $[HCO_3^-]$ 15 mEq/L.

What is the acid–base disorder and the likely etiology?

Analysis:

1. What is the acid–base condition? Acidemia as evidenced by pH 7.30.
2. What is the primary process? Metabolic because $[HCO_3^-]$ is decreased and $PaCO_2$ is not increased as would be expected for a respiratory acidosis.
3. Is the respiratory compensation adequate? Expected $PaCO_2 = 1.5 \times [HCO_3^-] + 8 \pm 2 = 32 \pm 2$ mmHg. Thus, respiratory compensation is adequate.
4. Calculate the anion gap. AG = $[Na^+] - ([Cl^-] + [HCO_3^-])$ = 13 mEq/L, which is high in this patient with a low albumin (corrected AG = 20.5 or expected AG for albumin of 1 g/dL would be around 4.5). Thus, a high AG metabolic acidosis exists.
5. Calculate the Δgap. $\Delta gap = (\text{measured Anion Gap} - \text{normal Anion Gap}) = (AG_{adjusted} - 12) - (24 - HCO_3^-) = (20.5 - 12) - (24 - 15) = 0.5$ mEq/L or $((AG - AG_{expected}) - (24 - [HCO_3^-]) = (13 - 4.5) - (24 - 15) = 0.5$ mEq/L. Thus, the Δgap is insignificant, and another coexisting metabolic disturbance is likely not present.

Answer: The acid–base condition is high AG metabolic acidosis likely due to sepsis and Fournier's gangrene.

Case 8-3

A 68-year-old female with chronic renal failure presents with fever, severe right lower quadrant pain, and diarrhea for 2 days. Laboratory: Electrolytes: Na^+ 135 mEq/L, K^+ 3.4 mEq/L, Cl^- 106 mEq/L, albumin 3.5 g/dL (lower limit of normal) Arterial blood gas results: pH 7.44, $PaCO_2$ 12 mmHg, PaO_2 74 mmHg, $[HCO_3^-]$ 8 mEq/L.

What is/are the acid–base disorder(s)?

1. What is the acid–base condition? The pH is at the alkalemic end of the normal range; thus, a primary alkalosis is likely present.
2. What is the primary process? Respiratory because $PaCO_2$ is decreased and $[HCO_3^-]$ is not increased as would be expected for a metabolic alkalosis.

3. Is the respiratory alkalosis acute or chronic? In acute respiratory alkalosis, the reduction of 28 mmHg in $PaCO_2$ would correspond to a decrease in bicarbonate of around 2.8 mEq/L. The expected bicarbonate would be around 21 mEq/L. In chronic respiratory alkalosis, the decrease of 28 mmHg in $PaCO_2$ would correspond to a reduction in bicarbonate of around 9.8 mEq/L.
4. Is the metabolic compensation adequate? The expected bicarbonate would be around 14 mEq/L. The bicarbonate concentration of the patient is lower than expected for either acute or chronic alkalosis. Thus, there is an associated metabolic acidosis.
5. Calculate the anion gap. $AG = [Na^+] - ([Cl^-] + [HCO_3^-]) =$ 21 mEq/L, which is elevated. Thus, an anion gap metabolic acidosis also exists.
6. Calculate the Δgap. $\Delta gap = (AG - \text{normal AG}) - (24 - [HCO_3^-]) =$ −7 mEq/L. Thus, a coexisting normal anion gap acidosis is also present.

Answer: The coexisting acid–base disorders are (1) primary respiratory alkalosis, (2) anion gap metabolic acidosis, and (3) hyperchloremic (normal anion gap) metabolic acidosis. The respiratory acidosis and the anion gap acidosis are likely due to sepsis from an intra-abdominal source. The additional process of the normal anion gap acidosis may be related to the diarrhea.

The Fencl–Stewart Approach to Acid–Base Disorders

The application of the Fencl–Stewart (physical-chemical) approach to acid–base analysis has led to recent developments in the identification, quantification, and understanding of mechanisms for acid–base disorders commonly found in critically ill patients. The physical-chemical approach is entirely complementary to the traditional approach and changes nothing about the measurement or classification of acid–base disorders. The difference between the conventional and Stewart approaches lies in the understanding of the mechanisms involved in acid–base regulation. The observation that metabolic acidosis is associated with a decrease in plasma bicarbonate remains valid. However, the implication that these changes cause the acidosis is not.

According to the physical-chemical approach to acid–base analysis, pH is regulated through manipulation of three variables: strong ion difference (SID), weak acid buffers (Atot), and $PaCO_2$. SID is the net charge balance of all strong ions. This includes both the cations (sodium, potassium, calcium, magnesium) and the anions (chloride, lactate). The difference is referred to as SID. In healthy humans, this number is close to 40 mEq/L. The smaller the SID, the larger the hydrogen ion concentration. An increase in sodium relative to chloride increases the SID and the pH. An increase in chloride relative to sodium reduces the SID and the pH. The SID is balanced by an equal negative force comprising mostly weak acids (Atot). These weak acids include albumin and phosphates. When the Atot increases, metabolic acidosis ensues. A rise in the concentration of albumin increases the Atot and produces acidosis. A fall in albumin concentration reduces the Atot and produces alkalosis. In summary, a fall in the SID (hyperchloremia), a rise in Atot (hyperphosphatemia), and a rise in $PaCO_2$ (hypoventilation) produce acidosis. A rise in the SID (hypochloremia), a fall in Atot (hypoalbuminemia), and a fall in $PaCO_2$ (hyperventilation) produce alkalosis[10–12] (Table 8.12).

Table 8.12. Acid–base abnormalities: the Fencl–Stewart approach.

Acid–base disturbance	Example
Acidosis due to ↑ $PaCO_2$	↓ ventilation
Acidosis due to ↓ SID	↑ chloride, ↑ proteins
Acidosis due to ↑ A_{TOT}	↑ phosphate
Alkalosis due to ↓ $PaCO_2$	↑ ventilation
Alkalosis due to ↑ SID	↓ chloride, ↓ albumin
Alkalosis due to ↓A_{TOT}	↓ phosphate

The Acid–Base Physiology of Crystalloid Solutions

Crystalloid solutions are a mainstay of perioperative and critical care medicine and include normal saline (chloride: 154 mEq/L) and Ringer's lactate (chloride: 109 mEq/L). Infusion of large volumes of normal saline increases chloride concentration reducing the SID and hence the pH. The administration of Ringer's lactate does not increase chloride concentration, does not reduce the SID, and does not cause acidosis. Scheingraber examined acid–base changes in patients undergoing surgery. Patients received 30 mL/Kg/h of 0.9% saline or Ringer's lactate. The Ringer's lactate group had a mean pH of 7.41 and the saline group had a mean pH of 7.28. Both groups had an initial SID of about 38 mEq/L. The SID in the Ringer's lactate group fell to 33 mEq/L and in the saline group to 28 mEq/L. The study showed that the infusion of 0.9% saline, but not lactated Ringer's solution, caused a metabolic acidosis with hyperchloremia and a concomitant decrease in the strong ion difference. As the SID falls, the hydrogen ion concentration increases.[13,14]

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9
Analgesia and Sedation

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Providing the critically ill patient with sedatives to minimize anxiety and recollection of unpleasant events and providing adequate analgesia is an integral function of the critical care team. However, there is a fine balance between providing comfort and causing over-sedation with the possibility of adverse outcomes in both scenarios. Treating pain, anxiety, and delirium are all priorities of utmost importance.

Inadequate analgesia and sedation may result in increased sympathetic tone, ventilator asynchrony, and unwanted removal of endotracheal tubes, intravenous access, and drains. Reports detail the development of posttraumatic stress disorder (PTSD) in cohorts of ICU survivors. There is evidence that PTSD is not uncommon in patients who survive critical illness.[1,2] Although in those patients, the PTSD seems to be related more to the recollection of delusions than actual facts, anxiety has been reported as a risk factor.[3] Conversely, overmedicated patients may result in fewer ventilator-free days, longer ICU stays, and a higher incidence of other complications such as venous stasis, skin ulcerations, neuromuscular weakness, and ventilator-associated pneumonia.

Delirium in the critically ill has raised new perspectives in relation to the way we manage sedation and analgesia. Typically, ICU therapy is focused on the treatment of multiple organ dysfunction syndrome presenting as renal, cardiac, hepatic, or pulmonary failure. Brain function is often viewed in the prism of a complication of sedation therapy, either too little or too much. However, the recent literature supports the notion that delirium is an independent syndrome and serves as a valid prognosticator of future adverse events and may be a valid clinical marker of brain function.[4,5] A goal-oriented sedative and analgesic regimen should be instituted not only to provide the needed comfort to patients, but also to prevent over utilization of these medications, which carry multiple adverse effects including delirium. A goal-directed approach starts with proper assessment, frequent re-evaluation, and appropriate use of the pharmacological armamentarium. In this chapter, assessment and management of analgesia and sedation, including delirium, in the critically ill patient will be discussed. We based our discussion on the Society of Critical Care Medicine (SCCM) Guidelines for the sustained use of sedatives and analgesics.[6] However, new data have emerged in this area since the SCCM guidelines were published and will be reflected in this text.

Analgesia

Pain is commonly encountered by intensive care unit patients. Not infrequently, pain is the primary cause of agitation in the ICU patient. Pain in the ICU setting is not limited to traumatic injuries or surgery. It can be triggered by the placement or presence of cannulas, catheters, or endotracheal tubes. Pain is also experienced during common procedures such as suctioning and turning. Puntillo et al. reported that procedural pain was often described as sharp, stinging, stabbing, shooting, and awful; and that less than 20% of patients received opiates before such procedures.[7] Furthermore, patients with chronic pain syndromes often have their baseline pain aggravated by position or immobility while in the ICU. Additionally, there are physiologic changes associated with pain in the critically ill patients that can adversely affect their ICU course. Inadequate analgesia often

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results in increased sympathetic tone, causing tachycardia, hypertension, and increased systemic vascular resistance. These changes may lead to increased myocardial oxygen demand and myocardial ischemia if oxygen delivery cannot be increased. In patients with intracranial processes, pain might increase the intracranial pressure and worsen their outcome. Postoperative pulmonary complications are also more likely in patients with inadequate pain control. "Splinting" or limiting the depth of respiration as a result of pain after surgery causes a reduction in tidal volume and functional residual capacity. Paired with the inhibition of cough, postoperative pulmonary complications such as atelectasis, respiratory infection, and hypoxemia are more likely. The risk of developing deep venous thrombosis and pulmonary embolism may increase secondary to pain-related immobility. Unrelieved pain may lead to physical suffering and psychic suffering. It has been reported that 63% of patients in the ICU rated their pain as being moderate to severe in intensity.[8] Schelling et al. reported that 40% of ARDS survivors recalled having pain while in the ICU and that those patients have a higher frequency of chronic pain issues when compared with control.[9] Furthermore, those ICU patients had higher PTSD scores than controls.

Therefore, it is of paramount importance to provide adequate analgesia to the critically ill. The initial step corresponds to a systematic and consistent assessment of pain, followed by provision of appropriate pain control and further assessment to ensure the attainment and maintenance of therapeutic analgesia.

Assessment of Pain

The most reliable indicator of pain is the patient's self-report. If the patient is able to communicate the location, characteristics, aggravating/alleviating factors, and the intensity of their pain, that will allow the provider to gain a good understanding of the patient's pain experience. Unfortunately, this might not be an option when caring for the sedated, confused, or mechanically ventilated critically ill patient. Additionally, the literature is relatively scarce in the research conducted to validate pain assessment tools in the critically ill.[10] Traditionally, the use of pain scales such as the visual analog scale and the numeric rating scale have been employed in the assessment of pain in intensive care units, but new behavioral-based scales have been tested with success in the critically ill and will be discussed.

The Visual Analog Scale (VAS) is a measurement instrument that attempts to measure a characteristic or attitude that is believed to range across a continuum of values that cannot be easily or directly measured. In the VAS used for pain, this characteristic is intensity. On a 10 cm horizontal line, the amount of pain that a patient feels ranges across a continuum from no pain in one end to an extreme amount of pain in the other end. This scale requires ability to understand the abstract concept of the VAS line and then relate it to distance from a zero mark.[11] Additionally, difficulties in understanding the VAS have been reported in some patient populations, such as the elderly.[12]

The Numeric Rating Scale (NRS) is a 0–10 point scale that patients are given. The patient then chooses the point on the scale that most correlates with their pain level ranging from 0 for no pain to 10 for worst pain. The use of a numeric scale might be simpler to understand (e.g., 7 is a higher value number than 3 and so on), and thus might provide a better correlation than a distance mark. Data on the noncritically ill suggest that this numerical scale is preferred by patients.[11,13] The NRS has been used in the cardiac surgical population during their ICU stay with good results.[4] Finally, the SCCM guidelines suggest that due to the possibility of using NRS by writing or speaking, and its applicability in many age groups, it might be a better option than VAS for the assessment of pain in the critically ill.[6]

For patients who cannot communicate their pain level by these scales, observation by the care provider might be useful. Physiological parameters such as increased heart rate, blood pressure, and respiratory rate might serve as indicators of pain, but they may prove inaccurate and result in under or over treatment of pain. However, critically ill adults might manifest different behaviors such as facial expressions, body movements, or posturing when suffering from noxious stimuli.[10] Different behavioral pain scales in the critically ill have been created and have demonstrated to be more valid than relying on physiological parameters as indicators of pain in the noncommunicative critically ill patient.[10,15–18]

Agents for Analgesia

Almost all critically ill patients, particularly those receiving mechanical ventilation, will receive an analgesic agent. A wide variety of pharmacological agents are available for analgesia and, while recommendations have been made regarding the "best" analgesic for ICU patients, practice varies widely between and within ICUs. The choice of agent can be based on many factors, including the relative need for analgesia, the pharmacodynamics and pharmacokinetics of the drug in question, route and ease of administration, the tolerance profile, and the cost. An ideal agent would be the one with rapid onset of action, no active metabolites, easy titration, lack of accumulation, and low cost. While many studies have been conducted comparing the effectiveness of various agents, there is relatively little published information on variations in analgesic drug use among units or across national and international boundaries.

Opioids

Currently, the mainstay of analgesic therapy in the ICU patient is intravenous opioids. These medications work by stimulating opiate receptors in the spinal cord and central nervous system,

and possibly in the periphery. Multiple receptor subtypes have now been identified, with some receptors more involved in analgesia than other. The Mu-1 receptors are associated with supraspinal analgesia. The Kappa receptors are also associated with analgesic effects. Opioids are classified as natural opium alkaloids, such as morphine and codeine; semisynthetic derivatives, such as oxycodone, hydromorphone, and heroin; and the synthetic opioids, such as fentanyl, meperidine, and methadone.[19]

Side effects of opioids are varied, and represent the limiting factor in therapy. The most worrisome dose-limiting side effect of this group of drugs is respiratory depression. In this regard, large amounts of opioids can be safely administered to critically ill patients who are mechanically ventilated. However, other side effects in the central nervous system (over-sedation) and the gastrointestinal system (ileus) can impact the management of the patient. It is important to educate health care providers, as well as patients and their families, regarding the use of potent analgesics in order to dissipate any fears or misconceptions that often lead to the inadequate administration of these agents.[6]

Opioids should be titrated to a desired effect for analgesia. The most effective route of administration in the ICU is continuous intravenous infusion, as repeated bolus injections of opioids tend to result in peaks and troughs of over-sedation and inadequate analgesia. Instead, it is more efficient to supplement baseline continuous infusion with short-acting formulations to prevent the pain associated with additional procedures in the ICU.

Morphine

Morphine is the agent most widely used in the ICU.[19] It has both analgesic and anxiolytic effects and can be conveniently administered by bolus dose or continuous infusion in patients in whom prolonged analgesia and sedation are necessary. A loading dose of 5–10 mg, followed by an infusion of 2–5 mg/h, titrated to control pain and anxiety, is usually employed. Responses to morphine vary considerably. Morphine can cause hypotension either as a consequence of drug-induced bradycardia or as a consequence of histamine release.[20] Morphine-induced bradycardia occurs as a result of stimulation of the vagal nucleus in the medulla. Systemic vasodilation as a consequence of morphine-induced histamine release can be seen with doses as low as 0.1–0.2 mg/kg. This is more pronounced in volume depleted patients. The depressant effect on the medullary respiratory center is difficult to predict. Initially, respiratory rate slows more significantly than tidal volume is reduced, but as the morphine dose is increased, a profound depression of total minute ventilation results.

Morphine is metabolized by the liver, and its metabolites are normally excreted in the urine. The elimination half-life of one of its main metabolites, morphine-6-glucuronide, is 1.5–4.0 h; but in patients with impaired renal function, drug effect can persist for more than 24 h.[20] Therefore, fentanyl or hydromorphone, which have no metabolites, are better options for patients with renal impairment.

Fentanyl

Fentanyl is a synthetic opioid with high lipid solubility, which permits rapid penetration of the central nervous system and equilibration between blood and brain drug levels. Fentanyl has a more rapid onset of action and shorter duration of action than morphine and is 75–200 times more potent. Due to its rapid onset of action, it is recommended by the SCCM guidelines in patients with acute distress.[6] However, due to its lipid solubility, it can accumulate in fatty stores and, after repeated doses or prolonged infusions, it results in tissue accumulation and prolonged elimination times. When administered in the ICU by continuous infusion, it offers little advantage over morphine. Due to its pharmacokinetic properties, fentanyl may be a useful opioid in patients requiring frequent neurological examinations. It is a useful drug for short-term, painful ICU procedures, particularly when used in combination with a benzodiazepine.[20] Systemic hemodynamic effects resulting from vasodilatation are less significant with fentanyl than with morphine, therefore it is a better option for the patient with hemodynamic instability.

Hydromorphone

Hydromorphone is a derivative of morphine, but has eight times more potency and a slightly shorter duration of action. Furthermore, it lacks any active metabolite and does not cause histamine release. It is suggested for use in patients with hemodynamic instability and/or in those with significant acute distress.[6]

Remifentanil

Remifentanil is a 4-anilidopiperidine derivative of fentanyl that is a specific Mu opioid antagonist metabolized by plasma esterases. This particular metabolic property provides this drug with characteristics that would make it a desirable agent for use in the ICU: organ-independent metabolism, lack of accumulation, and rapid offset of action.[21] Although no large studies are available for the use of this drug in the critically ill, remifentanil could be used in patients where rapid recovery from the sedative effects is desired, such as in patients requiring frequent neurological evaluations.[6]

Meperidine

Meperidine is a synthetic opioid analgesic that is one-eighth as potent as morphine when administered parenterally. It is metabolized in the liver to normeperidine, an active metabolite. Meperidine has an elimination half-life of 3–4 h. Normeperidine has an elimination half-life of 15–30 h. Often, toxic levels of normeperidine can be responsible for alterations in

a patient's mental status and seizures. Therefore, meperidine should be used with caution in patients with decreased hepatic or renal function and in patients who require repeated doses. As a consequence, it is not widely used in ICU patients.[20]

Nonopioid Analgesics

Nonsteroidal anti-inflammatory (NSAIDs) medications have a role in postoperative pain management by decreasing the need for opioids, and thus probably decreasing the potential for opioid-related complications such as postoperative ileus and respiratory depression.[22] NSAIDs work by blocking the cyclooxygenase enzymes and reduce prostaglandins throughout the body. As a consequence, ongoing inflammation, pain, and fever are reduced. Since the prostaglandins that protect the stomach, support platelets function and promote blood clotting also are reduced, NSAIDs can cause ulcers in the stomach resulting in bleeding. Ketorolac is a very potent NSAID and can be used as an adjuvant for moderately severe pain in combination with an opioid. It can be administered parenterally and, thus, is used often in the ICU setting. However, ketorolac causes gastric ulcers more frequently than any other NSAID and is, therefore, not used for more than 5 days.[22]

Acetaminophen is another agent used to relieve mild pain or discomfort in the ICU setting. It is an analgesic and antipyretic whose exact mechanism of action is not well known, but it is believed to elevate the pain threshold and reduce fever through its action on the heat-regulating center of the brain. Several studies have shown that in combination with an opioid, acetaminophen produces a greater analgesic effect than higher doses of the opioid alone.[23]

Epidural Analgesia

The administration of local anesthetics and opioids in the epidural space is not an infrequent method of postoperative analgesia.[19] Epidural analgesia has been shown to facilitate the early return of function (ambulation, coughing, deep breathing, and enteral alimentation) in patients after abdominal surgery. Several randomized studies compared general anesthesia plus intravenous opioids versus epidural anesthesia plus postoperative epidural analgesia in patients who might require postoperative intensive care, suggesting better outcomes when epidural anesthesia/analgesia is used. For instance, for peripheral vascular surgery, the use of an epidural was associated with improved graft survival.[24] Cancer patients undergoing major abdominal surgery who had epidurals showed decreased incidence of tachycardia, myocardial ischemia, myocardial infarction, shorter time to tracheal extubation, earlier discharge from ICU, earlier discharge from hospital, and lowered total cost than those who did not.[25] Patients undergoing partial colectomy and/or radical retropubic prostatectomy had decreased time to recovery of bowel function and lowered hospital charges when epidurals were used for analgesia than not.[26] In post-thoracotomy patients, those who received epidural analgesia, had improved lung function and better pain control.[27,28]

Placement of the epidural catheter close to the dermatomes of surgery and a continuous infusion of bupivacaine and morphine (in low doses), maximize the concentration of analgesics at the site where the nociceptive fibers enter the spinal cord, allow the use of the lowest doses of each medication, and minimize the side effects and complications of the therapy. In addition, epidural local anesthetics probably have two beneficial effects in the gastrointestinal system: they decrease the need for parenteral opioids (minimizing the gut-slowing opioid side-effect) and may have direct stimulatory effects on the bowel.[29] In the blunt thoracic trauma patient with multiple rib fractures or flail chest at risk of developing pulmonary contusion, it has been shown that pain control via epidural catheter allows for aggressive pulmonary toilet, coughing and deep inspiratory effort, thereby decreasing the need for intubation and mechanical ventilation and improving outcomes[30]. It is the recommended analgesic method by the EAST Practice Management Guidelines Work Group for blunt thoracic trauma victims.[31]

Although epidural analgesia has many benefits, it is not without complications. Thus, the decision to place an epidural catheter must take into account the potential benefits of epidural analgesia and the inherent risks.[31] Some of the complications include, but are not limited to, accidental dural puncture, intravenous injection, hypotension, high spinal and epidural block, abscess, and hematoma formation. The appearance of cerebrospinal fluid through either the epidural needle or catheter signifies a dural puncture. If this occurs, the epidural may be attempted again at a different interspace. The risk of postdural puncture headache is increased because of the large needle size used. Intravascular injections leading to neurological and/or cardiac complications can be prevented by preinjection aspiration of the epidural catheter and the use of 3–4 mL test dose of local anesthetic with epinephrine. Increments on the baseline heart rate suggest the epidural catheter is in the intravascular space. Sometimes, catheters migrate intravascularly hours after the initial placement in the epidural space. Therefore, a test dose is always warranted before reinitiating an epidural infusion. Hypotension is dependent on the level of sympathectomy and the patient's volume status. Provision of intravascular fluid prior to the initiation of the neuroaxial block and careful titration of the medication prevents hypotension, which would require further intervention most of the time. Inadvertent intrathecal injection of an epidural dose of local anesthetic can result in a high spinal block leading to apnea or cardiovascular collapse. The use of a test dose before injection of the initial local anesthetic bolus, incremental injections, and aspiration of the catheter before reinjection aid in the detection of an intrathecally placed catheter and reduce the risk of a high or total spinal blockade.

Unfortunately, there are limitations to the use of epidurals in critically ill patients. Epidurals are generally avoided in patients who are septic, have a localized infection at the site

of needle placement, or are therapeutically anticoagulated in order to prevent epidural abscess and hematoma formation. Patients who develop these complications often present with radicular pain that may progress to paraplegia if not diagnosed and treated promptly.

Sedation

The role of sedative agents in ICU therapy is less clear and defined and may be somewhat subjective. Ideally, the critically ill patient should be comfortable with their surroundings, and sleepy but easily arousable upon command. Unfortunately, achieving the desired state is not always easy. In fact, it is often challenging and depends on many factors such as degree of ventilator dependency, need for interventional procedures, patients' prior substance abuse, and environmental stimuli. Nonpharmacologic means, such as frequent reorientation, provision of adequate analgesia, and sleep promotion, should be employed before providing sedatives. Sedatives are commonly used as an adjunct to provide anxiolysis, treat agitation, treat withdrawal, and promote sleep. In general, a goal level of sedation should be determined for each patient, provision of adequate therapy instituted, and frequent reassessment should be performed. In order to achieve these goals in a consistent manner, utilization of standard scales is recommended. There are different sedation assessment scales with validity and reliability in adult patients. These include the Ramsay Scale, the Sedation–Agitation Scale, and the Richmond Agitation–Sedation Scale.

The Ramsay Scale (Table 9.1) was first described in 1974. Ironically, it was not created for the assessment of agitation in the ICU per se, but to study a drug with sedation properties.[32] It measures three levels of awake states and three levels of asleep states. Although widely used, it has been criticized for its lack of clear discrimination and specific descriptors to differentiate between the various levels. The Sedation–Agitation Scale (SAS) was described by Riker et al.[33] (Table 9.2) and has been proven to be reliable and valid in critically ill adults.[34] This scale scores a patient's level of consciousness and agitation from a seven-item list describing patient behavior.

Table 9.1. Ramsay Scale.[6,32]

Definition	Description	Score
Patient anxious and agitated or restless or both	Awake	1
Patient cooperative, oriented, and tranquil		2
Patient responds to commands only		3
A brisk response to a light glabellar tap or loud auditory stimulus	Asleep	4
A sluggish response to a light glabellar tap or loud auditory stimulus		5
No response to a light glabellar tap or loud auditory stimulus		6

More recently, the Richmond Agitation–Sedation Scale (RASS) shown in Table 9.3 was developed by a multidisciplinary team at Virginia Commonwealth University in Richmond, Virginia.[35] A unique feature of RASS is that it uses the duration of eye contact following verbal stimulation as the principal means of titrating sedation. RASS has been demonstrated to have excellent inter-rater reliability in a broad range of adult medical and surgical ICU patients, and to have excellent validity when compared to a visual analog scale and selected sedation scales. This agitation–sedation scale has been shown highly reliable among multiple types of health care providers. The RASS has an expanded set of scores (10-point scale) at pivotal levels of sedation that are determined by patients' response to verbal versus physical stimulation, which will help the clinician in titrating medications. In addition, Ely et al. validated this scale for its ability to detect changes in sedation status over consecutive days of ICU care, against constructs of level of consciousness and delirium, and correlated with the administered dose of sedative and analgesic medications.[36] It is the authors' opinion that this scale is probably the most integral and user-friendly scale available and would suggest its use.

Although these scales are often effective in the evaluation and assessment of sedation, there are times when these different scoring systems fail to produce sufficient information. This is especially true in the deeply sedated patients who have become unresponsive to any external stimulation.[37] However, whether a person is awake, asleep, active, or inactive, the brain continuously emits electrical signals. The ideal amount of sedation and analgesia and its effects can be measured by an electroencephalogram (EEG). The classic EEG, with multiple leads and large size machine, is awkward and cumbersome, which prevents its routine use in the ICU setting.

Table 9.2. The Sedation–Agitation Scale.[6,33]

Definition	Description	Score
Pulling at ETT, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side	Dangerous agitation	7
Does not calm despite frequent verbal reminding of limits, requires physical restrains, biting ETT	Very agitated	6
Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions	Agitated	5
Calm, awakens easily, follows commands	Calm and cooperative	4
Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts again, follows simple commands	Sedated	3
Arouses to physical stimuli but does not communicate or follows commands, may move spontaneously	Very sedated	2
Minimal or no response to noxious stimuli, does not communicate or follows commands	Unarousable	1

Table 9.3. Richmond Agitation–Sedation Scale.[35]

Description	Term	Score
Overtly combative or violent; immediate danger to staff	Combative	+4
Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff	Very agitated	+3
Frequent nonpurposeful movement or patient–ventilator dysynchrony	Agitated	+2
Anxious or apprehensive but movements not aggressive or vigorous	Restless	+1
Alert and calm		0
Not fully alert, but has sustained (more than 10 s) awakening, with eye contact to voice	Drowsy	−1
Briefly (less than 10 s) awakens with eye contact to voice	Light sedation	−2
Any movement (but no eye contact) to voice	Moderate sedation	−3
No response to voice, but any movement to physical stimulation	Deep sedation	−4
No response to voice or physical stimulation	Unarousable	−5

Procedure for Patient Assessment

1. Observe patient. Is patient alert and calm (score 0)?
   Does patient have behavior that is consistent with restlessness or agitation (score +1 to +4 using the criteria listed above, under DESCRIPTION)?
2. If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary.
   Can prompt patient to continue looking at speaker.
   Patient has eye opening and eye contact, which is sustained for more than 10 s (score −1
   Patient has eye opening and eye contact, but this is not sustained for 10 s (score −2).
   Patient has any movement in response to voice, excluding eye contact (score −3).
3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder.
   Patient has any movement to physical stimulation (score −4).
   Patient has no response to voice or physical stimulation (score −5).

Several devices now exist that simplify bedside interpretation and improve reliability. Two of these devices are the bispectral index (BIS®, Aspect Medical Systems, Norwood, MA) and the SEDline® also known as the Patient State Index (PSI) monitor (Hospira, Lake Forest, IL). The BIS device uses a digital scale from 100 (completely awake) to 0 (isoelectric EEG).[38] Most of the literature regarding the value of BIS is from its use in the operating room. In fact, three large-scale clinical trials conducted in the United States and abroad evaluated more than 30,000 patients to investigate the incidence of awareness with recall and the impact of BIS monitoring on predicting and preventing awareness. Study findings revealed that BIS-guided anesthesia reduced the incidence of awareness with recall by approximately 82%.[39] The PSI, a 4-channel processed electroencephalograph, also uses a digital scale to determine depth of anesthesia and has been proven efficacious in allowing the practitioner to titrate anesthetic, allowing faster emergence.[40]

It is tempting to extrapolate the results from the anesthesia literature into the assessment of sedation in the ICU. Unfortunately, these devices have not been studied completely to standardize their use in the ICU setting. Thus far, BIS has shown several limitations in the ICU environment. For instance, in the absence of neuromuscular blockade, muscle-based electrical activity may artificially elevate BIS scores.[34] Nasraway and colleagues suggested a suboptimal and inconsistent correlation between BIS and the SAS.[41] The authors attributed these findings to the influence of excessive muscle movement by the patient on the BIS values and reliability. A more recent study suggests that BIS use does not provide additional benefits in terms of amount of sedation used, the length of mechanical ventilation time, or the length of ICU stay.[42] There is not significant literature supporting the use of the PSI in the ICU either. Additionally, they do not seem able to detect delirium.[43] Therefore, routine use of these devices cannot be recommended for assessment of sedation in the ICU until the value and validity are confirmed.

Another point of consideration is the means by which sedation is provided in the ICU setting. Oftentimes, critically ill patients who are mechanically ventilated are given continuous intravenous infusions of sedative drugs to treat anxiety and agitation. This provides a more constant level of sedation and results in increased patient comfort.[44] However, continuous infusions of sedatives have some disadvantages. Continuous infusions result in the accumulation of the drugs and accompanying delays in the improvement of mental status, prolong ventilator requirements, prolong ICU stays, and increase the likelihood of developing ventilator-associated pneumonias. Also, extended sedation prevents adequate assessment of mental status, especially in neurologic injury. It also limits the clinician's ability to interpret physical examinations. In a randomized, controlled trial involving 128 adult patients who were receiving mechanical ventilation and continuous infusions of sedative drugs in a medical ICU setting, Kress et al. found that daily interruption of sedative drug infusions decreased the duration of mechanical ventilation and the length of stay in the intensive care unit.[45] Furthermore, the study showed a decrease in the use of benzodiazepines and improvement in the ability of the clinicians to perform daily neurologic examinations. This reduced the need for diagnostic studies to evaluate unexplained alterations in mental status.

Agents Used for Sedation

The SCCM guidelines propose an algorithm approach as a general guideline for the use of sedatives in the critically ill.[6] It is important to note that having clearly defined assessment methods and goals for sedation are a key part of this proposed pathway. In addition, correcting potential causes, environmental modifications, and pain control are considered in the initial steps of the algorithm. Once those steps are taken, as discussed previously, we can touch upon the medications used

for sedation. We will discuss benzodiazepines, propofol, and alpha-agonists. Haloperidol and atypical antipsychotics will be described in the delirium section.[6,46]

Benzodiazepines

This group of drugs includes sedatives and hypnotics that block the acquisition and encoding of new information and potentially unpleasant experiences (anterograde amnesia) but do not induce retrograde amnesia.[6] Their mechanism of action is the potentiation of the inhibitory effects of the GABA receptor system in the central nervous system. Although they lack any analgesic properties, they have an opioid-sparing effect by moderating the anticipatory pain response. They do not have significant hemodynamic effects unless given in large bolus doses particularly to a hypovolemic patient. Midazolam is suggested in acute agitation events due to its rapid onset of action and short half-life. Long-term infusions with midazolam are not recommended, since it will accumulate in peripheral tissues and lead to a prolonged elimination time once the infusion is stopped. Due to its lower lipid solubility and lack of active metabolites, lorazepam has been used when sedation is anticipated for longer periods of time. Although the use of this medication is widespread, recent data suggest that it can be a risk factor in the development of delirium.[47] In addition, if large doses of lorazepam are needed to achieve the desired level of sedation, developing a hyperosmolar anion gap acidosis secondary to propylene glycol is a potential risk.[48]

Propofol

Propofol is an intravenous, general anesthetic agent. However, sedative and hypnotic properties can be demonstrated at lower doses.[6] Compared with benzodiazepines, propofol produces a similar degree of amnesia at equisedative doses in volunteers. Propofol has a rapid onset and short duration of sedation once discontinued. This is a major advantage in the critical care population. Adverse effects most commonly seen with propofol include hypotension, bradycardia, and pain upon peripheral venous injection. The hypotension is dose related and more frequent after bolus dose administration or in the hypovolemic patient.

Propofol is available as an emulsion in a phospholipid vehicle, which provides 1.1 kcal/mL from fat and should be counted as a caloric source. Hypertriglyceridemia and pancreatitis have been reported following use of propofol in the ICU and routine monitoring of serum triglycerides is suggested.[49]

Recently, reports of the propofol infusion syndrome (PIS) have populated the literature. A recent review by Kam et al. describes this entity.[50] PIS is characterized by cardiovascular collapse with acute refractory bradycardia leading to asystole, in the presence of one or more of the following: metabolic acidosis, rhabdomyolysis, hyperlipidemia, and enlarged or fatty liver. There seems to be a relation between a dose higher than 80 mcg/kg/min and a duration of the infusion for more than 48 h.[50,51] The risk might be increased when catecholamines are administered simultaneously and in the head injury patient.[51,52] It is proposed that the syndrome may be caused by either a direct mitochondrial respiratory chain inhibition or impaired mitochondrial fatty acid metabolism mediated by the propofol. Additionally, this drug requires a dedicated intravenous catheter when administered as a continuous infusion because of the potential for drug incompatibility and risk of contamination. Fospropofol disodium (AQUAVAN®, MGI Pharma, Minneapolis, MN) is a water soluble prodrug of propofol that when hydrolyzed releases propofol and might resolve the issues related to the fat content in propofol, but clinical trials are still ongoing.[53]

Alpha-Agonists

Recently, the role of central alpha-agonists for sedation in the ICU has increased and will probably play an expanding role in the future. Clonidine has been used to augment the effects of other sedation agents as well as opioids and to treat drug withdrawal syndromes in the ICU.[54,55] As it takes 48 h to achieve therapeutic blood levels with the patches, enteric administration for the first 48 h is recommended. The more selective [alpha]-2 agonist, dexmedetomidine, is approved for use as a sedative with analgesic-sparing activity for short-term use (<24 h) in patients receiving mechanical ventilation. Patients remain sedated when undisturbed, but arouse readily with gentle stimulation. Dexmedetomidine reduces concurrent analgesic and sedative requirements and produces anxiolytic effects comparable to benzodiazepines with no concomitant respiratory depression. In terms of side effects, bradycardia and hypotension may occur – oftentimes correlated with bolus infusion, particularly if intravascular volume depletion and/or high sympathetic tone are present. The use of dexmedetomidine beyond the 24-h period has been reported, as well as the use for drug withdrawal and even delirium.[56,57] Despite these reports, the role of dexmedetomidine in ICU clinical practice is limited because of a lack of mortality and other morbidity endpoints, such as ICU length of stay, hospital length of stay, time to extubation, long-term complications after discharge from the ICU, and delirium.[58] Furthermore, cost and the 24-h time limitation may be barriers to a more widespread use of this agent in the ICU.

Delirium

While goal-directed analgesia and sedation might provide many ICU patients with much needed comfort and relief, it is only one of a number of environmental and treatment-related factors that may contribute to the development of delirium in the critically ill patient. Once believed to be a common and somewhat accepted complication of ICU care, delirium is now believed to be preventable in some instances.[59,60] Delirium is beginning to be identified as a prognostic marker of more

insidious outcomes and may be used to identify brain failure during acute illness.[5] Literature documents the continuation of cognitive decline in ICU survivors, oftentimes lasting from months to years after hospital discharge.[61] Shockingly, in many cases, delirium is oftentimes neither monitored for nor assessed by ICU clinicians during routine patient care. This is despite the Society for Critical Care Medicine's (SCCM) 2002 guideline recommendation for daily delirium assessments incorporated into patient care along with sedation and analgesia assessments.[6]

One of the many obstacles facing clinicians is the many synonyms in medical terminology for this syndrome. Commonly used terms for delirium include: ICU psychosis, septic encephalopathy, ICU encephalopathy, acute brain dysfunction, confusion, etc. Using appropriate terminology may help to foster increased monitoring and recognition of delirium in daily patient care.

Delirium exists in three essential subtypes: hyperactive, hypoactive, and mixed (Fig. 9.1). Unfortunately, delirium is commonly diagnosed only when the patient has exhibited signs of hyperactive behavior; usually in the form of pulling at lines, attempts at self-extubation, grabbing at staff personnel, etc. This poses a problem, given that only about 5% of ICU patients exhibit purely hyperactive delirium. Hypoactive and mixed subtypes are much more predominant (>60% each).[62] This notion of delirium manifested by aggressive behavior, in conjunction with the perception from health care givers that delirium is an anticipated occurrence of ICU care,

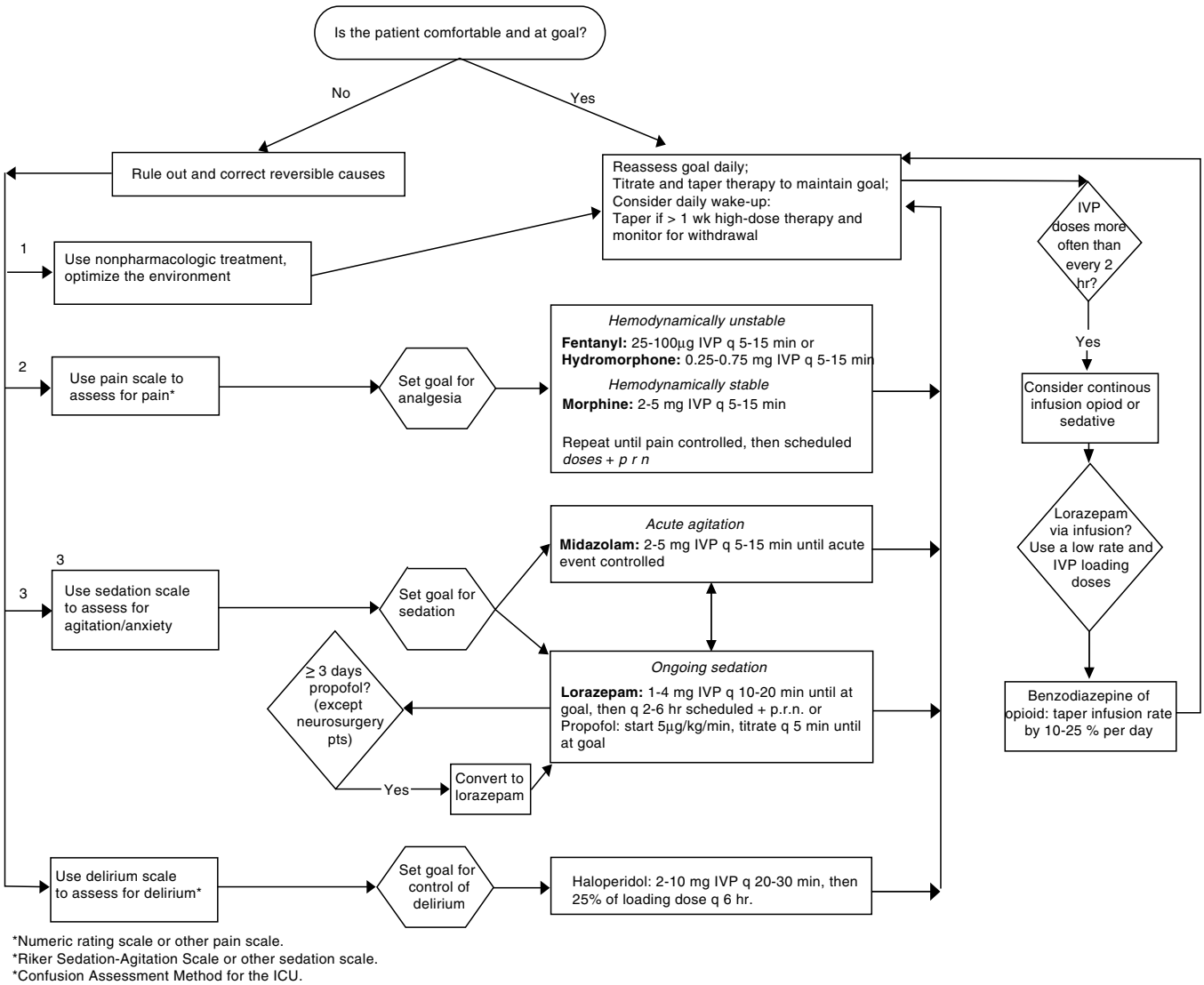

FIG. 9.1. Delirium exists in three essential subtypes: hyperactive, hypoactive, and mixed. Reprinted with permission from Jacobi J, Fraser G, Coursin DB, et al. Clinical Practice Guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30:119–141, WoltersKluwer.

compounds the appropriate recognition and treatment of the syndrome.

Classically, delirium is defined as an acute onset or change in mental status, inattention, disorganized thinking, and disturbance in consciousness, and is caused by the general medical condition. Since many patients in the ICU are intubated, sedated, and otherwise unable to articulate, assessment of delirium is an issue. There are, however, several bedside tools that are clinically validated for the diagnosis of delirium.[63,64] Both of these tools incorporate features from the DSM IV definition of delirium and are relatively simple and easy for daily clinical use. The CAM-ICU tool has been reported most frequently in the literature and incorporates both a sedation assessment (by means of the RASS) and delirium assessment, making it time efficient for use in clinical practice by completing two clinically essential assessments at once. The incorporation of scales and objective assessments into patient care may help to achieve appropriate levels of sedation and analgesia, help prevent transition to delirium, and provide a common means to communicate sedation, analgesia, and delirium goals between clinicians.

There are multiple hypotheses for the pathophysiology and etiology of ICU delirium. The brain is postulated to possess its own local inflammatory response in response to, or in conjunction with, a systemic response.[65] Delirium may be related to a dysregulation of the neurotransmitters gamma-aminobutyric acid (GABA), acetylcholine, and dopamine. Other potential factors contributing to the development of delirium may be: mechanical ventilation, electrolyte abnormalities, restraints, catheters, medications, and hypoxemia.

It is estimated that the average ICU patient possesses ten risk factors for delirium at one time. Older patients and patients with a previous history of cognitive impairment or psychiatric disease are at much greater risk of developing delirium. Other common risk factors include: psychoactive medications, drug or alcohol use, surgery, severity of illness, functional status, catheterization, visual/audio deficits, sleep deprivation, and untreated pain. Psychoactive medications, particularly benzodiazepines, are noted to be a leading cause of transitioning into delirium. Investigators have found that cumulative lorazepam administration greater than 20 mg was an independent risk factor for transitioning into delirium.[47] Undoubtedly, the routine administration of psychoactive medications as a standard practice of ICU care increases the prevalence of delirium. This further enforces the need of performing assessments and titrating sedation/analgesia therapy to predefined endpoints by means of scales and objective measures. Alternatively, a benzodiazepine-sparing approach to sedation, using propofol or dexmedetomidine, may prevent the transition into delirium, though this has yet to be validated in a well-conducted trial.

The incidence of delirium portends significant consequences. Delirium, by itself, is an independent risk factor for mortality amongst mechanically ventilated critically ill patients.[5] After controlling for severity of illness, previous comorbidities, coma, and the use of psychoactive medications, delirium was associated with a threefold greater rate of mortality. This is in accordance with earlier work in hospitalized ward patients.[66] Additionally, the development of delirium was associated with a longer ICU/hospital length of stay and increased costs.[67] In fact, the incidence of delirium was independently associated with 30% greater hospital costs. When scaled to adjust for severity of delirium, there was an association between delirium severity and hospital costs; that is, the more severe the delirium, the greater the associated cost of care. However, it should be noted, that all of these data come from work in medical ICU patients. There are data that the presence of delirium in critically ill surgical patients is associated with fewer ventilator-free days and longer ICU and hospital length of stay.[4] Whether delirium is an independent risk factor for mortality in surgical ICU patients remains to be answered.

Since the development of delirium in the ICU may be the result of practices ingrained in ICU care, it would be prudent to develop a multidisciplinary approach to the prevention and treatment of delirium. First and foremost, the development and implementation of a large-scale sedation, analgesia, and delirium assessment tool for use by all clinicians seems intimidating. However, it is evident that this is quite possible, as evidenced by the Vanderbilt experience and many other institutions.[68] There is evidence that delirium can be prevented through concerted efforts affecting multiple points of patient care. The Yale Delirium Prevention Trial focused on six factors for hospitalized general medical patients: (1) orientation activities, (2) early mobilization, (3) nonpharmacologic support to decrease use of psychoactive medications, (4) prevention of sleep deprivation, (5) eyeglasses and hearing aids for impaired patients, (6) and noise reduction. Additionally, a study of elderly postoperative hip fracture patients focused on: (1) oxygen delivery to the brain, (2) fluid and electrolyte replacement, (3) analgesia, (4) bowel and bladder function, (5) nutrition, (6) mobilization, (7) prevention of postoperative complications, (8) environmental stimuli, (9) treatment of delirium symptoms, and (10) reduction of psychoactive medications.[59] Both of these projects were effective in reducing the development of delirium in ward patients. Unfortunately, there is no evidence to date in the ICU literature that prevention is effective in decreasing the development of delirium. However, this should not serve as a deterrent to institutions in developing a formalized plan to decrease the incidence of delirium.

Once diagnosed, it is easy to jump to pharmacologic means to treat delirium, mistakenly using benzodiazepines for this goal. However, since the use of medications is frequently a large cause of the development of delirium, it would seem logical to begin treatment by identifying deliriogenic medications and limiting and/or removing their use. Though psychoactive medications, such as opioids and benzodiazepines, are commonly used in ICU care, it seems reasonable that if use is targeted to achieve clinical endpoints, delirium may be avoided. Also, treating any underlying disease state (i.e., sepsis, hemorrhage, hypoglycemia) is preferred. In addition, simple

interventions can be implemented into standard practice, such as minimizing noise, frequent reorientation, normalizing sleep patterns, removing unnecessary catheters, mobilization, and transfer from the ICU environment.

When resorting to pharmacological treatment of delirium, it should be stressed that there is no evidence to validate any of the discussed recommendations. Using a standard treatment algorithm may not fully apply to each patient, as each patient may have varying and complex etiologies for their delirium. Additionally, since there is no published literature as of yet, no definitive dosing or monitoring recommendations can be made. It is advisable to use the lowest necessary dose for the shortest duration of time to achieve the prespecified goals of therapy. Haloperidol injection can be used to achieve control of the delirious patient. The optimal dosing and regimen of haloperidol have not been well defined. Haloperidol has a long half-life (18–54 h) and loading regimens are used to achieve a rapid response in acutely delirious patients. A loading regimen starting with a 2-mg dose, followed by repeated doses (double the previous dose) every 15–20 min while agitation persists, has been described.[6,46,69,70] Once the desired effects are achieved, haloperidol is commonly given via intermittent intravenous injection. Many clinicians fear the side effect profile of haloperidol (neuroleptic malignant syndrome, QTc prolongation, dystonic reactions, etc.) though these may be rare with brief use in the ICU setting. Some clinicians favor using "atypical" antipsychotic medications (olanzapine, quetiapine, risperidol, and ziprazidone) to avoid these side effects. Also, "atypical" antipsychotics may have a broader effect on neurotransmitters than haloperidol, also affecting serotonin, acetylcholine, and norepinephrine to elicit a potentially greater cognitive effect. They can be provided via the enteric route, which is an obvious advantage. However, caution should be used as these drugs can have multiple drug interactions

Knowing the adverse survival and posthospital discharge effects of delirium, it is now incumbent on ICU caregivers to focus on the prevention, assessment, and treatment of delirium. Given the recent burst of literature into this field of ICU care and drawing from previous non-ICU research, there is hope that delirium management in the ICU can be improved. However, a multidisciplinary approach is necessary to achieve positive outcomes.

Conclusions

Sedation and analgesia remain a formidable challenge to the intensivist-led team providing care to the critically ill. However, better assessment tools to determine initiation of therapy, choice of agents, and subsequent adjustments to desirable levels help us to keep our patients pain free and comfortable while recovering from a critical illness. As we gain more knowledge and develop better understanding of delirium and its causes, we will be better prepared to utilize the nonpharmacological and pharmacological therapies to manage this entity.

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10
Neuromuscular Blocking Agents

Rafael A. Ortega, Gerardo Rodríguez, and Rubén Azocar

Neuromuscular blocking agents have, perhaps, the most fascinating history among the drugs used in anesthesiology and intensive care. For centuries, South American aborigines had used curare to hunt animals before Claude Bernard showed in 1850 that these drugs act peripherally, blocking conduction where motor nerves meet the muscle.[1] These historical facts should serve to remind us that this group of drugs is lethal when misused and that while paralysis occurs, intellectual function remains unaffected.

The administration of sedatives and analgesics does not preclude the possibility of patient awareness. Considering that recall can occur even under general anesthesia, it is not surprising that paralyzed patients in the intensive care unit (ICU) may experience unrecognized wakefulness.[2] Being paralyzed and in pain can be horrifying. The experience may lead to serious psychological consequences ranging from anxiety attacks to sleep disturbances, nightmares, and flashbacks. This neurotic condition is now commonly referred to as posttraumatic stress disorder. It is imperative to pay meticulous attention to the sedation and analgesia of patients when they are pharmacologically paralyzed. When health care providers suspect awareness, communicating with the patient using touch and words of encouragement has been suggested to attenuate psychological distress.[3]

Neuromuscular blocking agents are indeed a double-edged sword in the ICU. They can be lifesaving in critical situations, such as airway management and respiratory failure, but they also can cause serious complications, including venous thrombosis, bedsores, and muscle atrophy. The worst scenario is undoubtedly the inability to ventilate or intubate the patient's trachea after the administration of one of these drugs. Individuals administering neuromuscular blocking agents must be experienced in airway management, and resuscitation equipment must be readily available.

However, since the introduction in 1942 of curare as a muscle relaxant during general anesthesia, neuromuscular blocking agents have gradually secured their place, despite their inherent dangers, and continue to be one of the most useful tools in the management of the surgical and critically ill patient. The variety of neuromuscular blocking agents and the understanding of monitoring techniques have increased considerably over the last two decades. The purpose of this chapter is to provide an overview of the pharmacology, indications, and considerations when using neuromuscular blocking agents in the management of patients in the ICU.

Indications

There are many situations in the ICU during which the use of neuromuscular blocking agents may be indicated.[4,5] Although there are practice parameters for the use of these agents, there are few data in adults that confirm that outcome is improved by their use.[6,7] The most frequent indication is respiratory failure with decreased pulmonary and chest wall compliance and high ventilatory pressures.[8] Some believe that maximum effort should be made to achieve the most effective ventilation with sedatives and analgesics before using a paralytic agent.[9] However, there are many patients who are best managed with the addition of a neuromuscular blocking agent. In addition,

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there are clinical situations, such as the prevention of shivering, in which paralysis may be indicated independent of the ability to optimally ventilate a patient.

The following is a list of possible indications for use of neuromuscular blocking agents in the critically ill patient:

- Airway management
- Decreased chest wall and/or pulmonary compliance
- Respiratory asynchrony with mechanical ventilation
- Elevated airway pressures (reducing barotraumas)
- Muscular rigidity, such as in tetanus,[10] status epilepticus, and others
- Intracranial hypertension[11,12]
- Central neurogenic hyperventilation
- Severe agitation refractory to sedative hypnotics
- Facilitating procedures or diagnostic tests
- Prevention of shivering
- Minimizing metabolic demands and oxygen consumption[13]
- Maintaining stable surgical drafts

Neuromuscular Transmission Physiology

Striated muscles are innervated by myelinated fibers originating in the anterior horns of the spinal cord.[14,15] These motor neurons shed their myelin as they approach the skeletal muscle fibers and divide into branches called nerve terminals. There is no physical contact between the nerve terminal and the motor fiber. This gap, which is called the synaptic cleft, is where the neuromuscular blocking agents exert their paralyzing effects. Although cardiac and smooth muscle contract by different mechanisms, neuromuscular blocking agents can indirectly influence them. For example, curare may release histamine and cause bronchospasm, and pancuronium can block muscarinic cardiac receptors and trigger tachycardia.

Acetylcholine is synthesized in the motor nerve terminal and stored within nerve fiber endings. Acetylcholine release occurs both spontaneously and by the arrival of a nerve impulse. Calcium is an important ion in this neuromuscular release process. Acetylcholine release is greatly depressed by the absence of calcium. After acetylcholine is released, it diffuses across the neuromuscular junctional cleft and binds to the nicotinic receptors on the motor end plate. This causes changes in the ion permeability of the receptor. Sodium and calcium ions move inward and potassium moves outward, which results in an increase in the positive direction in the resting potential of the membrane (from −90 to −45 mV or as much as 74 mV). The change in the transmembrane potential is referred to as the end plate potential. When this threshold potential is reached, the action potential propagates over the surface of the muscle fiber, activating the excitation-contraction coupling mechanism and resulting in contraction. The membrane repolarizes when acetylcholine is hydrolyzed and broken down by acetylcholinesterase (Fig. 10.1).

Pharmacology

Neuromuscular blocking agents can be divided by their chemical structure into benzylisoquinolines and steroidal nucleus group; by their duration of action into ultrashort, short, intermediate, and long acting; and by the type of block into depolarizing and nondepolarizing[16] (Table 10.1). The choice of a neuromuscular blocking agent for sustained paralyses in

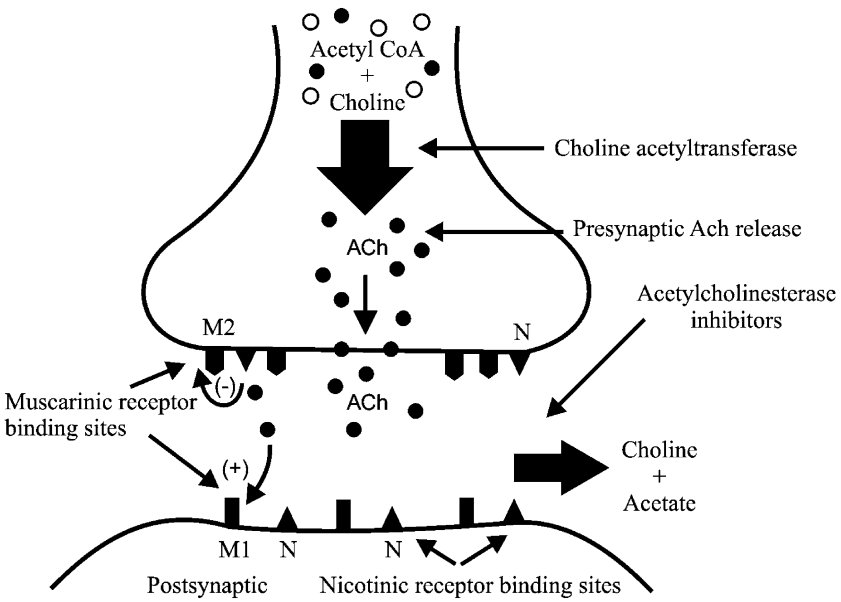

FIG. 10.1. Motor nerve terminal.

Table 10.1. Neuromuscular blocking agents by mechanism of action and duration of action.

Neuromuscular Blocking Agents	Ultrashort action	Short action	Intermediate action	Long action
Depolarizing	Succinylcholine	–	–	–
Nondepolarizing	–	Mivacurium[a]	Atracurium	d-Tubocurarine
		Rapacuronium[a]	Cisatracurium	Doxacurium
			Rocuronium	Metocurine
			Vecuronium	Pancuronium
				Pipecuronium[a]

[a]No longer commercially available in the USA.

the ICU must be guided by an understanding of the properties of the drug and by a cost-benefit analysis.[17] The relevant pharmacologic features of each neuromuscular blocking agent are discussed below.

Depolarizing Drugs

Succinylcholine is unique among the neuromuscular blocking agents. It is the only depolarizing drug in clinical use. Succinylcholine has the fastest onset of action and shortest duration of all neuromuscular blocking agents used today. Its chemical structure is unrelated to the benzylisoquinolinium or the steroidal nucleus group; rather, it resembles acetylcholine both in structure and in actions.

Succinylcholine binds to the nicotinic receptors mimicking the action of acetylcholine, thus causing depolarization across the postjunctional membrane. When compared with acetylcholine, the ester hydrolysis of succinylcholine by plasma cholinesterase is slow. This results in prolonged depolarization, which prevents normal recovery and renders the membrane unresponsive to acetylcholine. Succinylcholine's many effects stem from its similarity to the physiologic neurotransmitter. It has numerous adverse effects, including hyperkalemia (particularly in the presence of motor neuron denervation, such as critical illness polyneuropathy), dysrhythmias, and muscle fasciculations[18] (Table 10.2).

An elusive pharmacologic goal has been to find a drug with the rapid onset and very short duration of action of succinylcholine. In 1999, rapacuronium, a nondepolarizing neuromuscular blocking agent, was introduced into clinical practice.[19] Its pharmacologic profile challenged succinylcholine's supremacy as the fastest and shortest acting neuromuscular blocking agent. Rapacuronium rapidly gained popularity and indeed was used in lieu of succinylcholine for a variety of indications. Unfortunately, rapacuronium was found to trigger severe bronchospasm,[20] and several deaths resulted from its use. This led to the manufacturer voluntarily withdrawing it from the market. Thus, the quest for a drug with a pharmacologic profile similar to succinylcholine continues.

The main indication for use of succinylcholine in the critically ill patient is for rapid airway management. Although this drug is classified as an ultrashort neuromuscular blocking agent, a clinician must never rely on this brevity of action as protection against failed mask ventilation or endotracheal intubation attempts.

Table 10.2. Potential side effects of succinylcholine.

System	Effect
Cardiovascular	Bradycardia[a]
Central Nervous System	Increase in intracranial pressure
Gastrointestinal	Elevation of intragastric pressure
Musculoskeletal	FasciculationsMuscle pains
	Prolong paralysis[b]
Metabolic	HyperkalemiaTrigger for malignant hyperthermia
Ocular	Increase of intraocular pressure

[a]Increased risk of bradycardia especially after repeated dosing.
[b]Prolonged paralysis may occur due to pseudocholinesterase deficiency, excessive dosage, or repetitive dosing.

Nondepolarizing Muscle Relaxants

Atracurium

Atracurium is broken down by the Hoffmann's elimination process and ester hydrolysis independent of plasma cholinesterase. The Hoffmann elimination process is dependent on temperature and pH. Cold temperature and acidosis slow down the process. This drug is useful in patients with renal failure because its biodegradation is completely independent of kidney function. Atracurium releases histamine and may cause hypotension. Use of atracurium over a long period may lead to the accumulation of laudanosine, a breakdown product known to cause seizure activity in animals. Although, its potential for central nervous system effects is a consideration, atracurium has been used in the ICU, and toxic concentrations of laudanosine are difficult to attain, even in critically ill patients.[21]

Cisatracurium

Cisatracurium is one of the many isomers that form atracurium. It is more potent than atracurium without causing significant hemodynamic changes because it does not release much histamine. Cisatracurium also is biodegraded by the Hoffmann's elimination process and ester hydrolysis, but its

breakdown generates less laudanosine formation. This drug can be useful in the ICU because it does not significantly alter hemodynamics. Therefore, it compares favorably with steroid derivatives allowing faster recovery from the neuromuscular block when an infusion is discontinued. The drug's duration of action is minimally affected by kidney or liver disease.[22] Studies have compared atracurium and cisatracurium by continuous infusion in critically ill patients. Appropriate levels of neuromuscular blockade were achieved with both drugs, but lower doses of cisatracurium were required for the same degree of relaxation.[23,24]

d-Tubocurarine

Curare is the oldest, and the prototype of the clinically available nondepolarizing neuromuscular blocking agents. It is rarely used today except to prevent succinylcholine-related muscle fasciculations. The use of neuromuscular blocking agents to prevent fasciculations does not prevent succinylcholine-related hyperkalemia. d-Tubocurarine releases histamine and frequently causes hypotension, particularly after it is rapidly injected.

Doxacurium

Doxacurium chloride is a mixture of three stereoisomers. It is a long-acting, neuromuscular blocking agent without active metabolites. Doxacurium is the most potent neuromuscular blocking agent available today and it has no autonomic, cardiovascular, or histamine-releasing side effects.[7,25] Doxacurium has been used in critically ill patients. However, its use in the presence of renal dysfunction is cautioned due to a potential for prolonged neuromuscular recovery.[26] It is rarely used in the ICU. Its potency may make it a cost-effective choice in carefully selected patients.

Metocurine

Metocurine is a d-Tubocurarine analog; however, it releases less histamine and triggers fewer hemodynamic changes. It is contraindicated in patients with iodide sensitivity. Metocurine is rarely used today in the operating room or ICU.

Mivacurium

Mivacurium, a benzylisoquinoline of short to intermediate duration of action, was discontinued from production in 2006. It was the only other neuromuscular blocking agent that was broken down by plasma cholinesterase; and, therefore, could result in an intense and prolonged neuromuscular block in patients with the atypical enzyme.[27] Fast injection could cause enough histamine release to result in transient but significant hypotension. Its withdrawal leaves a void in the short acting category of neuromuscular blocking agents.

Pancuronium

Pancuronium is the oldest of the aminosteroidal neuromuscular blocking agents and, according to the Society of Critical Medicine's practice guidelines, it is the preferred paralytic agent for most critically ill patients.[6] Although pancuronium triggers tachycardia secondary to is vagolytic properties, it is rarely of clinical consequence in patients who have no cardiac disease.

Pipecuronium

A long-acting neuromuscular blocking agent, pipecuronium is no longer commercially available in the USA or Canada. Though it resembles pancuronium in potency and chemical structure, it does not have significant cardiovascular effects. Pipecuronium has been used to maintain patients paralyzed in the ICU.[28]

Rapacuronium

Rapacuronium, an aminosteriod, nondepolarizing drug, is no longer available in the USA. As mentioned earlier, this drug had the potential to replace succinylcholine in many situations because of its rapid onset and short duration of action. In 2001, the manufacturer voluntarily withdrew rapacuronium bromide (Raplon®) from the market after receiving reports of severe bronchospasm after its administration.[20]

Rapacuronium has an onset of action of 1 min and a clinical duration of less than 20 min. Although it resembled succinylcholine's rapid onset of action,[28] its duration was longer. To terminate its effects in a manner resembling succinylcholine's duration, the administration of an anticholinesterase agent was required.[30] Despite its unique properties, succinylcholine still remains the only true ultrashort acting neuromuscular agent.

Rocuronium

Before the introduction of rapacuronium, a rapidly acting neuromuscular blocking agent, rocuronium, was probably the most appropriate choice as a nondepolarizing alternative to succinylcholine during rapid-sequence induction of anesthesia. Rocuronium has been used as a continuous infusion in the ICU.[31]

Vecuronium

Vecuronium, an aminosteroidal drug without significant hemodynamic effects, has been widely used in the ICU. Its lack of vagolytic properties might make it a preferable agent in patients with cardiac disease.[6] Metabolism is hepatic and its by-products are excreted primarily in the bile. The active metabolite, 3-desacetylvecuronium, is renally excreted, and therefore may accumulate in renal failure patients.[32]

The administration of these agents by either boluses or infusions has been studied, and with continuous infusions the

amount of drug administered may be larger. However, better control of ventilation and comparable recovery times have been found in groups of patients who received continuous infusion.[33,34]

Monitoring Neuromuscular Block

Soon after the introduction of pancuronium to clinical practice in 1967, it was administered to critically ill patients to manage mechanical ventilation.[35] Subsequently, a variety of agents were introduced. Initially, the effects of these agents were monitored clinically.[36] However, reports of prolonged paralysis and weakness after neuromuscular block began to emerge.[37,38] It has been postulated that these complications may arise from prolonged use of neuromuscular blocking agents and from drug or active metabolite accumulation. In addition, direct damage to the nerve, muscle, or neuromuscular junction has been found.[39] The Food and Drug Administration and pharmaceutical manufacturers have advocated the use of peripheral nerve stimulators in pharmacologically paralyzed patients. Despite these reports and recommendations, a 1992 survey showed that only 34% of anesthesiologists used peripheral nerve stimulation to assess neuromuscular blockade in the ICU.[40] Similar findings have been reported by other authors.[41]

In an effort to develop practice parameters for the use of neuromuscular blocking agents in the critically ill patient, the American College of Critical Care Medicine and the Society of Critical Care medicine have developed practice guidelines for sustained neuromuscular blockade.[6] These guidelines state that clinical monitoring in conjunction with peripheral nerve stimulation is essential to prevent accumulation of the drug or its metabolites.

The impact of prolonged neuromuscular weakness in terms of cost has also been addressed. There appears to be an increase in continued mechanical ventilation and hospital stay. This prolongation of care may have a significant economic impact.[42]

Recent studies compared clinical versus peripheral nerve stimulation monitoring. The researchers demonstrate that the group monitored with peripheral nerve stimulation required smaller doses of drug. Additionally, this group had improved neuromuscular function rate of recovery.[43,44] Unfortunately, the use of peripheral nerve stimulators in critically ill patients can be technically troublesome and may not effectively reflect the degree of respiratory muscle paralysis.

The Nerve Stimulator

Peripheral nerve stimulators generate electrical currents sufficiently intense enough to change the neuron membrane resting potential from baseline to threshold level and generate an action potential. Thus, peripheral nerve stimulation can provide the clinician with an estimate of the intensity of the neuromuscular block. However, clinically, the resulting muscle contraction is usually measured subjectively. The use of a force transducer would provide a graphic representation with response quantification. Different patterns of stimulation with varying implications can be obtained with a nerve stimulator. The most common tests are described.

Single Twitch

The single twitch test is supramaximal stimulus lasting 0.2 ms at a 0.1 Hz frequency. A control baseline muscle twitch is needed to compare the degree of blockade after the administration of a neuromuscular blocking agent.

Sustained Tetanus

The use of high electrical frequencies (greater than 15–20 Hz) can achieve sustained tetanus. Fusion of single contractions occurs and results in a prolonged contraction. After a stimulus of 50 Hz for 5 s, in the presence of a partial block caused by a nondepolarizing neuromuscular blocking agent, the contraction begins to fade. If this does not occur, it can be assumed that the block has disappeared sufficiently to allow the diaphragmatic and the laryngeal musculature to regain strength. However, tetanic stimulation is painful and provokes posttetanic facilitation (i.e., increased response to a stimulus after sustained tetanus).

Train-of-Four

A sequence of four supramaximal stimuli with a frequency of 2 Hz (four stimuli 0.5 s apart) is provided (Fig. 10.2). During partial curarization, fading of the second, third, and fourth twitches is seen or felt. Progressive disappearance of the responses (from the fourth to the first) corresponds to a

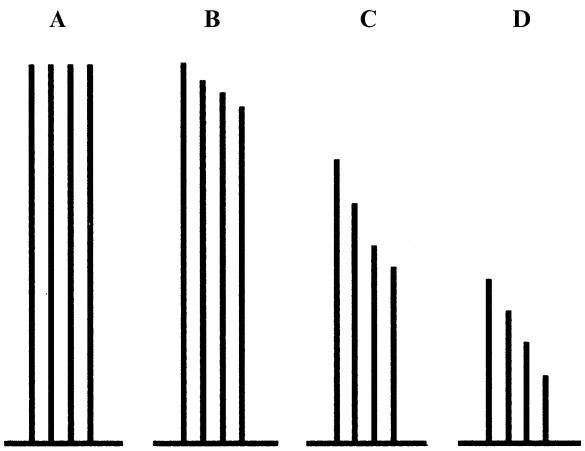

FIG. 10.2. A sequence of four supramaximal stimuli with a frequency of 2 Hz (four stimuli 0.5 s apart).

75%, 80%, 90%, and 100% receptor block, respectively. The ratio between the amplitude or strength of the fourth twitch to the initial one defines the train-of-four ratio. A ratio of 0.75 correlates well with a return of single twitch to baseline, sustained response to titanic stimulation for 5 s, and/or sustained head lift for 5 s. Train-of-four is the recommended pattern of stimulation for ICU monitoring, because it is more comfortable for the patient, does not require a "control" height, and does not induce changes in subsequent stimulation.

Double-Burst Suppression

As residual curarization, it may be difficult to assess fade using the train-of-four ratio. It is advocated that with the use of a frequency of 50 Hz applied twice, 60 ms in duration and 750 ms apart, a fade could be noted in minor degrees of paralysis. Absence of tactile fade double-burst suppression excludes clinically significant block.

Posttetanic Count

In cases of profound neuromuscular blockade where no twitches can be elicited, application of a tetanic stimulus of 50 Hz for 5 s followed by single twitch stimulus 3 s later provides an estimate of the level of paralysis. As the block recedes, and before the train-of-four is present, a posttetanic count response is noted. There is a relation between the number of posttetanic twitches, the degree of blockade, and the time before spontaneous recovery occurs. Train-of-four usually returns with a posttetanic count of 8–12 twitches.

Electrode Placement

The electrodes usually are placed over the ulnar nerve and/or the facial nerve. In the former position, the response is evaluated at the abductor pollicis muscle and in the latter position at the orbicularis oculi muscle. However, one must be careful when evaluating these muscles because the response may not be reflective of the degree of blockade of the diaphragm or accessory muscles of respiration. This is explained by the fact that different muscles have different sensitivities to neuromuscular blockade. Depending on the type of fiber (fast twitch vs. slow twitch), blood flow, and the receptor-muscle ratio, different muscles have different responses. Recovery time for the orbicularis muscle is comparable with the diaphragm and the orbicularis muscle to neuromuscular block.[45–47] This may result in the presence of diaphragmatic activity even though there are no twitches present when monitoring the abductor pollicis. Therefore, it would seem that monitoring of the orbicularis muscle reflects more accurately the degree of paralysis of the respiratory muscles (Fig. 10.3). However, direct stimulation of the orbicularis muscle occurs more easily and may confound the interpretation.

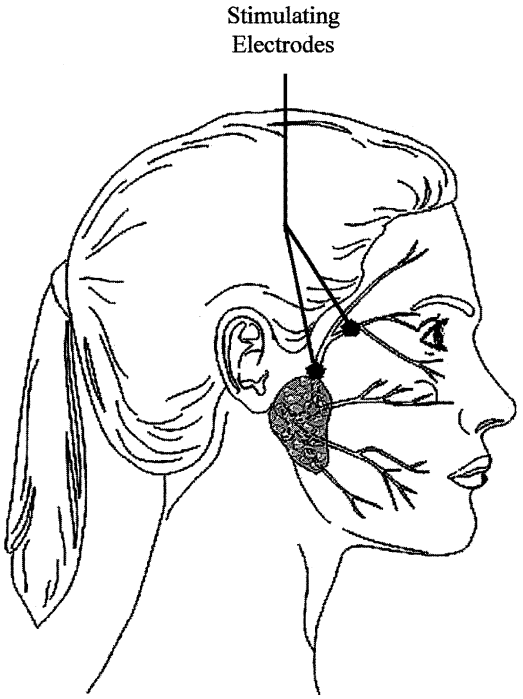

FIG. 10.3. Proper electrode placement for stimulating the facial nerve.

Interpretation Errors

Difficulty in interpreting the results of nerve stimulation can be the result of nerve group differences and device-related errors, among others.[48] Device-related errors are usually related to electrical problems such as weak batteries, inadequate current output, or poor wire integrity. Critically ill patients usually are edematous, and diaphoretic with oily epidermis. This can affect both lead placement and electrical current transmission. Finally, other common sources of error include incorrect anatomic placement or detachment of the electrode pads, the use of visual rather than tactile assessment, and not allowing enough time for repolarization. Combining the clinical monitoring with the use of the nerve stimulator is recommended in order to optimize patient care and minimize complications during chemical paralysis.[5]

Complications of Neuromuscular Blockade

The complications of neuromuscular blockade in the ICU can be described as short-term (ventilator disconnect, accidental extubation), mid-term (edema, hypostasis, bedsores, venous thrombosis), and long-term (prolonged paralysis, muscle atrophy). In addition, the possibility of patient awareness and its deleterious consequences is also present. Many of the controversies surrounding the use of these agents in the ICU are related to long-term complications.

Multiple cases of altered muscle function related to prolonged neuromuscular blockade were reported when these

agents were introduced into the ICU.[33–49] To better understand this phenomenon, Watling and Dasta reviewed the literature from 1980 to 1993[50] and postulated that there are two distinct mechanisms. The first is pharmacokinetic and related to drug accumulation or its active metabolites, resulting in prolonged paralysis. The second is a pharmacodynamic effect, probably related to neuromuscular damage, resulting in a motor neuropathy and manifested clinically as muscle weakness. Other investigators have classified these as short-term and long-term complications. In their view, short-term problems have a pharmacologic explanation, whereas long-term complications seem to be toxic in nature, more complex, and difficult to manage.[51]

Prolonged paralysis has been associated with persistent presence of the drug or its metabolites in plasma. Alterations in renal and hepatic clearance are proposed mechanisms.[52] Inadvertent overdoses, drug interactions[53–55] (Table 10.3), electrolyte imbalances (hypermagnesemia, hypophosphatemia), acidosis, hypothermia, and underlying muscle disorders (polyneuropathy of critical illness, myasthenia gravis) are also involved.[56]

The myopathic phenomenon is less clearly understood. The term acute quadriplegic myopathy (AQM) has been used to characterize this problem.[57] The resultant muscle weakness may require prolonged mechanical ventilation and hospitalization.[37,50,58] Nerve, muscle, or neuromuscular junction damage has been implicated. Clinically, these patients present with paresis or flaccid paralysis of the diaphragm and of both distal and proximal muscles groups. Sensory function and muscle groups innervated by cranial nerves are usually spared. Deep tendon reflexes are also decreased.[59] Plasma creatinine kinase levels may be increased up to 100-fold and electrophysiologic studies reveal a myopathic process with no evidence of neuromuscular transmission disorder or generalized neuropathy.[59–61] Others report electrodiagnostic evidence of necrotizing myopathy.[62,63] There is both histopathologic and electrophoretic evidence of degenerative changes, including fiber atrophy with a general decrease in myofibrillar protein content, partial or complete loss of myosin, and myosin-associated proteins, necrosis, and regeneration involving type 1 muscle fibers.[59,63,64]

There seems to be a relationship between the use of steroidal neuromuscular blocking agents and the concomitant use of large doses of corticosteroids in the patients who develop myopathies.[64] This was initially reported in patients with status asthmaticus who received this combination of drugs.[65–67] Apparently, denervation increases the number of glucocorticoid receptors in the muscle, which may lead to an abnormal response to steroidal drugs.[68]

However, other mechanisms of injury appear to be involved because similar cases have been reported with the use of benzylisoquinolones.[19,69,70] Also, AQMs in the ICU, unrelated to the use of steroids or paralytic agents, have been reported.[71] The mediators of the systemic inflammatory response during sepsis, ischemia, and prolonged inactivity are mentioned as contributing factors in what seems to be a multifactorial entity.[63,64,72]

Table 10.3. Drug interactions with neuromuscular blocking agents.

Drug	Effect on muscle blockade
Antibiotics(amiglycosides, vancomycin, clindamycin, tetracycline, bacitracin)	Potentiation
Anticonvulsants(phenytoin, carbamazepine)	Resistance
Antidysrhythmics(lidocaine, calcium channel blockers, quinidine, procainamide)	Potentiation
Antihypertensives(trimethaphan, nitroglycerine only for pancuronium)	Potentiation
Dantrolene	Potentiation
Furosemide (Dose related)	
• <10 µg/kg	Potentiation
• 1–4 mg/kg	Resistance
Ketamine	Potentiation
Local anesthetics	Potentiation
Magnesium sulfate	Potentiation
Steroids	Potentiation

Reversal of Neuromuscular Blockade

In order to achieve the return of neuromuscular function after the administration of neuromuscular blocking agents, there are two options. The first is to await spontaneous recovery. The second is to chemically reverse the nondepolarizing neuromuscular block with a combination of acetylcholinesterase inhibitors and anticholinergic agents.

With the exception of succinylcholine, neuromuscular blocking agents act competitively to antagonize acetylcholine at the neuromuscular junction. Inhibition of acetylcholinesterase, the enzyme responsible for the inactivation of acetylcholine, results in more acetylcholine available at the neuromuscular junction. This causes displacement of the muscle relaxant and reestablishes neuromuscular function. This is the desired effect of acetylcholinesterase inhibitors at the nicotinic receptors when used to reverse a paralytic agent. However, the acetylcholine increase also affects muscarinic receptors by producing unwanted side effects such as bradycardia and bronchospasm. In clinical practice, only reversible acetylcholinesterase inhibitors are used.

The most commonly used agents are neostigmine and edrophonium.[73] Although neostigmine is less potent than edrophonium, its effects last longer because of the presence of a covalent bond. Edrophonium only attaches to acetylcholinesterase by electrostatic attraction and hydrogen bonding. The choice of agent and the time needed to obtain full reversal depends on the muscle relaxant used and the degree of block. As a general rule, if there is no evidence of muscular function by peripheral nerve stimulation, such as train-of-four with no twitches or no response to sustained tetanus, reversal should not be attempted. Excessive doses of an acetylcholinesterase inhibitor may have the paradoxical effect of potentiating a neuromuscular block.

Table 10.4 Reversal of neuromuscular blockade: cholinesterase inhibitors, ideal anticholinergic combinations, and dosages.

Anticholinesterase drug	Recommended dosage	Ideal anticholinergic combination	Recommended dose per mg of anticholinesterase drug
Neostigmine	0.04–0.08 mg/kg	Glycopyrrolate	0.2 mg
Edrophonium	0.5–1 mg/kg	Atropine	0.014 mg

Unwanted muscarinic effects from an acetylcholinesterase inhibitor can be attenuated with the administration of an anticholinergic drug. Atropine and glycopyrrolate are the most commonly used drugs for this purpose. Atropine has a faster onset of action than glycopyrrolate. Thus, it is usually combined with edrophonium while the slower acting glycopyrrolate is more commonly paired with neostigmine (Table 10.4).

Sugammadex

Sugammadex is a novel neuromuscular reversal agent currently under investigation. Its radical pharmacology might obviate the utility of certain neuromuscular blocking and reversal agents in the near future. A modified gamma-cyclodextrin with unique selective relaxant binding properties, sugammadex forms a tight, hydrophilic complex with steroidal blocking agents.[74] It does not bind to benzylisoquinolinium-based drugs. Sugammadex binds rocuronium 1:1 with high affinity. It also binds to vecuronium and pancuronium, but to a lesser extent. The rapid binding of sugammadex to rocuronium produces a rapid reversal of intense neuromuscular blockade.[75] The highly hydrophilic complex is efficiently renally excreted. There are no apparent side effects, either with the administration of sugammadex or the resulting complex. The rapid reversal of profound neuromuscular blocks by sugammadex may change the way succinylcholine is employed. Sugammadex will allow the administration of high doses of rocuronium to allow for a rapid onset of action and its effects can be rapidly terminated by the administration of sugammadex.

Conclusions

The use of pharmacologic paralysis in the ICU remains controversial. Although it may benefit some patients, it is not devoid of complications and increments in costs and workload. The following guidelines are offered for the rational use of these agents:

1. Limit using neuromuscular blocking agents to clinical circumstances in which their benefits outweigh the risks. In some scenarios appropriate sedation may be sufficient to obtain the desired effects.
2. Base drug selection on their pharmacological properties and the patient's clinical picture.
3. Combine clinical monitoring with the use of a nerve stimulator. Prolonged paralysis or weakness increases morbidity and hospitalization costs.
4. Recognize drug interaction and disease states that potentiate or prolong their action.
5. Consider costs.
6. Ensure sedation and analgesia in paralyzed patients.

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11
Optimization of the High-Risk Surgical Patient

Nawaf Al-Subaie and Andrew Rhodes

The normal acute physiological response to critical illness is to increase the oxygen delivery and consumption. Normal values are considered abnormal in the context of acute critical illness, and patients who achieve specific supra-normal hemodynamic variables have a better outcome. This forms the basis of optimization as these hemodynamic variables attained by survivors become a therapeutic target that achieved artificially by the use of intravenous fluids and inotropes under the guidance of cardiac output monitoring. This approach has been shown to improve the tissue oxygenation and prevents organ dysfunction and death in the high-risk patients undergoing major surgery.[1,2] This chapter focuses on the perioperative optimization and the reader should refer to relevant chapters for the specific management of trauma and sepsis.

There are more than 2.8 million surgical operations performed every year, resulting in 20,000 deaths within 30 days of an operation according to the National Confidential Enquiry into Post Operative Deaths (NCEPOD) in England, Wales, and Northern Ireland. The risk of death in a surgical population is less than 1%; however, some patients undergoing major surgery have a mortality of 15–50%. This is mainly observed in patients with limited physiological reserves, requiring emergency surgical procedures.[3] It is, therefore, important to be able to identify the patients at risk and apply appropriate clinical interventions to reduce the risk of morbidity and mortality.

Identifying the High-Risk Patient

A number of scoring systems exist that help in the identification of high-risk patients. American Society of Anesthesiologists status (Table 11.1) is widely used as part of the preoperative anesthetic assessment, but it is subjective and lacks accuracy in determining the risk associated with a specific procedure. The Goldman cardiac risk index (Table 11.2) is a compilation of factors that correlate with the development of postoperative cardiac complications.[4] The physiological and operative severity score of the enumeration of mortality and morbidity (POSSUM) is a well validated scoring system, which can be used in determining the estimated overall morbidity and mortality of surgical populations, and thus accurately identify the patients at risk.[5] Original perioperative optimization work, pioneered by Shoemaker and colleagues, used specific criteria (Table 11.3) to identify patients with an average mortality of about 25%.[1]

Cardiopulmonary exercise testing done on elderly patients scheduled for major surgery shows strong correlation between postoperative mortality and patients' anaerobic threshold.[6] This is the point where aerobic metabolism fails to supply adequate amounts of adenosine triphosphate energy substances to the body, and anaerobic metabolism starts to replace the resultant deficit.[7] Anaerobic threshold is measured by subjecting patients to an increasing level of exercise, with concurrent monitoring of inhaled and exhaled oxygen and carbon dioxide. This method is currently considered the most objective in identifying the at-risk group.

It is important to identify specific groups of patients who may benefit from different perioperative therapeutic strategies, such as beta blockade. The latestAmerican College of Cardiology and American Heart Association 2006 guideline update on the perioperative cardiovascular evaluation for noncardiac surgery lists the indications of the perioperative beta blockade therapy in the light of available evidence.[8]

The Process of Optimization

Shoemaker and colleagues identified certain hemodynamic values that are observed in high-risk patients who survive surgery.[9] The median of these values (Table 11.4) was targeted

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Table 11.1. American Society of Anesthesiologists (ASA) physical status classification system.

I.	A normal healthy patient
II.	A patient with mild systemic disease
III.	A patient with severe systemic disease
IV.	A patient with severe systemic disease that is a constant threat to life
V.	A moribund patient who is not expected to survive without the operation
VI.	A declared brain-dead patient whose organs are being removed for donor purposes

The addition of an "E" indicates emergency surgery.

Table 11.2. Goldman cardiac risk index.[4]

Risk factor	Points
Third heart sound (S3)	11
Elevated jugulovenous pressure	11
Myocardial infarction in past 6 months	10
ECG: premature arterial contractions or any rhythm other than sinus	7
ECG shows >5 premature ventricular contractions per minute	7
Age >70 years	5
Emergency procedure	4
Intra-thoracic, intra-abdominal or aortic surgery	3
Poor general status, metabolic or bedridden	3

Patients with scores >25 had a 56% incidence of death, with a 22% incidence of severe cardiovascular complications.
Patients with scores <26 had a 4% incidence of death, with a 17% incidence of severe cardiovascular complications.
Patients with scores <6 had a 0.2% incidence of death, with a0.7% incidence of severe cardiovascular complications.

Table 11.3. Shoemaker and colleagues criteria for identifying patients at high risk of perioperative complications.[1]

- Current or previous severe, cardio-respiratory illness (myocardial infarction)
- Stroke, heart failure, chronic obstructive pulmonary disease, severe asthma
- Acute abdominal catastrophe with hemodynamic instability (pancreatitis, perforated bowel with peritoneal soiling, severe gastrointestinal bleeding)
- Acute renal failure (acute onset renal dysfunction with urea >18 mmol or creatinine >265 mmol/liter)
- Severe multiple trauma (more than three major organs involved or more than two systems or surgical opening of more than two body cavities)
- Evidence of limited physiological reserve in one or more vital organs in elderly patients more than 70 years
- Shock (MAP < 60 mmHg, urine output < 0.5 ml/kg/h)
- Acute respiratory failure (PaO2 < 8 kPa, FIO2 > 0.4, shunt fraction >30%, mechanical ventilation required for >48 h)
- Septic shock

Table 11.4. Shoemaker et al. target hemodynamic goals.[1]

- Cardiac index >4.5 L/min/m2
- Pulmonary artery occlusion pressure <18 mmHg
- Oxygen delivery index >600 mL/min/m2
- Oxygen consumption index >170 mL/min/m2

as a therapeutic goal, and this resulted in a reduction of organ dysfunction and death in subsequent interventional studies.[1,2,10] The process of perioperative optimization as described by this group requires preoperative intensive care unit admission, pulmonary artery floatation catheter as a cardiac output monitoring method, intravenous fluids, and inotropes.

Other hemodynamic goals have also been targeted, such as maximum stroke volume and mixed venous saturation, with favorable impact on morbidity and length of hospital stay; however, reduction in mortality is significant only when an oxygen delivery index of 600 mL/min/m^2 is targeted.

Factors determining oxygen delivery are cardiac output, the product of heart rate and stroke volume, and oxygen content, which is mainly determined by the hemoglobin concentration and its degree of saturation. Cardiac output is improved by intravenous fluid administration titrated to achieve maximum stroke volume, and red blood corpuscle (RBC) transfusions are used to increase the total blood oxygen carrying capacity, while oxygen administration results in an increase in hemoglobin saturation. Adequate pain control, maintenance of normothermia, and prompt management of postoperative shivering are also important; the first two result in an increase in afterload and subsequent reduction in stroke volume, while shivering increases the metabolic rate by up to 300%, which can be detrimental to the high-risk patient.

Intravenous Fluid Therapy and Blood

The aim of intravenous fluid administration is to maximize the patient's stroke volume and achieve a higher oxygen delivery. This is illustrated by the Frank-Starling law, which states that the energy of contraction is proportional to the length of the muscle fiber before contraction.[11] Fluid administration for the purposes of optimization is by aliquots of a specific volume and type to achieve a specific goal – an intervention called fluid challenge. The therapeutic goal is to increase the stroke volume, and, if this is achieved, then the fluid challenge is repeated until no further favorable response occurs (Fig. 11.1). The choice of fluid – whether a crystalloid or colloid – remains open for debate, as clinical evidence of their effect on mortality is lacking.[12,13] Crystalloids have been associated with tissue fluid accumulation and possible diffusion hypoxia as a result,[14] while colloids are comparatively more expensive and associated with anaphylaxis and coagulation abnormalities. In addition, most colloids available for clinical use are suspended in 0.9% NaCl with the associated chloride load and subsequent metabolic acidosis.[15] The volume administered depends on the estimated fluid deficit, patient's cardiovascular reserves, and whether there is active intravascular fluid loss such as bleeding. The faster the fluid challenge infused, the higher the magnitude of the physiological response. If the latter is not sustained, then the fluid challenge should be repeated. Typically, 250–500 mL of either a crystalloid or colloid is given over 10-15 min period, expecting an increase, for example in stroke volume, by 10%. Central venous pressure

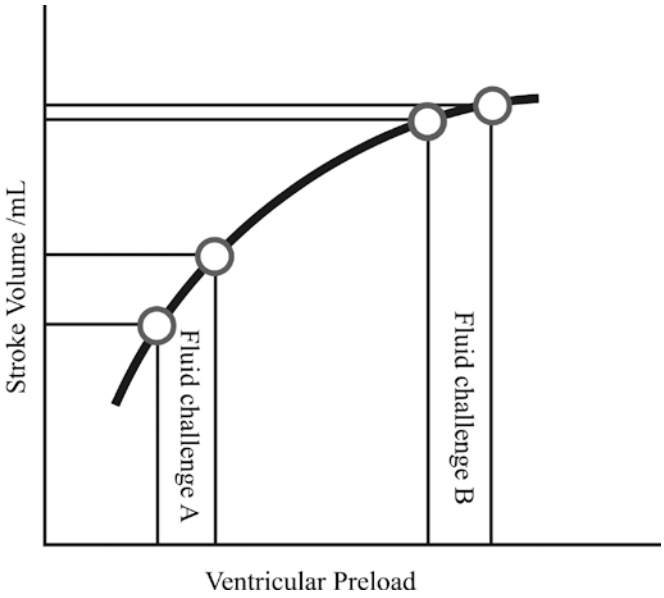

Fig. 11.1. The effect of intravenous fluid challenges on stroke volume. Fluid challenge A resulted in a significant increase in stroke volume as depicted on the *y* axis. This indicates that "fluid responsiveness" and fluid challenges should continue until a pattern similar to fluid challenge B is observed.

can be monitored during this process as a "safety limit." If the pressure increases beyond a specific point determined by the clinician, then the process is aborted.[16]

RBC transfusion, as part of an optimization strategy, traditionally aims for hemoglobin of 8–10 g/dL.[1,2,10] However, if the targeted oxygen delivery is achieved despite a lower hemoglobin level, then the RBC transfusion may not be required.

Cardiac Output Monitoring

Original perioperative optimization work utilized pulmonary artery floatation catheters (PAFC) as a means of monitoring flow.[1,2,10] Recently, a number of studies involving heterogeneous groups of patients failed to show a favorable outcome when PAFC was used to guide the hemodynamic therapy.[17] There are methodological limitations to this work; specific indications for the insertion of PAFC were not in place and a well-defined therapeutic strategy based on the data obtained from pulmonary catheterization was lacking. This contrasts with using this technique in the context of peri-operative optimization, where specific patients who are at significant risk are targeted and a goal-directed therapy approach is adopted based on PAFC measured variables.

Other methods of hemodynamic monitoring are currently available that avoid some of the risks associated with PAFC. Transesophageal Doppler monitor utilizes the principles of sound to measure the blood velocity in the descending aorta when appropriately placed in the esophagus. This is used to calculate the stroke volume and cardiac output.[18] Arterial pulse contour waveform analysis calibrated with Lithium dilution (LiDCOplus, LiDCO Ltd, Cambridge, UK) can also be used to measure the flow.[19] PiCCO (PULSION Medical Systems, Munich, Germany) utilizes thermodilution for the purpose of calibration,[19] where cardiac output is measured by applying the Stewart-Hamilton[20] equation to the temperature-time curve produced by injecting saline though a central venous catheter.

Recent work targeting either mixed or central venous saturation as therapeutic goals showed promising results, both in postcardiac surgery patients[21] and in early sepsis.[22] Venous saturation is a reflection of the adequacy of oxygen delivery if sampled centrally. Mixed venous saturation is taken from the pulmonary artery via a pulmonary artery floatation catheter, while central venous saturation is measured in blood from the superior vena cava. The latter is readily accessible as most patients undergoing major surgery have central venous access. Central venous saturation of 64.4% and less was found to be associated with postoperative complications[23]; and a value of 70–75% is targeted if this hemodynamic variable is part of a goal-directed therapeutic strategy.

Inotropic Support

Once the patient is given sufficient amount of intravenous fluid to achieve the maximum stroke volume possible and the oxygen delivery index remains less than 600 mL/min/m2, then an inotropic agent is considered (Fig. 11.2). Both the dobutamine and dopexamine have been used as part of perioperative optimization strategies; however, the pharmacological properties of the latter being predominately a dopaminergic, beta 2 (β2) agonist may favor its use.[24] Dopexamine is also claimed to have some anti-inflammatory properties independent of its inotropic effect.[25]

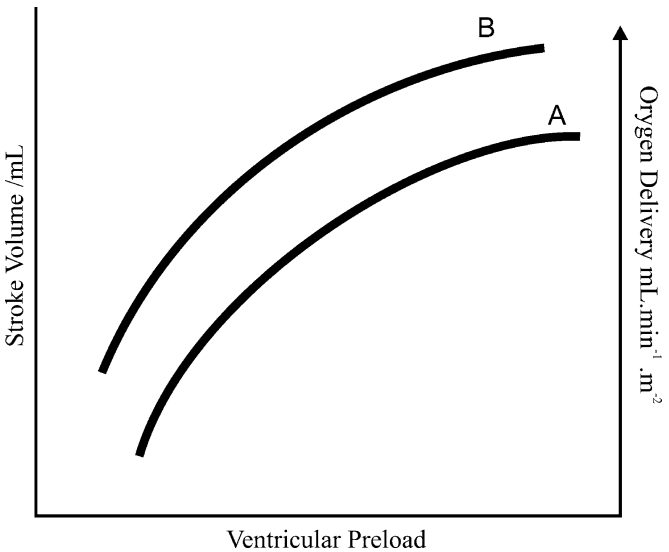

Fig. 11.2. The effect of inotropic support on the Frank-Starling curve. There is an upward and leftward shift of the curve, which results in an improvement of the stroke volume for same left ventricular preload. Curve A is before commencing of inotropes and curve B represents the resultant change in preload-stroke volume relationship.

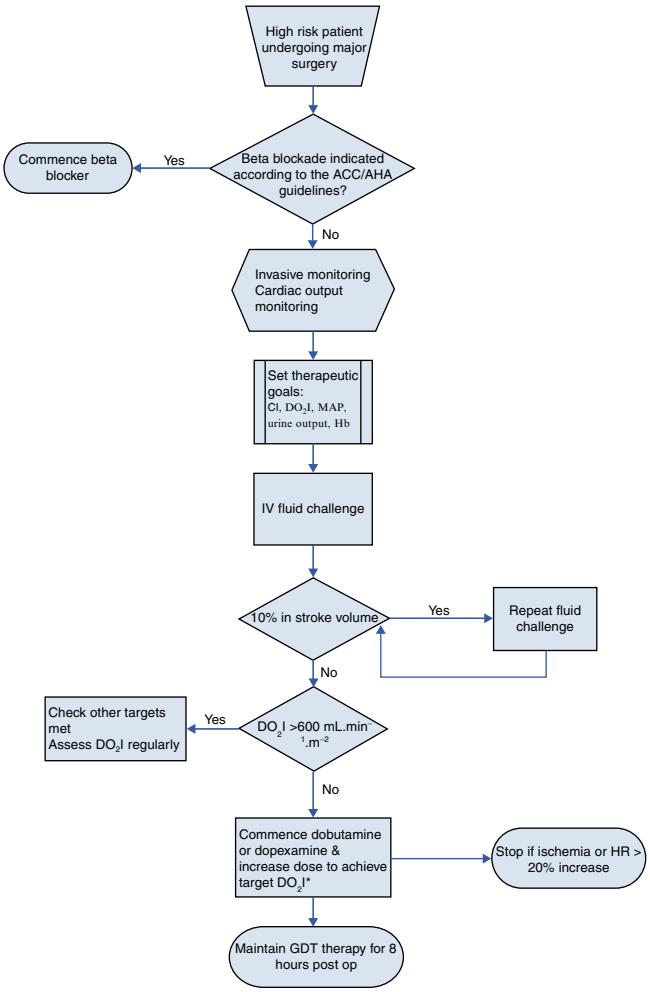

FIG. 11.3. Generic optimization algorithm. Assessment of stroke volume change can be done with any validated method of flow monitoring. *Dobutamine is commenced at 2.5 µg/kg/min and increased in increments of 2.5 µg/kg/min up to a maximum of 20 µg/kg/min. Dopexamine is commenced at 0.25 µg/kg/min and increased in increments of 0.25 µg/kg/min up to a maximum of 1 µg/kg/min.

Figure 11.3 is a generic optimization algorithm demonstrating the interactions between all the factors discussed above.

The Timing of Optimization

In order for perioperative optimization to have any beneficial effect, it should begin before the onset of organ dysfunction.[26] Initial optimization work requires patients to be admitted pre-operatively to a high dependency care facility where cardiac monitoring can be instituted and goal-directed therapy with intravenous fluid and inotropes commenced.[1,2,10] Optimization can also be commenced in the operating theater. Transesophageal Doppler has been used to maximize the stroke volume in a number of studies, which resulted in an overall decrease in the postoperative morbidity and length of hospital stay. Mortality, however, was not changed.[27–31] This may be related to the low-to-intermediate risk population studied, and the fact that oxygen delivery was not specifically targeted. In addition, mortality reduction was only shown in patients where an oxygen delivery index of >600 mL/min/m^2 was achieved. In those patients with limited cardiac reserves, this goal is unlikely to result from adopting a stroke volume optimization strategy without the use of inotropic therapy.

Pearse et al. found that a goal-directed strategy targeting an oxygen delivery index of >600 mL/min/m2 reduced complications and length of hospital stay even if commenced postoperatively and maintained for 8 h.[32]

Conclusion

Optimization of high-risk patients undergoing major surgery is a goal-directed therapeutic strategy based on the use of cardiac output monitoring, intravenous fluids, and inotropic support to achieve set hemodynamic indices. There is an improvement in outcome if this strategy is utilized in the appropriate patient groups before the onset of organ dysfunction.

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12
Cardiopulmonary Resuscitation

Andreas Schneider, Erik Popp, and Bernd W. Böttiger

Cardiopulmonary resuscitation (CPR) should be a basic skill for every intensive care physician. An estimated 200,000 individuals suffer from in-hospital cardiac arrest in the United States each year.[1,2] Half of these incidents occur in intensive care units (ICUs).[3] Restoration of spontaneous circulation (ROSC) can be achieved in 40–50% of patients resuscitated in-hospital, yet only 15–20% survive to be discharged.[3,4]

These data illustrate that cardiac arrest is still a major challenge to medical care. They also point out that management of cardiac arrest consists of two different steps of equal importance: cardiopulmonary resuscitation per se and postresuscitation care. Only optimal therapy in both phases will lead to a favorable outcome.

Our knowledge about such an optimal therapy is continuously growing. Every five years, the International Liaison Committee on Resuscitation (ILCOR) holds a series of meetings wherein recent progress is evaluated and therapeutic recommendations are derived.[5] On the basis of these recommendations called the "Consensus on Science," international guidelines for CPR are released; the most recent of these guidelines were released in 2005.[6,7] The following review on CPR is based on these guidelines. It is focused on CPR of adult patients.

Pathophysiology of Cardiac Arrest

There are manifold etiologies that can underlie cardiac arrest (Table 12.1). In patients suffering from out-of-hospital cardiac arrest, acute myocardial infarction is, by far, the leading cause.[8–10] However, conditions leading to in-hospital cardiac arrest are often more complex. In general, patients in hospital are "sicker." Therefore, other internal pathologies gain in importance. Cardiac arrest frequently develops more subacutely, with respiratory insufficiency or hemodynamic instability being present prior to the final event.[3,11]

Regardless of the etiology, the final common path is the cessation of cardiac mechanical activity. In contrast, cardiac electrical activity, is preserved initially in many cases. The pattern of this electrical activity is of utmost importance for therapeutic and prognostic considerations (see below), yet it is irrelevant for the sequelae of cardiac arrest on the body.

The arrest of cardiac pumping leads to an immediate and rapid decline of the arterial blood pressure and, consecutively, the antegrade blood flow.[12–14] Complete suspension of blood flow occurs within a few minutes, when arterial and central venous pressures have equilibrated. The pathophysiology of cardiac arrest can, therefore, be described as whole-body ischemia. The sequelae are often attributed to the interruption of peripheral oxygen supply. However, even though oxygen is surely a critical factor, ischemia is more than mere hypoxia.[15,16] Ischemia also cuts off the supply of other substrates such as glucose, and it leaves metabolic products such as lactate and hydrogen ions uncleared. Ischemia and mere hypoxia produce different physiological and pathophysiological responses, indeed.

Cardiac arrest represents ischemia of the whole body, but not all body tissues are affected uniformly. Most obvious is the high susceptibility of the brain. Clinically, only 5–6 s after the onset of circulatory arrest, the patient loses consciousness.[17] Molecularly, cerebral tissue oxygen tension declines continuously, reaching 0 after about 2 min.[18,19] Simultaneously, neuronal energy in terms of adenosine triphosphate (ATP) is depleted and metabolites like adenosine, lactate, and hydrogen ions accumulate.[20–22] Dysfunction of the cell membrane ion pumps leads to a severe breakdown of cellular homeostasis.[23,24] One particular consequence is a massive accumulation of cytosolic calcium due to the failure of the calcium efflux pumps, the opening of the voltage-gated calcium channels, and the activation of ligand-gated channels by released excitatory amino acids, such as glutamate and aspartate.[24–27]

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Table 12.1. Causes of cardiac arrest[194,195]

Cardiac:	Myocardial infarction Cardiomyopathy
	Valvular diseases
	Congenital heart defects
	Primary electrophysiological abnormalities
Noncardiac:	Pulmonary embolism
	Bleeding
	Lung diseases
	Stroke
	Metabolic or electrolyte disorders
	Trauma
	Intoxication

This calcium overload is considered a key factor in cellular toxicity.[28,29]

If the ischemia persists long enough, it will finally lead to neuronal necrosis over the whole of the brain.[30] However, reperfusion due to CPR and ROSC leads to rapid recovery of neuronal energetics.[19,21] Reperfusion therefore does stop neuronal degeneration to a certain degree, yet it does not necessarily lead to complete restitution. During reperfusion, restoration of oxygen supply leads to formation of free radicals, which might even aggravate cellular damage.[31–33] The main characteristic of the reperfusion period is that refueling ATP gives the cell the opportunity to actively react on the damage. This is associated with the expression of immediate early genes, a complex machinery involving both cell survival and cell death cascades.[34–38] These reactions can lead to delayed neuronal death, which is typically observed in so-called selectively vulnerable brain areas such as the CA-1 sector of the hippocampus, the nucleus reticularis thalami, or distinct layers of the cortex.[34–37] Clinical correlates of these lesions include impaired memory, attention, or executive functioning, which can be found in up to 50% of surviving patients.[39–41]

Besides the brain, the heart itself is severely affected by the circulatory arrest. After ROSC, a marked reduction of myocardial function can be observed.[42–45] Both systolic contractility and diastolic relaxation are affected, leading to pronounced hemodynamic instability. The underlying pathophysiology of this myocardial stunning is often complex. Similar to the brain, the myocardium is particularly susceptible to the state of global ischemia.[46] Furthermore, if there is a specific cardiac cause for the circulatory arrest, e.g., myocardial infarction, this of course contributes to the cardiac damage.[42,44,45] And finally, it was suggested that even therapeutic interventions during CPR could cause further damage to the heart, namely electrical defibrillation[47–49] and administration of epinephrine.[50] However, if postarrest myocardial stunning can be treated effectively with inotropic agents, it is usually self-limiting within 72 h.[43,44]

Cardiac arrest furthermore leads to activation of both the inflammatory[51–53] and the coagulatory system.[54,55] These factors can adversely affect organ function during reperfusion and therefore lead to multiple organ failure.

Signs and Diagnosis of Cardiac Arrest

Clinical Assessment

Cardiac arrest produces the clinical triad of loss of consciousness, no breathing, and no pulse. Consciousness should be assessed by both speaking to the patient and touching him. If the patient does not respond, he should initially be positioned supine on a flat surface. To avoid airway obstruction by the soft palate or the epiglottis,[56–59] the head should be fully extended and the chin lifted.[56,58–60] Breathing should be assessed by bending over the patient's face and then looking for chest movements, listening for breath sounds, and feeling for exhaled air. Up to 50% of patients suffering from cardiac arrest show agonal gasps during the first few minutes.[61] These should not be confused with normal breathing. Pulse should be checked at the carotid or the femoral arteries.

Both checking for breathing and pulse may prove difficult even for trained emergency and intensive care physicians.[62,63] As every delay in starting CPR after cardiac arrest might worsen the patient's outcome, a maximum of 10 s should be spent for each breathing and pulse check. If the patient lacks breathing and pulse, or if there is any doubt, CPR should be started immediately.

Technical Assessment

In intensive care units, the approach is often different. As most patients here are monitored, many cardiac arrests are detected by the monitoring equipments. A typical scenario could be the emergence of a characteristic electrocardiogram (ECG) rhythm such as ventricular fibrillation, in conjunction with a sudden decline of the arterial blood pressure. The ECG is of fundamental importance during CPR. If the patient has not been monitored before, it has to be established as soon as a defibrillator arrives.

There are four principle ECG rhythms that can be distinguished during cardiac arrest (Fig. 12.1). Ventricular fibrillation (VF) and ventricular tachycardia (VT) should lead to electrical defibrillation ("shockable rhythms"), whereas asystole or pulseless electrical activity (PEA) does not require electrical therapy ("nonshockable rhythms"). In in-hospital cardiac arrest, only 30% of patients show shockable rhythms on first assessment.[3,4] Shockable rhythms are not only associated with a significantly better prognosis, but their management is different from nonshockable rhythms.[3,4]

Cardiopulmonary Resuscitation

Mechanical CPR

Chest Compressions

The main goal during CPR is to restore perfusion of vital organs such as the heart and the brain. The concept of external chest compression was developed by Kouwenhoven in 1959.[64]

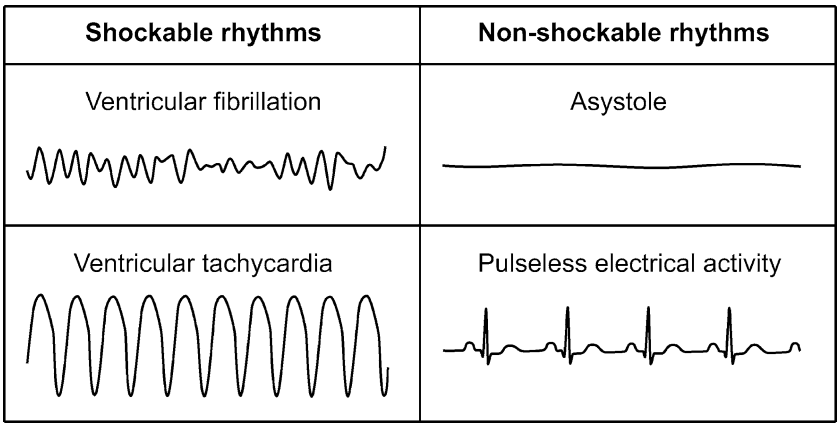

FIG. 12.1. ECG rhythms during cardiac arrest.

TABLE 12.2. Chest compressions during CPR[6,7]

Compression point:	Center of the chest
Compression rate:	100/min
Compression depth:	4–5 cm (1½–2 in.)
Compression to relaxation ratio:	1:1

TABLE 12.3. Ventilation during CPR[6,7]

Tidal volume:	500–600 ml
	Produce a visible chest rise
Ventilation rate:	Compression to ventilation ratio 30:2
	8–10/min in asynchronous ventilation with an advanced airway
Inspiratory time:	1 s
Inspired oxygen (FiO_2):	1.0

It creates antegrade blood flow by both increasing the intrathoracic pressure and directly compressing the heart.[65–67] Mean arterial blood pressure during standard CPR in conjunction with vasopressors can be expected at about 30–50 mmHg.[19,65,68,69] CPR is therefore able to produce a small yet critical amount of coronary and cerebral blood flow.[14,19,68,69]

There is only little and ambiguous data on ideal chest compression technique available.[69,70] The international guidelines from 2005 recommend to giving 100 compressions/min (Table 12.2).[6,7] The most important point is probably to minimize all interruptions in chest compressions.[71,72]

Ventilation

The classical mouth-to-mouth ventilation was introduced by Safar in 1958.[73] However, in in-hospital CPR, this form of ventilation is of minor importance as a resuscitation bag should usually be readily available. Bag mask ventilation not only helps to avoid frequent psychological hurdles of mouth-to-mouth ventilation,[74,75] but also allows the connection of an oxygen supply. Using a reservoir bag and high oxygen flow (about 12 L/min), the inspiratory oxygen fraction can be increased to almost 100%.[76,77] However, effective bag mask ventilation requires a great deal of practice.[78–80] A common complication of bag mask ventilation is gastric inflation, which predisposes for regurgitation and aspiration.[79,81]

During bag mask ventilation (as during mouth-to-mouth ventilation), chest compressions must be interrupted. As all interruptions are likely to impair resuscitation success,[71,72] the use of advanced airway devices must always be taken into account. In the hands of experienced personnel, endotracheal intubation is considered the gold standard for securing the airway.[6,7] However, when emergency intubation is attempted by less experienced staff, there is a considerable rate of tube misplacements.[82,83] In addition, the time needed to perform intubation may be critical. Ideally, laryngoscopy should be performed during uninterrupted chest compressions, which are then paused only during the actual insertion of the tube. According to the guidelines, intubation attempts should be abandoned after 30 s.[6,7] Instead of endotracheal intubation, supraglottic airway devices such as the laryngeal mask airway or the combitube can be an easy and safe alternative.[78,79,81]

Data on ideal ventilation parameters during CPR are limited. Yet it can be noted that too aggressive ventilation seems to impair the outcome.[84–86] The international guidelines from 2005, therefore, recommend tidal volumes of not more than 500–600 ml (Table 12.3).[6,7]

Compression-to-Ventilation Ratio

As stated above, all interruptions of chest compressions probably reduce resuscitation success.[71,72] At the same time, excessive ventilation should also be avoided.[84] Therefore, the compression-to-ventilation ratio was reevaluated during the revision of the guidelines in 2005. Unfortunately, there are no clinical data concerning different compression-to-ventilation ratios. However, on the basis of animal experimental data,[87,88] as well as mathematical considerations,[89] the compression-to-ventilation ratio was increased to 30:2.[6,7]

Recent investigations have shown that this ratio indeed leads to an increased number of compressions delivered during CPR, without reducing the quality of the compressions.[90–93] There is

even a first ray of hope that the new ratio could indeed lead to improved outcome.[93]

The described compression to ventilation ratio is only relevant for bag mask and mouth-to-mouth ventilation. After endotracheal intubation or insertion of advanced supraglottic airway devices, compressions should be delivered continuously. Then, a ventilation rate of 8–10/min is considered adequate [6,7].

Electrical Defibrillation

Application of electrical current during cardiac arrest can be traced back for over 200 years.[94] However, our current concept of terminating ventricular fibrillation and related rhythms by capacitor discharge was essentially propagated by Lown in the 1960s,[95,96] thus at the same time as basic CPR by means of external chest compressions and mouth-to-mouth ventilation evolved.

The electrical discharge is able to fully terminate all electrical activity within the heart for a short period.[97–99] When there is no recurrence of ventricular fibrillation afterwards, there is a chance for the sinus node to resume control. With this concept in mind, it becomes clear that electrical countershocks are only suitable for stopping abnormal electrical activity such as ventricular fibrillation and ventricular tachycardia. Here, countershocks mean a causal therapy. However, they are not appropriate for asystole and pulseless electrical activity. Asystole is characterized by the absence of electrical activity, and pulseless electrical activity emerges from mechanical problems during regular electrical activity.

Defibrillation success is largely dependent on time. With every minute that passes until defibrillation is attempted, the chance of survival decreases by 10–15%.[100,101] The importance of delivering defibrillation rapidly is emphasized by two recent randomized clinical trials on the use of automated external defibrillators (AEDs).[102,103] When basic CPR as performed by laypersons before the arrival of medical emergency service is complemented by public AEDs, survival after out-of-hospital arrest can be improved. Not surprisingly, such improvement diminishes as the length of time for the arrival of emergency medical service increases.[103]

In animal experiments, electrical defibrillation can produce myocardial damage.[47–49] However, it is highly questionable whether such damage also occurs in a clinical situation.[104,105] Cutaneous burns represent the only clinically proven adverse effect of electrical defibrillation.[106,107]

There are currently two different types of defibrillators available, delivering shocks with monophasic or biphasic waveforms. Biphasic defibrillators seem to attain higher defibrillation success and require less energy for successful defibrillation.[108–112] Investigations on defibrillation during electrophysiological procedures support this apparent superiority of biphasic defibrillation.[113] However, no study has shown a difference in survival after monophasic or biphasic defibrillation.[108–112]

The current guidelines do not specifically recommend either waveform (Table 12.4).[6,7] Appropriate energy levels are stated as 360 J for monophasic shocks and 150–200 J for biphasic shocks.

Table 12.4. Electrical defibrillation during CPR[6,7]

Position of electrodes:	Antero-lateral: one electrode to the right of the sternum, one electrode lateral to the left breast
Applications of electrodes:	Self-adhesive electrode pads Electrode paddles in conjunction with conductive gel or pads, paddles must be pressed firmly
Energy level:	360 J with monophasic waveforms 150–200 J with biphasic waveforms

Table 12.5. Drugs during CPR[6,7]

Drug:	Indications	Dose
Epinephrine	All cardiac arrests	1 mg every 3–5 min
Amiodarone	Refractory VF/VT	300 mg
Lidocaine	Refractory VF/VT, when amiodarone is not available	100 mg
Magnesium	Torsades de pointes Hypomagnesemia	8 mmol (2 g magnesium sulfate)
Atropine	Asystole PEA with a rate <60/min	1–3 mg
Bicarbonate	Severe metabolic acidosis Hyperkalemia Tricyclic antidepressant overdose	50 mmol
Thrombolytics	Pulmonary embolism Myocardial infarction, based on an individual decision	Depends on thrombolytic agent

Drugs

Epinephrine

Epinephrine (adrenaline) is perhaps the most important drug during CPR. Because of the activation of α-adrenoceptors, it leads to peripheral vasoconstriction resulting in increased blood pressure and improved myocardial and cerebral perfusion.[68,114–116] Animal experimental data suggest that the use of epinephrine (or other vasopressors) is utterly important for successful resuscitation.[117–119] However, there are no randomized clinical trials that have compared epinephrine with placebo in humans. There is an ongoing controversy about the potentially harmful effects of epinephrine. Because of its β-adrenergic properties, myocardial oxygen consumption increases and is not necessarily balanced by increased blood flow.[120,121] The use of epinephrine was even suspected to cause myocardial damage.[50,118] However, the clinical evaluation of other vasopressors such as vasopressin[122] or norepinephrine[123] has failed to produce favorable outcome compared to epinephrine. Thus, epinephrine remains the standard vasopressor for CPR (Table 12.5).[6,7] One milligram should be administered every 3–5 min. Higher doses of epinephrine are not associated with improved (or impaired) outcome.[124]

Amiodarone

Amiodarone is an antiarrhythmic agent that has been shown to effectively terminate both supraventricular and ventricular tachyarrhythmias.[125,126] Two randomized clinical trials have

investigated the use of amiodarone in out-of-hospital cardiac arrest with refractory ventricular fibrillation.[127,128] The first study compared 300 mg amiodarone to placebo, while the second study compared amiodarone 5 mg/kg to lidocaine 1.5 mg/kg. In both studies, patients receiving amiodarone were more likely to survive to hospital admission than the patients of the control group. However, neither of the two studies could detect differences in survival-to-hospital discharge. Still, amiodarone is the only antiarrhythmic drug for which at least a short-term benefit has been demonstrated in cardiac arrest. It is therefore the standard antiarrhythmic agent during resuscitation (Table 12.5).[6,7] Most recently, two retrospective analyses have questioned the value of amiodarone when compared with that of lidocaine in in-hospital cardiac arrest.[129,130] However, because both studies were highly susceptible to confounding (e.g., amiodarone was administered later in the arrest than lidocaine), amiodarone presently remains the first-line antiarrhythmic drug.

Magnesium

The use of magnesium during CPR is controversial. It had been suggested that magnesium could help to control ventricular fibrillation.[131,132] However, randomized clinical trials could not show a benefit from the application of magnesium compared to placebo, neither during CPR in general[133,134] nor in cases of refractory ventricular fibrillation only.[135,136] Yet, it seems that magnesium is particularly capable of terminating torsades de pointes, a distinct type of VT associated with QT prolongation.[137,138] This view is supported by experimental data on the electrophysiological mechanisms of torsades de pointes.[139] Therefore, magnesium is considered as first-line treatment in patients with torsades de pointes (Table 12.5).[6,7]

Atropine

Atropine is used during asystolic cardiac arrest on the assumption that increased vagal tone can perpetuate asystole.[140,141] However, there are few clinical studies that have focused on the specific impact of atropine on asystolic cardiac arrest; moreover, all of them were based on small numbers of patients, and none were randomized.[142–144] The results were contradictory, therefore not allowing for any definitive conclusions. Besides, there are larger epidemiological studies that found utilization of atropine during CPR to be associated with increased mortality.[145,146] However, this association should be taken with caution. There is a high chance of confounding – patients who require increased amounts of atropine might simply be "sicker" and therefore have impaired outcome. The current guidelines recommend application of atropine during asystole and pulseless electrical activity (Table 12.5).[6,7] Atropine represents a well-known drug with well-known adverse effects, and it seems unlikely that atropine will cause harm during CPR. With 3 mg of atropine, maximal vagolytic effect can be expected.[147]

Bicarbonate

During cardiac arrest, both CO_2 and lactic acid accumulate in peripheral tissues and can therefore cause systemic acidosis during CPR.[148,149] While administration of buffers such as bicarbonate seems logical, efficacy of such treatment is highly questionable. In a large randomized clinical trial of out-of-hospital cardiac arrest, patients received a combined buffer agent (bicarbonate/Tris/phosphate/acetate) or saline during CPR.[150] There were no differences in resuscitability between the two groups. Furthermore, it was suggested that bicarbonate could even aggravate intracellular acidosis during CPR.[151]

Reaction with H^+ leads to formation of CO_2, which can easily diffuse into cells when it is not eliminated by effective perfusion. Concluding, bicarbonate should be used reluctantly during CPR (Table 12.5).[6,7] The most important issue in acid-base homeostasis is probably effective circulation and ventilation.

Thrombolytics

There are two rationales for the use of thrombolytics during CPR. First, acute myocardial infarction and pulmonary embolism represent important causes of cardiac arrest, even though the proportion of acute myocardial infarction in in-hospital cardiac arrest[3,11] is not as high as in out-of-hospital cardiac arrest.[8–10] In both myocardial infarction and pulmonary embolism (without cardiac arrest), thrombolysis represents a standard therapy.[152,153] Second, deranged coagulation[54,55] is apparently involved in the emergence of microcirculatory disorders after cardiac arrest.[154,155] Several small studies suggest that thrombolysis during CPR might be beneficial, particularly in patients with pulmonary embolism, and also in those with myocardial infarction.[156–159] Randomized clinical trials investigating a general use of thrombolytics during CPR have produced different results.[160,161] Yet, these studies have consistently shown that thrombolysis during CPR is safe and not associated with increased bleeding complications. The current guidelines recommend that thrombolysis might be considered during CPR on a case-by-case basis, when pulmonary embolism or myocardial infarction is suspected (Table 12.5).[6,7]

Algorithms for CPR

Basic Cardiac Life Support

After confirmation of cardiac arrest, CPR must be initiated immediately. It is now recommended to start CPR with chest compressions rather than initial rescue breaths.[7] While oxygen content of peripheral tissues is rapidly consumed during cardiac arrest,[18,19] arterial oxygen tension remains high.[162,163] Therefore, initial ventilation would only delay chest compressions without having any advantages.

After the initiation of CPR, help must be requested including both personnel and equipment. As soon as possible, an ECG must be established, e.g., by means of a defibrillator. Further

management of cardiac arrest differs between shockable and nonshockable rhythms (Fig. 12.2).[6,7] As most patients on intensive care units are connected to a monitor, rhythm analysis can be done even prior to the start of CPR.

In addition, an advanced airway device and an intravenous access have to be established, if not already present. If an intravenous line cannot be established, an intraosseous access represents an easy, safe, and effective alternative.[164,165] However, neither the placement of an advanced airway device nor of the intravenous access should interfere with basic CPR. Even short interruptions in chest compressions can be associated with poor outcome.[71,72]

Advanced Cardiac Life Support: Shockable Rhythms

In shockable rhythms (VF, VT), electrical defibrillation represents the causal therapy.[97–99] The countershock should be applied as soon as possible after diagnosis has been established.

When cardiac arrest is observed on the monitor – as is usually the case in intensive care units – the countershock can be given even before mechanical CPR. Alternatively, a single precordial thump might be successful when no defibrillator is immediately available.[166–168] However, in cases of prolonged collapse, CPR should be performed before the first defibrillation.[14,169,170]

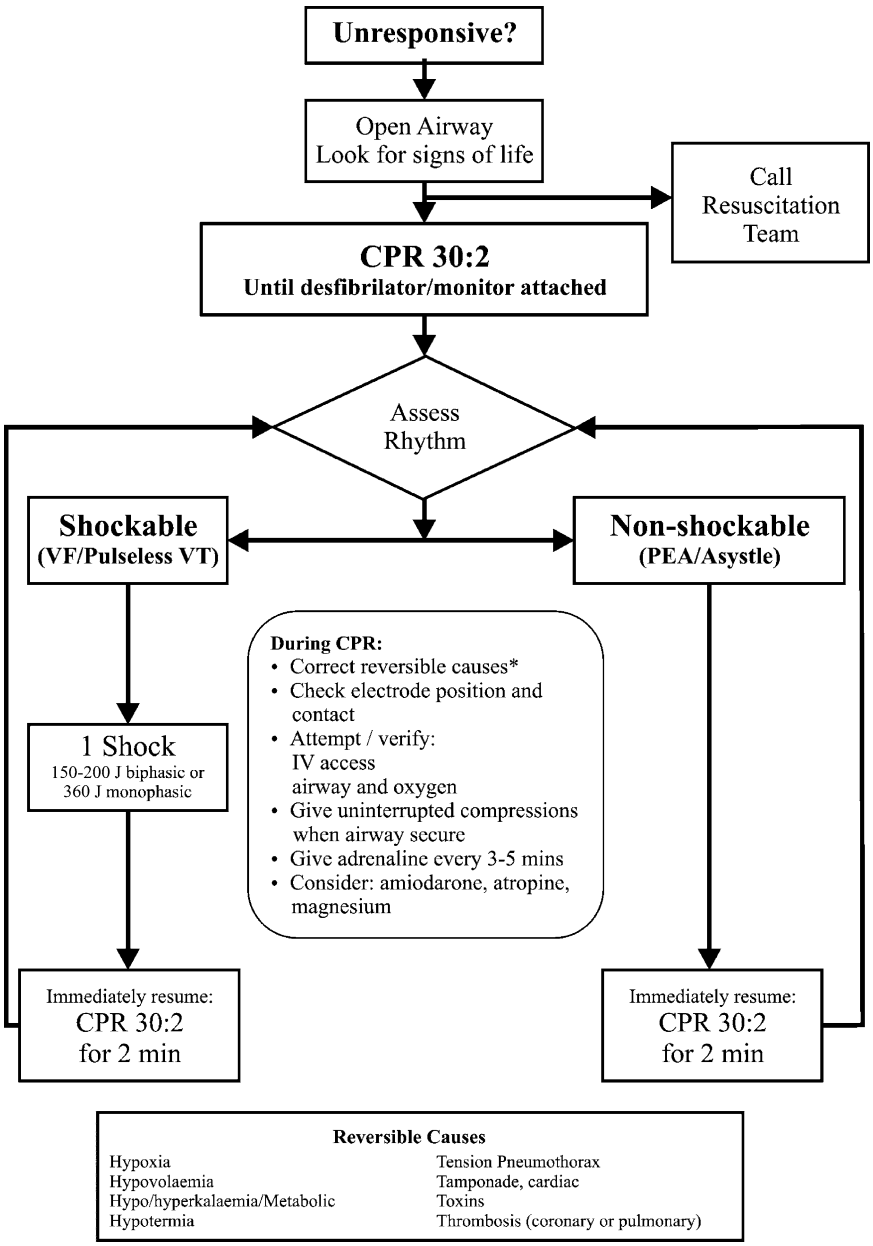

FIG. 12.2. Advanced cardiac life support algorithm. Reproduced from Resuscitation, Vol. 67, Suppl. 1. Nolan JP, Deakin CD, Soar J, et al. and the European Resuscitation Council. European Resuscitation Council guidelines for resuscitation, S39–S86, 2005, by permission of Elsevier.

The current guidelines recommend applying only one countershock at once.[6,7] Afterwards, CPR should be resumed immediately without checking the rhythm. On the one hand, a pulse can rarely be palpated immediately after defibrillation,[171] and on the other, on-going CPR is unlikely to cause any harm even if an organized rhythm is present.[172]

The algorithm for advanced cardiac life support implies a rhythm check every 2 min as a basic principle. When there is a potentially perfusing rhythm, the pulse should be palpated, followed by measuring blood pressure. When VF or VT is still present, the next countershock should be applied, again followed by immediate continuation of CPR. When asystole or PEA is present, CPR should be resumed immediately according for the algorithm for nonshockable rhythms.

With shockable rhythms, drug therapy should start after the second or thirdrhythm check. One milligram epinephrine should be administered prior to defibrillation (one dose of vasopressin 40 U IV may replace either the first or second dose of epinephrine). If there is still VF or VT present at the next rhythm check, 300 mg amiodarone should be given. Epinephrine (1 mg) should be repeated every 3–5 min.

Advanced Cardiac Life Support: Nonshockable Rhythms

When rhythm check reveals asystole or PEA, CPR must be resumed immediately. Defibrillation is not a therapeutic option. Different from shockable rhythms, 1 mg epinephrine should be given immediately. Again, there is the basic principle of analyzing the rhythm every 2 min (see above). If asystole or PEA with a rate <60/min is still present at the second check, 1–3 mg atropine should be given. Independent of the rhythm, epinephrine should be repeated every 3–5 min.

Postresuscitation Care

Prerequisites

Every patient with ROSC must be admitted to an intensive care unit. During the postresuscitation period, disturbances of physiologic homeostasis can severely impair outcome.[173–176] All patients must be subjected to continuous ECG and oximetry monitoring. Hemodynamics should be monitored by an arterial cannula, supplemented by measurement of cardiac output where appropriate. Furthermore, urinary catheterization is necessary. All comatose patients should be intubated and mechanically ventilated. A nasogastric tube is usually indicated, especially when the patient was bag mask ventilated during CPR. Basic diagnostics comprise a 12-lead ECG, an echocardiography, and a chest X-ray. Dependent on the situation, diagnostics must of course be extended. In particular, coronary angiography should be taken into consideration when acute myocardial infarction is suspected.

Goal-Directed Therapies

Blood Pressure

After cardiac arrest, many patients are hemodynamically unstable because of myocardial dysfunction, arrhythmias, and peripheral vasodilation.[42,44,45] Furthermore, most patients after cardiac arrest completely or partially lack autoregulation of cerebral blood flow.[176] In healthy individuals, cerebral blood flow remains constant during decreased arterial blood pressure. In patients after cardiac arrest, however, cerebral perfusion can drop critically.

Blood pressure management in the postresuscitation period has not been tested in clinical studies yet. Epidemiological studies suggest that hypotensive periods are associated with bad outcome.[174] Animal experimental data suggest that elevation of blood pressure might produce better outcome.[177] However, with regard to the lack of clinical data, it is currently recommended to aim the blood pressure at the patient's normal levels.[6,7] Hypotension should definitely be avoided.

Blood Glucose

In analogy to stroke,[178] hyperglycemia after cardiac arrest is associated with both increased mortality and impaired neurological recovery in survivors.[174,175] Unfortunately, there have been no clinical trials yet that have investigated blood glucose management in resuscitated patients. However, a randomized clinical study could show that strict glucose control to 80–110 mg/dl (4.4–6.1 mmol/L) reduces mortality of critically ill patients.[179] It is reasonable to apply blood glucose control to patients after cardiac arrest.[6,7]

Blood CO_2 Tension

While the need for sufficient ventilation in the postresuscitation period is obvious, hyperventilation must be avoided. Hypocapnia due to hyperventilation causes cerebral vasoconstriction.[173] The consecutive reduction of cerebral blood flow can possibly induce further cerebral ischemia. Ventilation parameters therefore should be adjusted to maintain normocapnia.[6,7]

Mild Therapeutic Hypothermia

Two randomized clinical trials have shown benefits of mild therapeutic hypothermia after cardiac arrest.[180,181] In both studies, comatose adult patients after out-of-hospital cardiac arrest with ventricular fibrillation as the initial rhythm were cooled to 32–34°C for 12 or 24 h, respectively. Compared to normothermia, mild therapeutic hypothermia led to both improved survival and improved neurological recovery. These results have been confirmed by a subsequent meta-analysis.[182] Mild therapeutic hypothermia is, therefore, clearly recommended in comatose adult patients after out-of-hospital VF cardiac arrest.[6,7] However, it is also reasonable to apply mild therapeutic

hypothermia in patients with nonshockable rhythms as well as in patients after in-hospital cardiac arrest.

There are various methods of cooling available. Most common are external surface cooling[180,181] or endovascular cooling with special catheters.[183,184] There are currently no studies available to recommend a particular way of cooling. However, it should be noted that the use of automated feedback-controlled systems leads to more stable temperature control.[184] Induction, but not maintenance, of hypothermia can also be established by cold infusions.[185,186] Infusion of ice-cold Ringer's solution (30 ml/kg in 30 min) has been shown to be easy as well as effective and safe.

Therapeutic hypothermia must not be done without adequate analgo-sedation of the patient. This is necessary to suppress physiological counter-regulation by means of vasoconstriction and shivering.[187] When the patient is mechanically ventilated, shivering can completely be suppressed by neuromuscular paralysis. In nonparalyzed patients, meperidine (pethidine) can be used for prevention and therapy of shivering.[188]

Mild therapeutic hypothermia seems to be tolerated well. Neither the two randomized controlled trials nor the subsequent meta-analysis found a statistically significant increase in complications.[180–182] There was only an insignificant trend toward higher incidences of bleedings and sepsis.

When patients are excluded from therapeutic hypothermia for any reason, body temperature must still be monitored. After cardiac arrest, many patients develop fever, which represents an independent risk factor for mortality.[174] Animal experimental data suggest that consequent treatment of fever with antipyretics reduces neuronal damage.[189]

Prognostication

Clinical Tests

Neurological examination is most significant in predicting the patient's outcome. Sedatives and relaxants must be discontinued prior to the examination. In a recent meta-analysis, five clinical signs were identified that reliably predicted death or poor neurological outcome.[190] These were absent corneal reflexes at 24 h, absent pupillary response at 24 h, absent withdrawal response to pain at 24 h, no motor response at 24 h, and no motor response at 72 h. However, there are no neurological signs that can predict outcome earlier than 24 h.

Supplementary Diagnostics

Clinical testing can be supplemented by somatosensory evoked potentials (SSEP). Bilateral absence of N20 response to median nerve SSEP within the first week predicts death or vegetative state with 100% specificity.[191] However, sensitivity is less than 50%. Biochemical parameters such as neuron-specific enolase (NSE) or astroglial protein S-100 lack specificity for predicting bad outcome.[192] However, when serum levels are low, maximum therapeutic efforts should be continued. At this time there is no sufficient evidence to support the routine use of computed tomography in patients following a cardiac arrest.[193]

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Part II
Neurocritical Care

13
Management of Closed Head Injury

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Introduction

Closed head injury (CHI) remains a devastating problem throughout the world, disproportionately affecting young people. Traumatic brain injury (TBI) is associated with more than 50,000 deaths in the United States annually.[1] Each year, an estimated 1.5 million Americans sustain a TBI. As a result of these injuries, 230,000 people are hospitalized and survive, and an estimated 80,000–90,000 people experience the onset of long-term disability.[2] Motor vehicle accidents remain the leading cause of death among people younger than 40 years of age.[3] While the fate of the injured is often decided at the moment of impact, timely medical intervention can frequently prevent further secondary injury and improve outcome. This chapter will focus on the medical and surgical management of patients with severe head injury, with an emphasis on the role of the critical care team.

Closed Head Injury

Physiology

Successful treatment of patients with a head injury requires an understanding of the anatomy and physiology of the brain and the surrounding structures. A common analogy is to compare the skull and its contents to a "closed box." The skull itself forms the rigid container or box. The bone of the skull is designed to protect its valuable contents and therefore, is remarkably stiff and inflexible. Contained within the skull are, essentially, three elements: the brain tissue, water (in the form of cerebrospinal fluid (CSF)), and blood. While the brain has several foramina throughout its base, the foramen magnum, located at the cranial-cervical junction, is the only passageway large enough to allow movement of CSF or brain tissue. While the rigid skull serves an important role in preserving the brain, it becomes an impediment when treating the trauma patient. Brain tissue, CSF, and blood occupy the entire volume of the skull, and the addition of an extra space-occupying mass will result in either elevating the pressure within the skull or a shift of contents out of the skull. The presence of a blood clot or increased tissue water in the brain (edema) causes an increase of the pressure inside the skull. If allowed to rise high enough, this pressure will eventually exceed the blood pressure and diminish the flow of blood to the brain, thereby causing brain death (Fig. 13.1). This is explained in a more scientific fashion by the Monro-Kellie Doctrine,[4] which states that the total volume of blood, CSF, and brain remains constant inside the skull, and a volume increase in one constituent must result in the reduction of volume in another constituent. Thus, the management of TBI involves techniques that reduce or eliminate the elevated pressure or volume within the skull. These techniques will be explored later in this chapter in detail, but essentially, they involve removal of the extra space-occupying mass, removal of one of the three elements (brain, CSF, or blood) or opening the box (craniectomy).

Certain physiologic features normally present in the brain can be exploited to assist in managing TBI. Arterioles that supply the brain are differentiated from non-CNS vessels by their ability to react to local changes in the environment. Cerebral autoregulation implies that these vessels are capable of altering the cerebral blood flow based on local phenomena, such as the partial pressure of carbon dioxide (pCO_2) in the blood, blood viscosity, metabolic alterations, and myogenic changes within the blood vessel smooth muscle. Carbon dioxide levels in the cerebral arterioles have a direct effect on blood vessel caliber: hypercarbia results in vasodilatation while hypocarbia results in vasoconstriction. The exact mechanism for this response is

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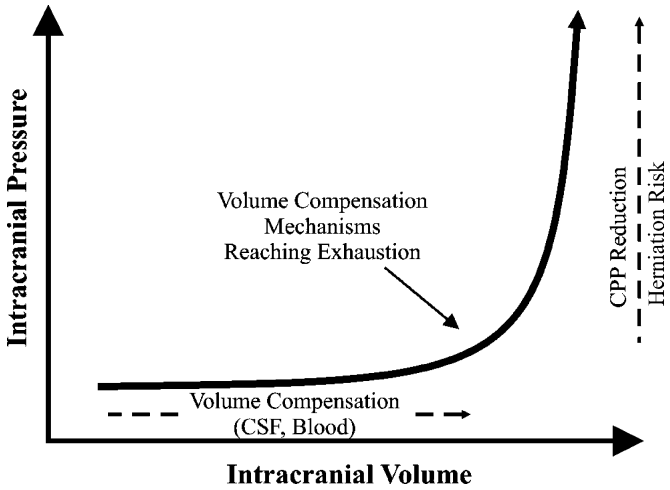

FIG. 13.1. The pressure–volume curve of the intracranial contents. As the volume of an expanding mass increases, ICP rises only slightly until the compensatory mechanisms are overcome. This point is reached at the elbow of the curve when further expansion of the mass causes a steep rise in ICP.

unclear, but it appears to be related more to the local changes in pH rather than pCO_2.[5,6] Local metabolism also plays a role in controlling local cerebral blood flow. Alterations in glucose levels, partial pressure of oxygen (pO_2), and lactate may also affect the vessel diameter. In addition, blood pressure has an effect on local vasodilatation as described in the myogenic theory of autoregulation. Cerebral vasodilatation is seen in response to hypotension, allowing the brain to maintain a constant flow throughout a variety of blood pressure swings. The fourth mechanism involved in autoregulation is viscosity. Lower blood viscosity results in greater cerebral blood flow with subsequent increased delivery of red cells to the brain.[7] This autoregulatory function allows the brain to maintain a precise milieu to optimize neuron function. This property can be manipulated artificially by altering the pCO_2 and changing the blood flow to the brain, thereby reducing the amount of blood in the skull and lowering the intracranial pressure (ICP). This will be explained in detail, later.

One of the difficulties in managing traumatic brain injuries is loss of cerebral blood flow (CBF) autoregulation. On a cellular level, the initial injury leads to structural damage of axons, neurons, and supportive cells causing lactic acid accumulation from anaerobic glycolysis. The ATP stores are then depleted from increased glycolysis, leading to failure of the ionic membrane pumps. Secondarily, the cellular membranes depolarize, and excessive excitatory amino acids (glutamate, aspartate) are released along with activation of ionic channels (*N*-methyl-D-aspartate, α-amino-3-hydroxy-5-methyl-4-isoxazolproprionate, and voltage-dependent Ca^{2+} and Na^{+} channels). Ultimately, release of Ca^{2+} and Na^{+} activates peroxidases, proteases, and phospholipases, triggering a cascade leading to cell death. These cellular changes lead to regional and global problems of hypoperfusion, hyperperfusion, CO_2 reactivity, vasospasm, metabolic dysfunction, excitotoxicity, oxidative stress, edema, and inflammation that have an adverse influence on brain tissues.[8] Most of the current treatment options target elements within these cascades and attempt to interrupt the progression leading to apoptosis.

Diagnosis

Physical examination remains the most reliable indicator of neurologic function. The complete neurologic exam includes the evaluation of the mental status, cranial nerves, motor system, and sensory system. The neuro exam is a dynamic process that takes place over a period of time. Changes in certain elements are often indicators of neurologic decline that require intervention and may exist prior to changes in imaging. An example of this is the classic presentation of an epidural hematoma. The patient may experience a transient loss of consciousness, but often appears quite intact at the initial examination. Over time, as the hematoma increases in size, the patient experiences a decline in function. Only serial neurologic examinations will show the change in status over time and allow for proper intervention.

The Glasgow Coma Score (GCS) was devised as a means of assessing the severity of head injury at the time of admission.[9] It has three components that require evaluation: the level of speech function, the ability to open the eyes, and the ability to demonstrate motor function. The calculation of the score is depicted in Table 13.1. The value of the GCS lies in the fact that it is easily obtained by any provider and allows for a means to objectively track a patient's neurologic status over time. The neuro exam also needs to determine if there are any focal deficits. Asymmetry in motor strength or sensory function will help in localizing lesions. Bilateral arm or bilateral leg weakness often implies spinal cord injury,

TABLE 13.1. Glasgow coma score

	Action	Points
Eye opening	Spontaneous	4
	To speech	3
	To painful stimulus	2
	None	1
Motor response	Obeys commands	6
	Localizes and responds appropriately to noxious stimulus	5
	Withdraws to noxious stimulus	4
	Abnormal flexion of upper extremities	3
	Extension of upper extremities	2
	No movement	1
Verbal response	Oriented to location, date, situation	5
	Confused	4
	Inappropriate words	3
	Unintelligible speech	2
	None	1

whereas unilateral weakness is consistent with an intracranial injury.

Radiographic Diagnosis

The mainstay in managing patients with CHI is the CT scan of the brain. Skull X-rays are of no value, and MRI scans are too cumbersome and time-consuming to be of use. CT scanners are ubiquitous in hospitals, with many larger centers having scanners in the Emergency Room and the Surgical Intensive Care Unit (SICU). In addition, there are portable scanners capable of imaging patients without requiring them to leave the safe environment of the SICU. Frequent CT scans of head-injured patients have become the standard of care and should be performed whenever a significant neurologic change occurs.

Pertinent radiographic findings on a CT are primarily related to the presence of a space-occupying mass or the development of diffuse brain swelling and elevated ICP. Mass lesions in a trauma patient are usually hematomas or parenchymal contusions. If large enough, these masses cause a shift of the brain within the skull and the development of focal pressure on the brain. The movement of the brain within the skull is called herniation and, depending on the anatomic location, herniation may become symptomatic (Fig. 13.2). The herniation of the temporal lobe over the edge of the tentorium into the region of the third cranial nerve is a classic form of herniation, leading to impairment of parasympathetic input to the pupil and pupillary dilatation (blown pupil). Other forms of herniation occur when the brain slides under the membrane (falx cerebri) dividing the hemispheres (subfalcine herniation). This can result in pressure upon the arterial supply to the brain, leading to stroke. A more ominous CT scan finding is the development of diffuse parenchymal swelling. In this setting, the spaces surrounding the brain that are normally filled with CSF become obliterated by the swollen parenchyma. The loss of these CSF cisterns around the brainstem and the loss of the normal sulcal pattern over the hemispheres are the characteristic CT findings.

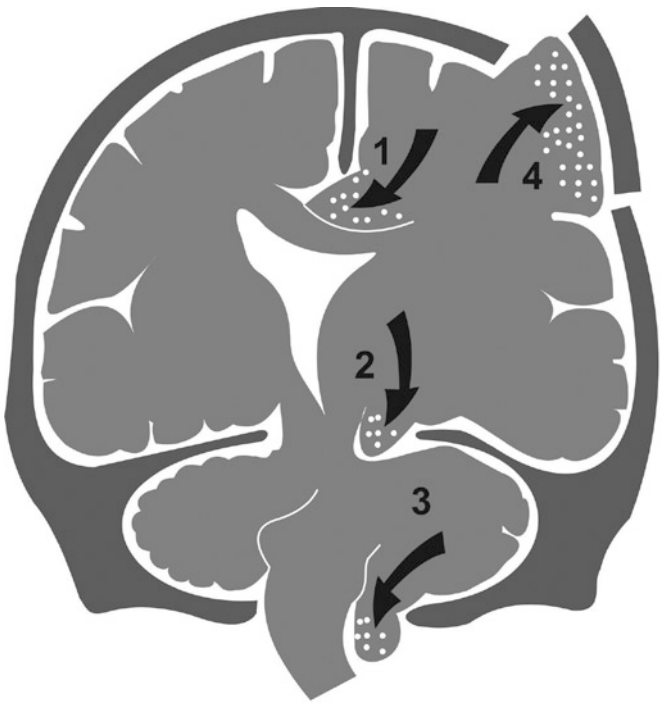

FIG. 13.2. Types of cerebral herniation: subfalcine herniation (1); uncal herniation (2); tonsillar herniation (3); external herniation (4).

Fractures of the calvarium and of the skull base are also quite easily appreciated on CT. If non-depressed, calvarial skull fractures are rarely treated. It is important to recognize basilar skull fractures as they may be a source of CSF leakage, which can lead to meningitis.

Surgical Management

The role of surgery in treating CHI is rather limited. Most patients with head injury do *not* require any type of surgical treatment. In the presence of clear mass effect from hematoma or contusion, surgery is sometimes employed to reduce the mass and swelling. There is clear benefit seen in patients with epidural hematoma. In these cases, the underlying brain is often not severely injured, and craniotomy to evacuate the growing hematoma is usually quite beneficial. However, the same cannot be said for acute subdural hematoma (SDH). The development of an acute clot in the subdural space is often an indicator of severe underlying brain injury, and removal of the clot is often ineffective in treating the brain injury. An acute SDH needs to be *differentiated* from a chronic SDH. This latter, more benign process generally occurs in the older population with a degree of cerebral atrophy. Often, a mild head injury or fall results in movement of the brain inside the skull, which may tear a vein on the cerebral cortex. The slow accumulation of venous blood in the subdural space is often asymptomatic. Over time, as the clot begins to resorb, changes in osmolarity of the red cells in the clot occur and increased vascular permeability develops. This results in a net inflow of fluid into the subdural space. Eventually, the increase in the size of the fluid collection can lead to pressure on the cortex with concomitant symptoms of headache, weakness, or disorientation. The surgical treatment of a chronic SDH can often be accomplished through the placement of one or two bur holes in the skull. Since the clot is liquefied, it usually drains out easily, often having the color of motor oil. In contrast, an acute SDH requires a craniotomy for evacuation of a formed clot. As mentioned previously, even the successful removal of the clot does *not* ensure a good outcome, as often the underlying brain has been severely injured and will *not* improve with surgery alone.

Surgery is also performed for the treatment of intraparenchymal contusions in the presence of uncontrolled elevated ICP. The indications for surgery in this group are less well-defined. Unlike extra-axial lesions (e.g., subdural and epidural hematomas), intraparenchymal lesions require resection of a

portion of the brain itself. Thus, the location of the contusion is often a deciding factor in whether or not to perform surgery. A contusion located within eloquent cortex, such as the speech or motor area, is often treated nonoperatively, as surgery in this area would be expected to leave the patient with a substantial deficit.

A more controversial surgical procedure is the 'craniectomy' or removal of the skull. Considering the notion of the "closed-box" model for ICP, the removal of the skull is essentially opening the box, thus relieving the pressure inside. The surgical procedure is not complicated: it involves removal of a large portion of the skull and opening the dura to reduce the pressure. The skull is not replaced; it is often stored in a tissue bank freezer or subcutaneously in the abdomen to be replaced at a later date when the swelling is reduced. The controversy arises from the fact that while craniectomy clearly reduces ICP, the overall effect on outcome is less clear. In the past, indiscriminate use of craniectomy to treat patients with refractive elevated ICP led to saving lives, but sadly left patients in a persistent vegetative state or with otherwise poor outcomes. More recently, studies have shown that selective craniectomy may not only save lives but also improve outcomes in patients with elevated ICP. The patients who seem to benefit from this procedure are those in whom the initial brain injury is not severe and who, over time, develop neurologic decline due to elevated ICP. If medical treatment is not successful in lowering ICP, then craniectomy seems to be beneficial. When used in patients with severe brain injury from the outset (admission GCS < 6), craniectomy has not been shown to be beneficial.[10]

Medical Management

In the absence of surgically resectable mass lesions, the treatment of patients with TBI is largely medical. After the initial injury, the primary issue facing these patients is the development of increased ICP. The brain, like other tissues, responds to injury by developing edema and swelling. Given the closed confines of the skull, the pressure inside the head increases. Initially, CSF leaves the skull through the foramen magnum into the spine. If the pressure continues to increase, eventually blood flow to the brain is diminished. The cerebral perfusion pressure (CPP) is calculated by subtracting the ICP from the mean arterial pressure (MAP). The normal CPP is between 70 and 90 mmHg. A CPP of less than 70 mmHg can lead to possible cerebral ischemia and stroke. If the ICP meets or exceeds the MAP (i.e., the CPP is <0), then blood flow to the brain ceases and brain death occurs. The medical management of TBI thus centers around the reduction of the ICP and the management of the MAP in order to preserve the CPP (Fig. 13.3).

In order to properly accomplish ICP reduction, an accurate measurement of the ICP is needed. This is usually done through the placement of an ICP monitor. The indications for ICP monitor placement are not standardized, but generally a

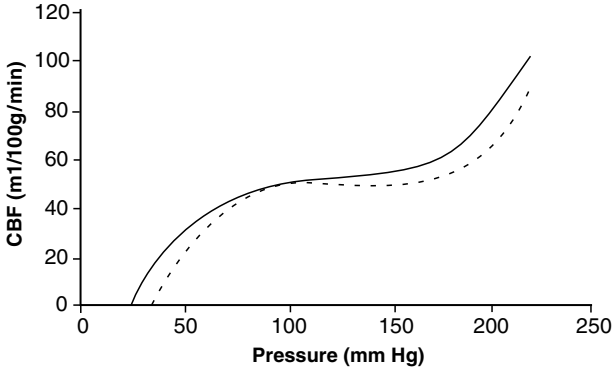

FIG. 13.3. Autoregulation only occurs between certain pressure limits. If the arterial pressure is reduced to values under the lower limit of autoregulation, organ perfusion is compromised.

GCS less than 8 or 9 would justify the placement of a monitor. With a GCS above this level, the patient's neurologic exam can serve as a reliable indicator of neurologic status. Below the level of 8 or 9, the exam becomes unreliable and, therefore, monitoring is helpful. Likewise, a patient requiring sedation for airway management or other reasons will not have a reliable neurologic exam and would benefit from monitoring. In addition, patients with head injury who require surgery for other problems, such as abdominal trauma or orthopedic injuries, may also need a monitor while under general anesthesia. Rough guidelines include monitoring patients with a GCS less than 8 and a head CT without obvious pathology if they meet two of the following three criteria:

1. Age greater than 45
2. Any episode of hypotension in the field (SBP < 90 mmHg)
3. Posturing on examination

Monitoring Tools

Intracranial monitors provide a quantitative reading of cerebral pressures and hence calculation of the cerebral perfusion pressure (CPP = MAP − ICP), thereby indirectly measuring the perfusion of the brain. In days past, this was done by placing a hollow screw into the skull with a fluid column connected to a manometer ("subarachnoid bolt"). Today, the gold standard for ICP measurement is the use of a ventricular drain, which can transduce the ICP and also permit drainage of CSF for management. The ventricular drain is placed within the ventricle and hence, sits in a fluid compartment allowing routine recalibration of measurements. Alternate monitoring tools, such as intraparenchymal monitors, transduce the ICP but do not permit drainage of CSF and are subject to drift of the zero line over time. They are calibrated against atmospheric pressure prior to placement within the cerebrum and hence, cannot be recalibrated without replacement. The placement of these monitors can often be done at the bedside, using a small incision at the coronal suture and a small twist-drill hole through

the skull. The monitor lead is then led out under the scalp to a pressure monitor device. These monitors can often be left in place for days, even weeks, before requiring replacement.

Alternate tools have been devised to help infer cerebral perfusion. Ideally, the perfect tool would engender low risk (noninvasive) and provide continuous, reliable data. Currently, no device has been devised that fulfills all these goals. Noninvasive devices clearly carry the advantage of limiting procedural risk (e.g., hemorrhage, infection) and can be used for an indefinite duration, but have their own intrinsic limits. Radiographic imaging techniques have been used to measure cerebral perfusion and provide data throughout the entire cerebrum (e.g., positron emission tomography (PET), single photon emission computerized tomography (SPECT), CT perfusion, MR spectroscopy), but only provide a single moment of information and require transportation of the patient to the imaging device; thus they have a limited role in the daily management of traumatic brain injury.

Other non-invasive devices include transcranial Continuous Electroencephalography (cEEG), Doppler ultrasonography (TCD), and near-infrared spectroscopy (NIRS). The use of *cEEG* in the ICU can detect early non-convulsive seizures, which are a source of secondary insult to the injured brain. Recent data from cEEG studies demonstrate that seizures occur in 15–20% of patients with severe TBI. About 50% of these seizures are of non-convulsive variety, and some occur despite the use of prophylactic phenytoin at adequate serum concentrations. *TCDs* use ultrasound principles to insonate main intracranial arteries and measure flow velocities. Calculations from the measurements can then be obtained to infer severity of vasospasm, response of autoregulation, flow velocity, and even CPP. Limitations of TCDs include technician-dependent results, noncontinuous data, and anatomic limitations.[11] *NIRS* entails placing several monitors across the patient's forehead and uses the absorption of light by red cells to calculate concentrations of oxygenated hemoglobin, deoxygenated hemoglobin, and cytochrome aa3. These values can be used to infer states of cerebral hypoxia and reduced CPP, but do not provide a specific value and only reflect global changes. NIRS does not provide any information regarding a penumbral region and only reflects global perfusion.[12]

More invasive measures include previously described ventricular drains, intra-parenchymal bolts, subdural monitors, epidural monitors, and jugular venous oximetry. These invasive devices provide a continuous reading that can be used to treat immediate changes, but are associated with procedural risk. Subdural and epidural monitors use fiber-optic technology and are simply placed at the appropriate depth. In theory, they may be associated with a lower risk of complications, but their validity and reliability have not been clearly established.

Jugular venous oximetry entails placement of a fiber-optic catheter into the internal jugular vein (commonly the right side) that is threaded rostrally to the jugular bulb. This technique samples the venous outflow of the cerebrum ($SjvO_2$) and permits calculation of the oxygen extraction of the brain (arteriovenous difference, a-vDO_2). The normal $SjvO_2$ is 60–70%, and typically levels below 50% and 55% have been associated with detrimental neurological outcomes, although one study suggested a lower threshold of 45% in TBI.[13] This type of monitoring provides a measurement of global oxygen extraction, but does not reflect regional differences.

Newer techniques include laser microdialysis, Doppler flowmetry, thermal diffusion flowmetry, and brain tissue oxygenation monitoring. *Microdialysis* involves placement of a microcatheter into the parenchyma of interest. The catheter perfuses physiologic fluid at a constant rate across a semi-permeable membrane, and extracellular metabolites can be collected and quantitated. Elevated extracellular lactate, reduced glucose, and an elevated lactate/pyruvate ratio have been associated with cerebral hypoxia and ischemia. This device has been used to monitor neurotransmitters and metabolites from epilepsy surgery, trauma, subarachnoid hemorrhages, and ischemic events but is not yet standard in management of these patients.[11,14,15] *Laser Doppler flowmetry* requires placement of a fiber-optic laser catheter into or against the parenchyma and measures movement of red blood cells using wavelength changes from the laser recorded by a photodetector. This allows regional measurement of flow, but does not provide a direct measure of CBF. *Thermal diffusion flowmetry* uses thermistors placed over the brain or intraparenchymally to measure the diffusion of temperature to correlate CBF.[10] *Brain tissue oxygenation monitoring* is also a new technique gaining popularity. It entails the placement of a microsensor within the parenchyma that uses a polarographic electrode to measure the brain partial pressure of oxygen, carbon dioxide, pH, and temperature. Normal ranges for these values have been established, and early correlations with outcomes and ischemia have also been reported, but more definitive experience is needed before widespread use is instituted. These recent monitoring tools have been used extensively in laboratory models and with select patients, but have not been widely tested as yet; thus, their validity and reliability remain to be proven.

Treatment of Intracranial Hypertension

To Increase Venous Outflow

The treatment of elevated ICP often involves reduction in one of the three normally occurring elements within the skull (Fig. 13.4). If blood – one of these components – can be safely removed, then ICP will be decreased. Head elevation encourages venous return to the heart. There are no valves in the cerebral venous circulation and, therefore, raising the head above the heart will result in diminishing the intracranial blood volume. Critics of this method of ICP reduction point to the fact that head elevation also reduces the MAP by placing the brain above the heart, thus failing to achieve the needed improvement in CPP. Nonetheless, head elevation remains a mainstay of ICP management.

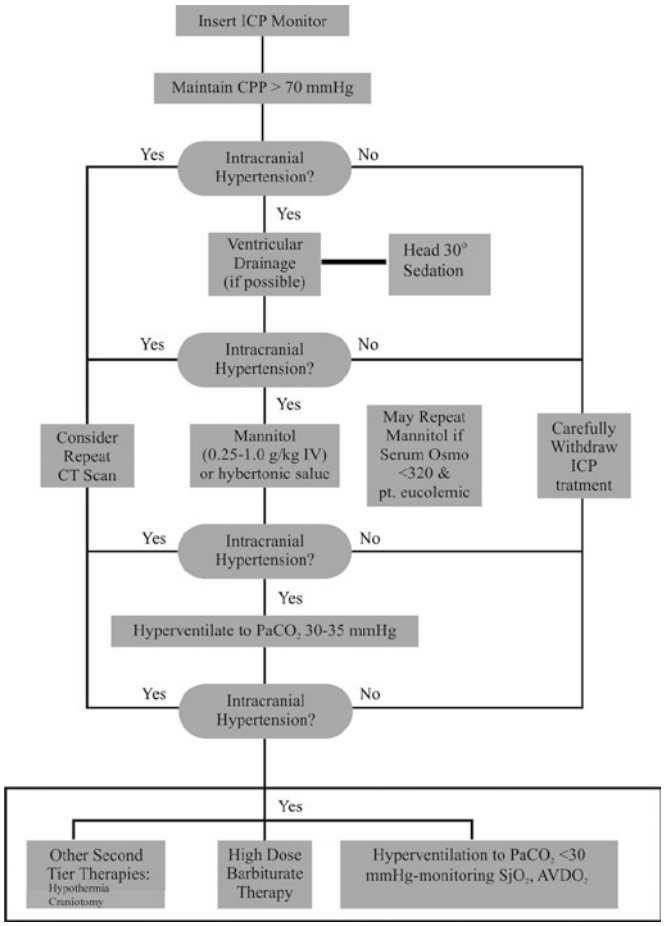

FIG. 13.4. Treatment algorithm for the management of increased intracranial pressure. $PaCO_2$ (arterial pressure of carbon dioxide); SjO_2 (jugular venous oxygen saturation); $AVDO_2$ (arterial venous oxygen content difference); CBF (cerebral blood flow).

CSF Removal

Removal of CSF is an efficient and safe method of treating elevated ICP. As pressure increases, CSF exits the brain through the foramen magnum at the base of the skull. When this proves inadequate, invasive methods are employed. Catheters placed into the ventricular system not only allow for the removal of CSF but also provide a convenient method of measuring the ICP. Placement of external ventricular drains (EVDs) is often done at the bedside with minimal sedation. A small incision is made in the precoronal region of the frontal bone. Using reliable external landmarks, a catheter can be placed into the ventricle quite precisely. Drainage of CSF is then controlled through adjusting the level of the drain reservoir. Elevating the reservoir will slow the amount drained, while lowering it will increase the rate of drainage. Catheters can remain in place for days or even weeks. The risk of infection rises with the length of time the catheter remains in place. Recently, the placement of antibiotic-impregnated dressings has been shown to lower the rate of EVD infection.

Osmotic Diuretics

Edema within cerebral tissue is a major contributor to elevated ICP. Methods to reduce edema often involve the use of osmotic diuretics to pull extracellular fluid into the vascular space, thus reducing intracranial volume. Mannitol is the agent frequently used in this setting. There are several mechanisms by which mannitol exerts its effects. Mannitol induces changes in blood rheology and increases cardiac output, leading to improved CPP and cerebral oxygenation. Improvements in cerebral oxygenation induce cerebral artery vasoconstriction and subsequent reduction in cerebral blood volume and ICP. Second, mild dehydration after osmotherapy is desirable and may improve cerebral edema, although severe dehydration can lead to hyperosmolality and renal failure. Finally, mannitol administration decreases CSF production. Mannitol can be given in bolus form in response to ICP spikes in elevation. The reduction of pressure is often dramatic and occurs within a few minutes after administration. In cases of prolonged ICP elevation, mannitol can be given in doses of 25 g every 6 h. Serum osmolarity must be followed closely, and the mannitol must be discontinued if serum osmolarity remains above 320 mOsm/L; otherwise, the risk of renal injury and acute tubular necrosis rises.

Alternatively, hypertonic saline used at various concentrations (from 3.0 to 23.4%) has been used as an osmotic agent to control elevated ICP. Several studies have corroborated the efficacy and safety of using hypertonic saline to control ICP.[16,17] Hypertonic saline has also been used as a volume expander and has not been associated with hypotension; therefore, it may be more valuable in controlling ICP in hemodynamically unstable patients. Hypertonic saline can be administered in a continuous or intermittent fashion, but typically it is given as boluses for elevation in ICP. Because of its propensity to cause thrombophlebitis, a central venous line is required to administer hypertonic saline, and serial serum sodium levels should be maintained around 150 mmol/L. Alternative measures to control ICP should be considered when serum sodium rises above 155–160 mmol/L. Randomized outcome trials comparing mannitol with hypertonic saline in various subpopulations of neurologic injury would add valuable information to the literature and provide a basis for establishment of the best clinical practices (Table 13.2).

Alteration in pCO_2

Hyperventilation reduces the pCO_2 in the blood. As mentioned in the physiology section, cerebral vessels are quite sensitive to changes in pCO_2 and pH. A reduction of pCO_2 results in a compensatory vasoconstriction of the cerebral arterioles, thereby lowering the blood flow and reducing the ICP. This, of course, can have deleterious consequences, as the reduction of blood flow may result in ischemia to vulnerable tissue. Thus, the use of hyperventilation ($PaCO_2$ 35–40 mmHg) is often restricted to

Table 13.2. Sodium content and osmolality of solutions administered to patients with TBI

Solution	Sodium concentration (mmol/kg)	Osmolality (mOsm/kg)
Lactated Ringer's	130	275
0.9% saline	154	308
20% mannitol	–	1,098
3% saline	513	1,026
7.5% saline	1,283	2,566
23.4% saline	4,004	8,008

treating spikes in ICP. Over time, the effect of chronic hyperventilation is reduced as other homeostatic mechanisms, such as the renal system, will correct the metabolic imbalance.

Sedation

Intravenous sedation is often required in the management of head-injured patients. There are no direct effects of sedation on controlling ICP; however, since many of these patients require ventilatory support, sedation is *needed* to allow for proper respiratory control. Fighting the ventilator will result in increased intrathoracic pressure, which will diminish venous return to the heart and result in increased ICP. Because IV sedation can decrease blood pressure and hypovolemia predisposes to hypotensive side effects, hypovolemia should be corrected before administrating sedative agents. Other deleterious consequences of IV sedation are related to the loss of the neurologic examination while the patient is sedated. The prolonged use of IV sedation and the loss of the neurologic examination is often an indication for the placement of an ICP monitor.

Pharmacologic Methods

Barbiturate coma was the mainstay treatment for elevated ICP in the past; however, the risks of barbiturates limit their usefulness. There are several mechanisms by which barbiturates exert their effect. The primary means by which barbiturates work is likely through the reduction of metabolic demands of the neural tissue, thereby lowering cerebral blood flow and intracranial blood volume. Pentobarbital is the most common agent used and requires a loading dose followed by a maintenance dose for days to even weeks. Continuous EEG monitoring is used in order to determine "burst suppression," a state which is equivalent to maximal reduction of cerebral metabolism. The downside to barbiturate use lies in the cardiac toxicity that is often encountered after prolonged usage. Hypotension is often the limiting factor, reducing the efficacy of barbiturates.

Temperature

Hypothermia has been shown to be effective in improving outcome after severe head injury.[18] Lowering core temperature to 33–35°C slows metabolic processes and also lowers the oxygenation requirement for cerebral tissues. This appears to be particularly important in the area of brain that is ischemic. This will cause a decrease in the ICP. The reduction in extracellular glutamate and free radical production also provides neuroprotection. Lowering the core temperature too far may have adverse effects on the circulatory system and impair the immune response, leading to an increased risk of infection. If this tissue can be preserved, then the overall outcome will be improved.

Neuroprotective Agents

Several differing treatments and medications have been devised to interrupt the detrimental neurophysiological cascade previously described. These measures attempt to prevent further secondary injury to brain tissue. Hyperbaric oxygen has been trialed with the intention of increasing brain oxygenation and hopefully, perfusion. Although there appears to be a trend for increased survival and lower ICPs among patients treated with intermittent hyperbaric oxygen, the functional outcome of patients was not clearly improved.[19,20] Non-definitive benefits, as well as costs and accessibility, have limited further application of this treatment.

Anti-epileptic medications, typically phenytoin, have also been evaluated to avoid secondary injury from seizures in trauma patients. Meta-analyses have corroborated that prophylactic phenytoin appears to reduce the risk of peri-injury seizures (approximately 1 week), but does not provide any protection against delayed seizures. Hence, anti-epileptics are routinely given for 1 week in severe head injury patients.[21]

Although many drugs have shown promising results in laboratory testing, thus far no phase-3 clinical trial has supported use of any neuroprotective agent. Medications with unproven benefits included nimodipine, polyethylene glycol-conjugated superoxide dismutase (PEG-SOD), dexanabinol, progesterone, magnesium, selfotel, and NMDA antagonists.[22–27] Most of the drugs target intermediate steps along the physiological cascades and attempt to prevent further cellular injury by limiting glutamate, Ca^{2+} and Na^{+} release. Other experimental drugs include erythropoietin, estrogen, minocycline, and cyclosporine.[26] Although many drugs are currently being tested in clinical trials, none have shown definitive clinical benefits to date. Steroids were thoroughly investigated for TBI as well and were associated with a higher mortality rate; thus, they are contraindicated for management of head injury.[28,29]

Conclusion

TBI remains a devastating problem, with an impact that not only affects the patient, but also the family and society as a whole. The cost for treatment and long-term care is staggering. Therefore, any meaningful improvement in the treatment of this condition will have a profound and positive effect. While the fate of the patient is often decided at the moment of

impact, the care and management of the head-injured patient in the days to weeks after the injury are crucial to maximize the potential for recovery. Recent work on neural regeneration in head injury has shown some promise,[30] but at present, this treatment is limited to research projects. The principles outlined in this chapter remain the mainstay in TBI to date.

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14
Spinal Cord Injuries

Fred H. Geisler and William P. Coleman

Cause and Nature of Injury

Approximately, 200,000 people in the United States have spinal cord injuries (SCI), and some 10,000 new injuries occur annually. Most new victims are between 18 and 30 years old. The lifetime costs of paraplegia for such patients can exceed several million dollars in medical support and lost wages. The potential mechanisms of injury include compression, distraction, acceleration–deceleration, and shearing forces, as well as direct section from penetrating injuries.

The clinical spectrum of SCI varies greatly. Some injuries involve massive transverse mechanical disruption of all neurologic tissue in the spinal cord, and it is unlikely that any medical, surgical, or pharmacologic intervention can improve neurologic recovery and prevent lifelong disability in these instances. However, in approximately 60% of the acute traumatic injuries, the mechanical injury to the spinal cord is more limited and partial neurologic injury is observed on clinical examination. In these patients, portions of the ultimate nervous tissue dysfunction may result from secondary processes such as local biochemical derangements, systemic hemodynamic consequences of the injury, or delayed mechanical movement of fracture fragments.[1–8] The treatment of these secondary processes forms the basis of medical or surgical therapy.

Experimental Treatments

Efforts to find new treatments are directed toward one or more of the following:

- Neuroprotection
- Repair/regeneration
- Plasticity enhancing
- Replace/assist function

Acute human SCI studies have been tabulated and discussed.[9–13]

Since the earlier, unsuccessful studies[14–22] of methylprednisolone sodium succinate (MPSS) by the NASCIS group and those[23–28] of GM-1 ganglioside by the Sygen group, there have now arisen[13] a large number of new therapies that either have begun, or are about to begin, clinical trials. In view of this activity, physicians should be aware of the experimental options. However, it is also important to remember that, as of this writing, there are no US Food and Drug Administration (FDA)-approved therapies with an indication to treat acute SCI. Therefore, although some of these possibilities are promising, they should be contrasted with the more proven methods, which will be discussed in detail in this chapter.

Three large studies of high-dose MPSS steroids in acute spinal cord injury followed patients during the 1980s and into the 1990s. The first, somewhat inconclusive, National Acute Spinal Cord Injury Study (NASCIS 1)[29,30], was followed by NASCIS 2[14,17–19,31] and NASCIS 3.[21,22] The usefulness of these studies was complicated by extra-scientific considerations and by published reports that are difficult to interpret objectively. The National Institutes of Health (NIH) conducted a public campaign in advance of the scientific publication of NASCIS 2 on May 17, 1990. They sent a fax on April 13, 1990 to some 19,000 emergency room physicians and hospitals. This fax was sent after a National Institute of Neurological Disorders and Stroke (NINDS) press release had resulted in coverage by the *New York Times* and the *Chicago Tribune* on March 31, 1990, by *Science News* on April 7, 1990, and by *Newsweek* on April 9, 1990. This led to widespread use of MPSS, off label. No application for regulatory approval for this indication was completed, and no agency ever approved it. Thus, scientific and clinical consensus was never allowed to develop naturally. Surgeons report[32] that MPSS is administered in acute SCI from fear of litigation, not belief in efficacy. Dr. Bracken,

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a statistician, reinforced this fear by testifying against physicians; he was deposed on June 9, 1998 in Civil Action File No. 96A-7768-6, Superior Court of Fulton County, Georgia.

Despite the seemingly positive wording in the Abstract and Conclusion sections of the NASCIS 2 and NASCIS 3 publications, both studies failed in their primary prospective analyses. In NASCIS 2, efficacy was found only in a secondary analysis of a subgroup: those treated ≤8 h, including 62 + 67 = 129 patients out of 487 randomized. NASCIS 3 found efficacy only in the 3–8-h subgroup, or 71 + 80 = 151 patients of 499 randomized. Critiques of the many further limitations of NASCIS data reporting and interpretation have appeared as letters to editors[33–39] (Our *Lancet* and *BMJ* letters), articles[40–51], and book chapters.[9,10]

The AANS/CNS "Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries" eventually rated[48] the NASCIS publications as Evidence Class III, citing flaws in study design, data presentation, interpretation, and analysis. These guidelines listed MPSS treatment only as an "option." The lack of demonstrated benefit must be weighed against documented risks. The later CRASH trial showed[52] a 3% greater mortality when corticosteroids were given to a multitrauma group with head injuries. If this increased mortality rate also held for MPSS in SCI, then giving it would require serious counterbalancing considerations.

Sygen (GM-1 ganglioside) showed a positive primary analysis in a pilot trial: the Maryland Study[23–25,27,53], which recruited in the 1980s. A subsequent multicenter trial [28,54–56] in the 1990s randomized 760 patients in 28 centers across North America. Some of its secondary analyses were significant, but this trial was not positive in its primary analysis. Although the study was ranked[48] by the AANS/CNS Guidelines as Class I evidence and they listed Sygen treatment as an "option," GM-1 is now difficult to obtain. The investigators of that trial have made its data freely available to other researchers[57] and have reanalyzed it in order to contribute to the clinical trial guidelines[13,58,59] developed by the International Campaign for Cures of spinal cord Injury Paralysis (ICCP).

GK-ii (gacyclidine) a glutamate (excitatory) amino acid antagonist has completed[60] a phase 2 trial that similarly missed its primary endpoint but gives some post hoc support. Other neuroprotective treatments that have not yet been clinically tested, or have received pilot studies with a small number of patients, include thyrotropin-releasing hormone[61], nimodipine[62], the tetracycline antibiotic minocycline[13], the kidney hormone erythropoietin[13], and transplantation of cells that secrete growth factors[13].

Transplantation of autologous macrophages and transplantation of bone marrow stromal cells are[13,63] controversial treatments that have conflicting basic studies and as yet incomplete phase 2 clinical studies. Other treatments directed toward repair or regeneration[13] have not started human trials specifically for SCI or are only in phase 1, including inosine; the rho antagonist Cethrin; the antidepressant rolipram; the antibody ATI-355; the bacterial enzyme chondroitinase; and transplantation of embryonic olfactory cortex cells, of nasal olfactory ensheathing cells, of Schwann cells, of human stem or progenitor cells, or of peripheral nerve bridges.

Animal models of Fampridine (4-aminopryrideine) suggest[13] it may improve conduction velocity in damaged, demyelinated axonal fibers, but several clinical studies[64–66] have produced conflicting results for a variety of endpoints.

Electrical stimulation of human neural tissue has produced new growth of axons in the direction of the negative charge, while distal tissue demonstrates the expected dieback. However, oscillating fields produced by reversing the polarity of the fields every 15 min have produced growth in both proximal and distal nerve fibers. This oscillating field stimulation when applied to the spinal cord has produced [67–69] regeneration at the site of injury in guinea pigs and dogs. A device (Andara OFS) for delivering this form of electrical stimulation to human spinal cord injury is implanted within 18 days of injury, left in situ for 15 weeks, and then explanted. An open-label trial in 14 human subjects with complete injuries has shown[70] statistical ($p < 0.001$) improvement at 1 year over baseline (mean 11.5 days) in ASIA pinprick, light touch, and motor scores. When compared[71] to the placebo group[54–56] of the Sygen GM-1 trial, a historical control known[13,58,59] to represent spontaneous recovery, there is a greater than expected improvement in pinprick ($p = 0.004$) and light touch ($p = 0.003$) sensation, but motor scores are similar. This improvement in sensory function appeared anecdotally to translate to increased sensation of bowel, bladder, and sexual organs, and decreased levels of pain, with no neuropathic pain reported.

Treatments with more Consensus and Evidence

Despite differences in the specific medical and rehabilitative protocols, superior results seem to occur at high-volume, specialized centers with multidisciplinary teams of experienced physicians, nurses, and paraprofessionals who manage the care phases from initial diagnosis and acute treatment through rehabilitation and long-term follow-up. The development of the emergency medical system with trained personnel delivering standardized protocol-based care at the accident scene and transport is a major factor in decreasing complications secondary to reinjury and/or pathologic processes before the patient is hospitalized. Surgical stabilization follows after patients are resuscitated from the other systemic injuries.

Consensus is developing[13] around certain features of direct medical or surgical intervention and rehabilitation, to be discussed in the main part of this chapter. The most agreed upon is using traction or surgery to relieve pressure caused by misalignment of the spinal column. The next most accepted therapy is stabilizing the column with rods and screws.

Although treatment of SCI varies from the North American preference for early stabilization to the European preference for a nonsurgical approach, neither approach has been proven scientifically superior. In a recent evidence-based review of the literature on timing, Fehlings and Tator[72] reported that

clinical studies provide some degree of evidence: "There is limited Class II evidence suggesting that either early (<25 h) or delayed (>200 h) surgical intervention is safe and equally effective." This was confirmed retrospectively in the Sygen multicenter data[54–56] when patients from a pooled group of early and late surgeries ($0 < x \leq 24$ h or $192 < x \leq 288$ h) and a group operated at intermediate times ($24 < x \leq 192$ h) were compared for their ability to make a recovery of two or more AIS grades (see below) at 26 weeks. The intermediate ($24 < x \leq 192$ h) group had lower recovery rates than the other patients within the first 288 h: reduced from 41.4 to 27.7%, which is a 33.1% relative reduction. However, that group included 328 out of 480 (=72.3%) surgeries within the first 288 h. The timing group that had about one-third less chance of recovery accounted for nearly three-fourths of operations within the first 12 days. These results perhaps suggest that both approaches have their validity: Early surgery may be more effective primarily, but late surgery may have better secondary properties. The STASCIS (Surgical Treatment of Acute Spinal Cord Injury) study, currently under way, may eventually shed light on this problem.

Active rehabilitation (primarily to enhance plasticity), in which the patient contributes voluntary efforts to task performance, appears[13] to be effective. Passive rehabilitation, with the therapist massaging limbs and moving them through the whole normal range of motion, should in any case be included, but may not be sufficient to provide full potential benefits. As damage to different neuronal tracts may not be equal and may not be complete, active strategies have been developed to extend the residual function still available. These include different combinations of repetitive voluntary movement training, strength training, and constraint limitation therapy (in which better functioning muscles are artificially limited so as to encourage use of ones with less function). Similar therapies have been tested in numerous clinical trials in other diseases, including after stroke. In SCI, body weight support with treadmill training has shown[13] increased recovery, although a phase 2 failed to show it superior to other forms of active rehabilitation.

A mode of therapy directed primarily to assist and replace function is[73,74] functional electrical stimulation (FES). There have been[13] many small clinical trials completed in FES of the phrenic nerve (to assist breathing) and of the sacral roots (to assist bowel and bladder sensation).

Rehabilitation therapies are comprehensively discussed and reviewed[75] in Spinal Cord Injury Rehabilitation Evidence (SCIRE), available online.

Acute Care Phases

The diagnosis and acute management of SCI can be divided into six phases: initial assessment and immobilization, medical management, anatomic alignment, radiologic diagnostics, surgical decompression, and stabilization. The initial management goals in SCI are to preserve the neurologic function present on arrival and to reverse the presenting neurologic deficits as much as possible. All patients, despite the severity of the initial injuries, are presumed to have incomplete spinal cord injuries with potential for recovery until serial neurologic examinations over 72-h document complete motor and/or sensory loss. This philosophy allows for the uncovering of the 5% of initially complete patients who will have meaningful neurologic recoveries.

These six steps strive to accomplish the following goals in the acute management of a patient with cervical SCI:

- Provide initial cardiopulmonary management, immobilization, and careful transportation to deliver the patient with the least possible SCI.
- Enhance blood flow to the injured spinal cord by reversing initial systemic hypotension and lowering any increase in spinal cord tissue pressure secondary to mechanical compression by displaced bone or tissue.
- Prevent reinjury to the already injured spinal cord by mechanically stabilizing the unstable fracture/dislocation and allowing routine nursing care of the other injuries.

The First Care Phase Begins in the Field

Personnel who treat patients before they are admitted to the hospital identify those with possible SCI by using a high index of suspicion, and an initial field screening and neurologic examination for motor and sensory deficits in all four extremities. Following a protocol-based procedure for splinting and immobilizing the spine, they place the patient on a backboard with his or her head and neck immobilized in a neutral position with devices such as a cervical collar and tape. The major goal is to reduce the risk of neurologic deterioration from further mechanical insults to the spinal cord; flexion of the neck offers the greatest potential for additional damage in patients with cervical fracture/dislocations. The backboard stabilizes the thoracic spine and lumbar spine during transfer and lifting motions, which decreases the forces on the spinal axis. A "sack-of-potatoes" maneuver with several people lifting without a backboard places large forces on the spine and has caused neurologic deterioration.

Maintenance of an airway and adequate ventilation during assessment and transport must supersede the goal of total neck immobilization; reluctance to move the neck of a patient with an identified or possible SCI with respiratory embarrassment may result in inadequate ventilation and eventual respiratory arrest. In response to this apparent dilemma, many emergency medical service protocols include field or immediate emergency room intubation of a patient with identified airway compromise. When the patient requires intubation, in-line manual traction often facilitates rapid placement of the endotracheal tube without overly compromising the immobility of the spinal cord.

In patients with numerous injuries, management of life-threatening injuries is mandated as the first priority. However, the displaced spinal column often can be quickly reduced with cervical traction and stabilized while multisystem work-up and surgery/treatment are ongoing.

A detailed history (from field personnel and family members) is obtained both as an indication of mechanism of injury and for medico-legal reasons. Knowledge of the type of traumatic incident (motor vehicle, motorcycle, diving, gunshot wound, or fall) identifies the probable mechanism of injury and often assists in determining the type of injury. The most common mechanisms of injury that result in SCI include forced flexion (motor vehicle crashes or posterior blows), flexion with rotation (motor vehicle incidents), hyperextension (falls), and vertical compression (axial loading, diving accidents); these mechanisms can occur singly or in combination. Penetrating wounds from gunshots or stabbing can pierce the spinal cord, causing mechanical disruption of the spinal cord tracts; a bullet passing near the spinal cord can cause cord concussion, producing a transient or permanent neurologic deficit.

The Second Care Phase Is Medical Support

Support is needed to reverse the physiologic changes that occur acutely as a consequence of cervical SCI. A severe cervical SCI, as evidenced by a major motor and sensory deficit below the level of the injury, physiologically interrupts the outflow of the entire sympathetic nervous system as it passes through the cervical spinal cord before it exits in the thoracic region. This interruption causes loss of vascular tone and of the ability of the body to accelerate the heart rate, which in turn results in the inability to maintain normal blood pressure. Patients in neurogenic shock typically present with hypotension and bradycardia, a state that differs from that of hypovolemic hypotension and tachycardia associated with blood loss from other injuries. The hypotension associated with the neurogenic shock of SCI usually can be reversed with a small dose of dopamine (3–5 μg/kg/min), which can be adjusted to maintain a mean blood pressure of 80–90 torr in a previously normal, young, healthy individual.

The immediate goals of medical management include maintaining arterial blood gases and vital signs in the normal range. A patient presenting with C5 quadriplegia requires close monitoring of respiratory status (tidal volume, vital capacity, and/or negative inspiratory force). Such a patient often has adequate spontaneous breathing immediately after the injury but later experiences a change in neurologic level (within 4–12 h), resulting in fatigue and necessitating intubation and mechanical ventilation. Serial monitoring of respiratory parameters provides early identification of impending ventilatory failure so that appropriate measures can be initiated before a major respiratory crisis occurs.

On arrival at the emergency room, patients with SCI are managed initially by a traumatology/anesthesiology team, which performs resuscitation and multitrauma evaluation. This protocol-based system of medical management includes a lateral cervical spine radiograph (Fig. 14.1a) with at least one view showing inferior to C7.[76] After a diagnosis of cervical fracture/dislocation with SCI, the patient is typically maintained in cervical traction during the entire admission phase, including all radiologic studies. Concurrently, consultation from the neurosurgery, orthopedic, and critical care teams is obtained.

Two large-bore intravenous catheters, a Foley catheter, and a nasal gastric tube, are inserted in patients with SCI for evaluation and management. A central line should be inserted for

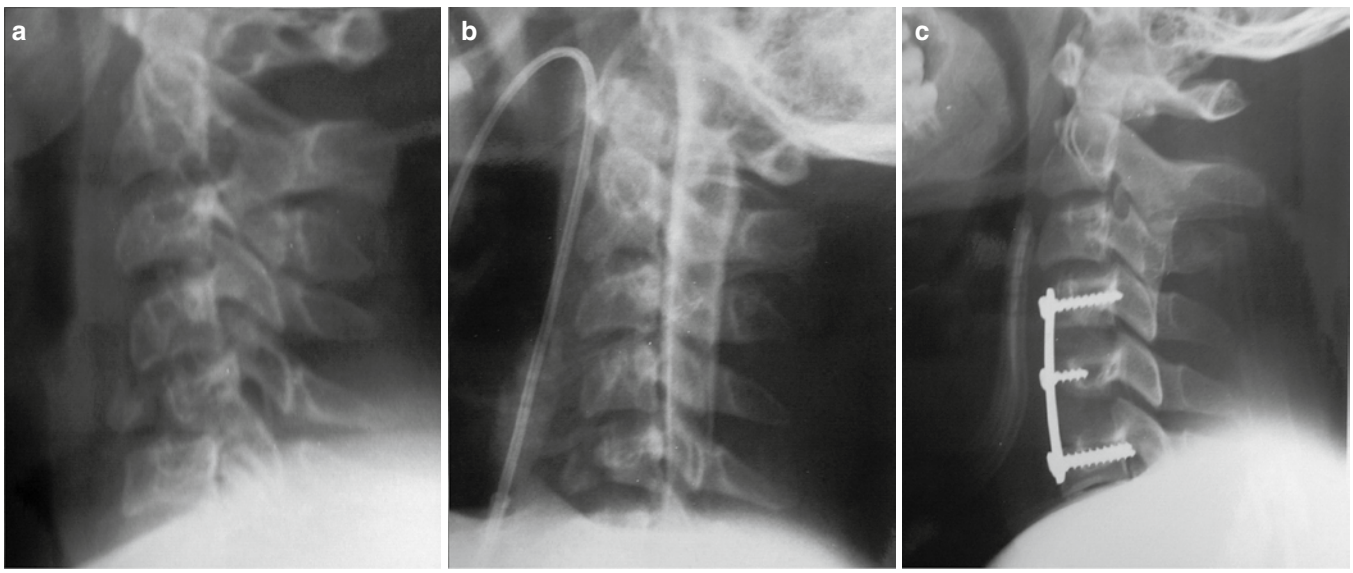

Fig. 14.1. (**a**) Acute traumatic C5 burst fracture with displacement of the posterior portion of the body into the spinal canal with severe spinal cord compression at the inferior corner of the body. (**b**) After cervical traction, with realignment of the C5 body fragments relieving the spinal cord compression. (**c**) Postoperatively, after a corpectomy of the C5 fragments, iliac crest graft arthrodesis, and internal stabilization with a plate-screw construct.

monitoring volume status and for the infusion of vasoactive medications. A Swan–Ganz catheter should be employed in any patient who remains hemodynamically instable or oliguric despite what is believed to be adequate volume replacement. Baseline laboratory work-up includes a complete blood count, electrolytes, amylase, clotting profile, type and cross, urinalysis, arterial blood gas, and electrocardiogram.

In addition to diagnosing spine and/or cord injury, the goal of the initial diagnostic work-up of the patient with multiple traumas is to identify other life-threatening injuries, including those involving the brain, the chest, and the abdomen. Such injuries, which are often occult, can be identified rapidly using a few diagnostic maneuvers. In addition to a physical examination and a lateral cervical spine roentgenogram, chest and pelvis roentgenograms are obtained. A head computed tomography (CT) scan and a diagnostic peritoneal lavage or CT abdominal scan complete the initial diagnostic assessment of the patient who has sustained blunt trauma. Usually, patients with cervical SCIs from motor vehicle or industrial incidents have multisystem injuries, whereas victims of diving injuries do not.[76]

During the first 72 h following SCI, patients receive a "hemodynamic push," in which the mean arterial blood pressure is maintained between 80 and 90 torr with the cardiac output in a normal to high-normal (1.5 times the normal output) range. Inotropic support with dopamine or dobutamine is usually necessary to attain these physiologic goals of medical support. The hemodynamic push is believed to enhance spinal cord perfusion during the neurogenic shock state, which begins at the time of injury. The cardiovascular parameters are carefully monitored and maintained throughout induction of anesthesia, and during surgery in patients who require early spinal decompression or stabilization, or during emergency surgery within the first 72 h after injury. Patients with SCI receive a short course of methylprednisolone steroid therapy (30 mg/kg intravenous bolus over 20 min followed 1 h later by a continuous infusion at 5.4 mg/kg/h for 23 h); however, the role of steroids in treating acute SCI remains controversial. Complications have been reported and the FDA has not approved the use of steroids in this specific patient population. Nevertheless, many physicians currently administer methylprednisolone to patients with SCI.[12,33,41,42]

The Third Phase: Reestablishing Bony Alignment of the Spinal Column

This is necessary in order to remove any direct mechanical compressive forces on the spinal cord or roots that could increase pressure in the local neurologic tissues; in almost all cases, this goal can be accomplished with Gardner-Wells cervical traction or Halo vest immobilization (Fig. 14.1a and b). Neurosurgeons believe that relieving this pathologically increased tissue pressure within hours of injury, along with the treatment of neurogenic shock, enhances tissue perfusion at the site of spinal cord damage and may well improve ultimate neurologic outcome. If a cervical fracture/dislocation is identified and is potentially reducible with traction (as most are), Gardner-Wells or Halo traction is applied and a rapid bony reduction/realignment with progressively increasing weights under radiographic control is performed. The cervical traction often can effectively decompress the cervical spinal cord within minutes of application, whereas hours are required to obtain the preoperative studies, medically stabilize the patient, and achieve surgical decompression of the spinal canal. In the thoracic and lumbar spine, traction forces cannot be used to perform an indirect decompression of the spinal canal as in the cervical area. These areas require surgical reduction, decompression, and internal stabilization.

The Fourth Care Phase: Radiology

Detailed, diagnostic radiologic procedures are used to define the bony damage and to verify decompression of the spinal cord and all nerve roots. The patient undergoes radiologic evaluation, which can include a cervical myelogram via a C1–C2 puncture with a water-soluble contrast agent (Fig. 14.1b), followed by high-resolution CT scan or magnetic resonance imaging (MRI) that includes sagittal reconstructions. The CT-myelogram provides superb bone detail of the fracture site and the anatomic relation of fractured or dislocated fragments to the spinal cord, whereas MRI occasionally provides better images of anterior disc, posterior ligamentum flavum, or spinal cord contusion. The initial reduction is performed on a Stryker frame, and the patient undergoes CT scanning on a Sukhoff transportation device in traction if needed, thus minimizing the likelihood of additional mechanical damage to the spinal cord. Plain radiographics of the entire spinal axis are obtained. The plain radiographics are used to assess spinal alignment from the initial evaluation through long-term follow-up.

Any complaint of neck pain, back pain, or muscle spasm may indicate a spinal column injury without neurologic deficit. These patients require serial radiologic and neurologic evaluations. If the cervical muscle spasm is severe and the neutral position radiologic studies demonstrate anatomic alignment, then flexion–extension lateral cervical radiographs are required several days after injury to uncover any potential posterior ligamentous injury that might result in an unstable cervical spine when the muscle spasm subsides.

The Fifth Phase: Surgical Decompression

Emergency or urgent surgical decompression is required for any mechanically compressed neurologic elements disclosed by the radiologic studies that were not previously decompressed by the anatomic bony alignment procedure of phase 3. Bone and soft tissue compressing the spinal cord or roots, as determined by the CT-myelogram and/or MRI, are surgically removed on an emergent basis, at which time internal stabilization and fusion are also performed. A majority of the emergent cervical cases are bilateral locked facets that cannot be reduced with traction. Almost all thoracic and lumbar fractures

with neurologic deficits require surgical decompression and/or internal stabilization. Details of the surgical repair are determined by the extent of the spinal cord compression, and the mechanical instability of the fracture dislocation and the surgical decompression. A complete description is beyond the scope of this chapter, but it has been covered in several spinal surgery textbooks.[77–80]

The Sixth or Final Care Phase: Mechanical Stabilization

Mechanical means are used to obtain vertical stability of the spinal column and prevent reinjury of the spinal cord from repeated movement of the unstable bony elements (Fig. 14.1c). The stabilization technique is individualized for each fracture and its expected instability. The techniques include internal stabilization with hardware, external splinting with a variety of braces, and prolonged cervical traction to allow the fracture to heal before subjecting it to gravitational forces.[77–80]

Detailed Spinal Cord Injury Neurologic Assessment

Motor and sensory functions in all four extremities are documented at the time of injury as well as on admission to the medical facility to provide a baseline for determining subsequent neurologic deterioration or improvement. These early examinations provide valuable prognostic information on the potential and time frame for neurologic recovery.

Consistency of spinal cord assessment is important, particularly in noting subtle changes in sensation and motor function. The American Spinal Injury Association (ASIA) standardized[81,82] the detailed neurologic examination of the patient with SCI. The assessment is derived from a detailed motor and sensory examination, shown in Fig. 14.2.

The motor assessment system provides a numerical grading system to document improvement or deterioration in function. It tests five key muscles in each limb, left and right, and grades

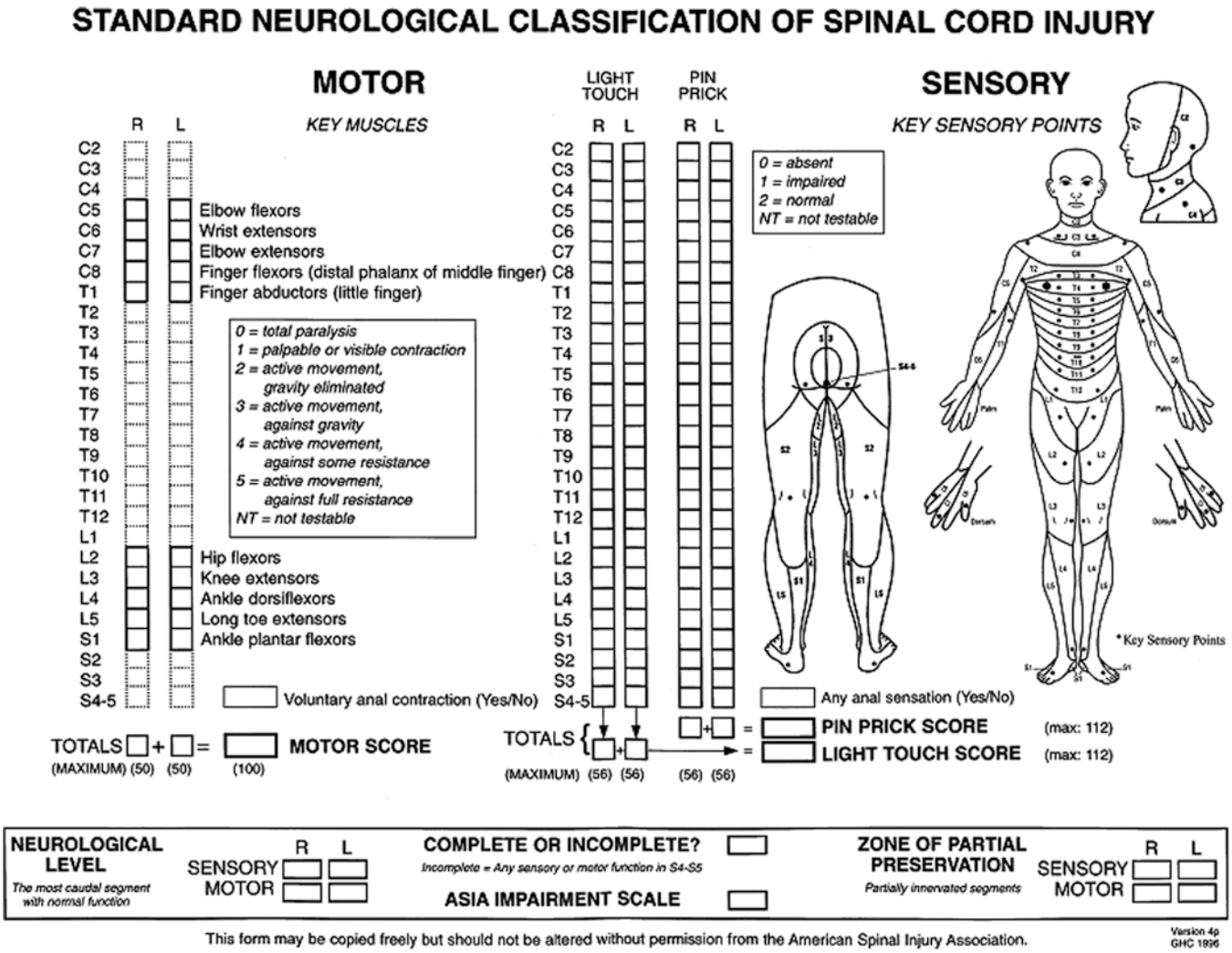

FIG. 14.2. The standard neurological classification of SCI worksheet from the American Spinal Injury Association[1] used to initially classify and monitor neurologic function.

the motor responses on a scale of 0–5 (0 representing total paralysis and 5 representing normal function). The motor score is the sum of the strengths of all muscles. Similarly, 28 dermatomes are graded for pinprick and light touch sensation and graded 0, 1, or 2, according to response as absent, impaired, or normal. These scores are added to give a total score for pinprick and for light touch.

Of particular note are the pinprick sensations in the sacral dermatomes around the rectum and voluntary rectal tone. They indicate sacral sparing, which may be the only remaining neurologic function in an incomplete, but nearly complete cervical spinal cord lesion. Their presence changes the patient category from complete to incomplete neurologic injury – an essential diagnostic distinction because patients with incomplete lesions may tend to have at least partial recovery of neurologic function, whereas those with complete spinal cord lesions often do not have significant neurologic recovery. In 1991, Waters et al. showed that this definition improves the ability to distinguish those patients who will eventually convert to incomplete status from those who do not.

An informal, but useful index is simply to count how many of the 20 examined motor groups have usable function, namely motor grades of at least 3.

An overall functional assessment is provided by the ASIA impairment scale (AIS):

A. Complete. No sensory or motor function is preserved in the sacral segments S4–S5.
B. Incomplete. No motor function below the neurologic level, but sensory function is preserved and includes the sacral segments S4–S5.
C. Incomplete. Motor function is preserved below the neurologic level, but more than half of key muscles below the neurologic level have a muscle strength grade less than 3.
D. Incomplete. Motor function is preserved below the neurologic level, and at least half of key muscles below the neurologic level have a muscle strength grade greater than or equal to 3.
E. Normal. Sensory and motor functions are normal.

The motor and sensory levels of injury are determined[82] separately on the left and right sides of the body as the most caudal level with normal function. For sensory segments this means having a grade of 2. The definition is more subtle for muscles, which are innervated by more than one spinal level: The motor level is the most caudal level with a grade of 3, provided that all higher levels have a grade of 5. In 1955, Long first related self-care and mobility to specific levels. Recent reanalysis of the Sygen data[54–56] shows that motor and sensory levels are not identical in many patients, either at injury or at 1-year post-injury, nor are their left sides necessarily identical to their right. Long (1955) and Welch (1986) based the prediction of self-care and ambulation on the motor level, so use of a single, combined level can be misleading for patients in whom the individual levels differ.

The skeletal level of injury is determined by radiographic examination as the level at which the greatest vertebral damage is found. This level may not correspond well with the neurological level. For example, recent reanalysis of the Sygen data[54–56] shows that of 80 placebo patients with complete injuries at baseline and with a neurological level of C5, only 36 had C5 as their bony level, by confirmed radiology; 11 had a higher bony level, 26 had a cervical bony level that was lower, and the remaining 7 had thoracic anatomical injuries.

For patients with complete injuries, the zone of partial preservation (ZPP) refers[82] to the longitudinal portion of the cord that is injured – but not completely – and, therefore, perhaps has best potential for salvage. The sensory or motor ZPP extends from the most rostral injured segment to the most caudal one that still has sensory or motor function, respectively.

The notions of the level of injury and ZPP place emphasis on picturing the cord longitudinally as a series circuits and finding the location and extent of interruption. In many patients, this notion works perfectly. Reanalysis of the Sygen data[54–56] shows substantial numbers of patients with complete injuries who are consistent with this pattern in that they regain much of their function in the ZPP, but not below it.

But in other patients this notion needs to be balanced with its complement: a crosssectional picture of the cord as a population of fibers. In the crosssectional picture, there might be differential patterns of injury: left versus right, sensory versus motor, and white matter versus gray. The Sygen data show many patients who exhibit differential injury in these dimensions at baseline, who show recovery outside the ZPP, or differential recovery later. It is suggested that such patients may be ones in which crosssectional asymmetries are important. The exact nature of their recovery can be very difficult to predict at baseline using any criteria now known.

Thus these two patterns, and mixtures of them, give rise to a variety of types of injury and a corresponding variety of prognoses. While it is true that the AIS grades show[13,58,59] strong prognostic patterns in all the known databases (few good recoveries among baseline AIS = A patients, more among AIS = B, and many among higher AIS grades) in a general sense, it can still be tricky to predict specifically for individual patients: Their potential can sometimes depend on features not apparent from the baseline exam. Physicians are warned against using prediction of outcome as a decisive guide for how aggressively to treat.

While many SCI patients and much of the older literature emphasize restoration of completely normal function – especially including the ability to walk – as the therapeutic goal, and while such goals are indeed of prime importance, it is crucial to realize that SCI is so devastating to patients that improvements that are numerically small on these scales or even not measured by them can be decisively important to a patient's self-image and ability to function. Anderson surveyed 681 SCI patients[83] for their own assessment of the improvements that would be most important to them. Among quadriplegic patients, only 9% mentioned walking movement as their first priority. This outcome ranked fifth out of seven functions mentioned: behind bowel and bladder function

(9%), upper body and trunk strength, and balance (12%), and sexual function (13%). The most important goal, mentioned by 48%, was arm and hand function. For paraplegics, sexual function was the most cited (26%), followed by bowel/bladder (18%), trunk strength (17%), walking movement (16%), and elimination of chronic pain (12%).

The presenting clinical syndromes for patients with incomplete SCI are as follows:

- Central cord syndrome: a lesion occurring almost exclusively in the cervical region that produces sacral sparing and greater weakness in the upper limbs than in the lower limbs.
- Brown-Sequard syndrome: a lesion that produces relatively greater ipsilateral proprioceptive and motor loss, and contralateral loss of sensitivity to pain and temperature.
- Anterior cord syndrome: a lesion that produces variable loss of motor function and of sensitivity to pain and temperature, while preserving proprioception.
- Conus medullaris syndrome: injury of the sacral cord (conus) and lumbar nerve roots within the spinal canal, which usually results in an areflexic bladder, bowel, and lower limbs from lesions at the caudal portion of the spinal cord. Sacral segments may occasionally show preserved reflexes (e.g., bulbocavernosus and micturition reflexes) with lesions more proximal in the conus that spare the caudal portion.
- Cauda equina syndrome: injury to the lumbosacral nerve roots within the neural canal resulting in areflexic bladder, bowel, and lower limbs from lesions below the caudal portion of the spinal cord.

During long-term follow-up, another scale, the Functional Independence Measure (FIM), is used to assess the ability to perform the activities of daily living[84] (Fig. 14.3). This scale monitors six areas of daily functioning: self-care, sphincter control, mobility, locomotion, communication, and social cognition. Each of the 18 items is evaluated on a seven-point scale to assess independent function. The FIM total score is obtained by summing across all 18 items. The FIM total score provides an estimate of the cost of disability, safety, dependence on others, and the need for technologic devices.

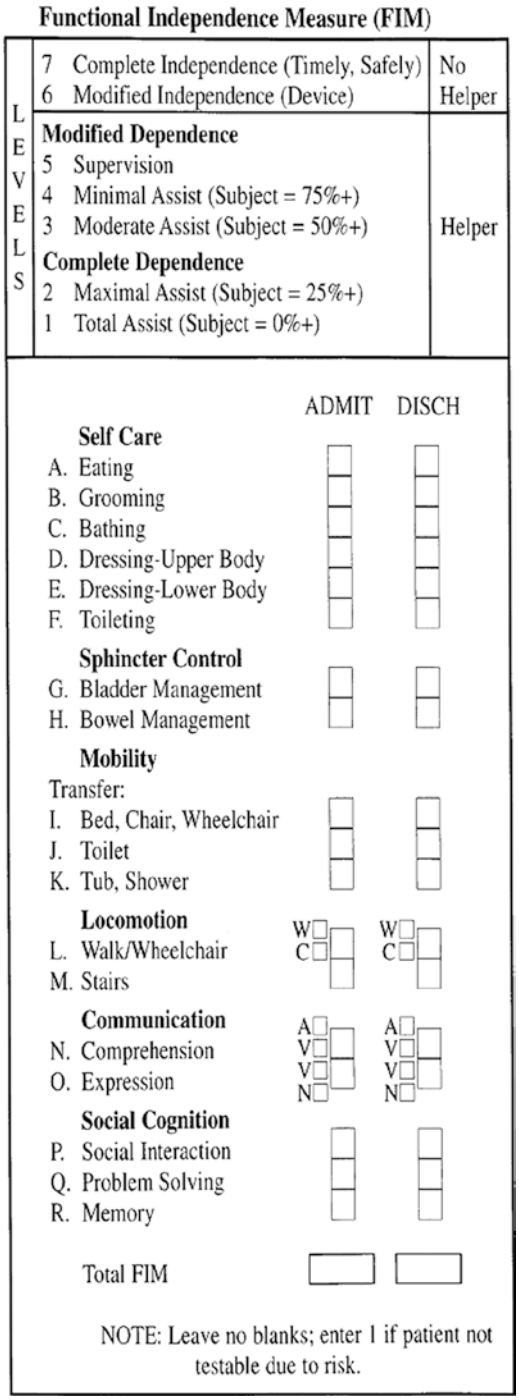

FIG. 14.3. The FIM, to monitor and evaluate the ability to perform activities of daily-life[10]. Reproduced from Geisler FH. Clinical trials of pharmacotherapy for spinal cord injury. Ann N Y Acad Sci. 1998;845:374–381 by permission of Blackwell.

Discussion

Clinicians must temper their expected ultimate outcome goals from spinal cord resuscitation and rapid spinal cord alignment with the realities of neurologic injury. SCI, like head injury, can be divided according to primary and secondary damage. The primary neurologic damage is destruction of tissue from either mechanical or ischemic insult between the time of the injury and initial medical care; it results in a permanent neurologic deficit. Although there is currently no way to alter this damage, nerve grafting in the future may bridge the damaged spinal cord segment. Secondary damage to the spinal cord occurs after the insult and is caused by a combination of delayed swelling, continuous mechanical reinjury to the injured spinal cord segment, and tissue anoxia. The injured segment is also subjected to low perfusion and/or release of endogenous factors (e.g., free radicals; catecholamines; arachnoidal acid metabolites; and changes in glucose utilization, oxygen utilization, and calcium flux) during the first few hours after the injury.

Pathophysiologically, when the spinal cord is injured by either mechanical or ischemic insult, the damaged area begins centrally in the gray matter and spreads centrifugally outward as the force of the impact increases. Within the first 15–30 min, the central gray matter is disrupted and small hemorrhages appear. This damage appears to be primary and thus irreversible. However, the peripheral white matter tracts are a low metabolic demand region and their ultimate demise may take hours to several days. Animal experiments of SCI indicate that spinal cord blood flow is a predictor of viability in that the subjects with increased blood flow in the white matter tended to recover, whereas those with decreased blood flow in the white matter go on to physiologic spinal cord changes located centrally. This has been verified in animal experiments using CT scan, MRI, and interoperative ultrasound.

The treatment of SCI remains controversial in terms of the type and timing of medical and surgical therapy. Basic physiologic bony support combines mechanical reduction and stabilization of the bony instability. This appears to allow the greatest chance for maximal recovery of neurologic function. Prompt initial resuscitation, the use of vasopressor agents during the first 72 h following injury, critical care management to prevent complications that contribute to morbidity, and surgical decompression with internal stabilization form the fundamental care plan for the victim of SCI. Research is currently ongoing with the hope of improving neurologic outcome with pharmaceutical therapy.

Pharmacologically active agents such as GM-1 ganglioside, other investigational medication, or electrical stimulation may demonstrate superior neurologic outcomes following SCI in the near future by enhancing natural injury recovery mechanisms.

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15
Ischemic Stroke

Jamary Oliveira-Filho and Walter J. Koroshetz

Ischemic stroke is becoming an increasingly important condition for intensivists to recognize and manage in order to minimize the neurologic injury. It is a major public health issue because it is the third leading cause of death and the leading cause of adult disability. Devastating ischemic brain injury often strikes patients who are in the hospital for treatment of an unrelated medical or surgical condition. About 5–10% of acute strokes occur in the critical care and postoperative units, and on the hospital floors. Stroke that complicates another illness is a cause of increased in-hospital stay, mortality, and long-term morbidity.[1] Stroke in the intensive care unit (ICU) can be classified into three major categories (Table 15.1) according to (1) the presence of a variety of adverse events associated with increased stroke risk, (2) the presence of conditions that cause critical care illnesses as well as ischemic stroke, and (3) stroke as the primary reason for critical care admission, seen much more frequently in the post-thrombolysis era. Postoperative stroke, though rarely seen after general surgery (0.08–2.9% of cases), occurs more frequently after cardiac or vascular procedures, and in patients with various cerebrovascular risk factors.[2]

The accurate diagnosis and treatment of acute stroke can be difficult in patients who are critically ill because the immediate postoperative period is complicated by the presence of sedation, paralysis, and metabolic derangements that may mimic or delay the diagnosis. Modern neuroimaging may be necessary for diagnosis. Standard stroke treatments such as anticoagulation and thrombolytic drugs carry a high morbidity because of the increased risk of bleeding from sites of previous tissue injury.

Signs and Symptoms

The patient presentation depends on the vascular territory that is involved and the mechanism of infarction. A new focal, neurologic deficit is often the earliest sign of when an ischemic event has occurred. It is important to realize, however, that some metabolic abnormalities, especially hypoglycemia, can also be responsible for focal neurologic deficits. Global depression in mental status indicates brainstem or bihemispheric dysfunction. The latter can occur as a result of diffuse global ischemia, bilateral hemispheric stroke, or encephalopathy secondary to sedative hypnotics, hypoglycemia, uremia, sepsis, hepatic failure, hypoventilation with CO_2 retention, or electrolyte abnormalities. Determining whether the deterioration in neurologic function is the result of a stroke or a metabolic encephalopathy is a common and sometimes difficult task in the critically ill patient (Table 15.2). It is especially difficult to accurately diagnose stroke in a patient who is already encephalopathic or recovering from anesthesia. Postoperatively, early presentation of a focal neurologic deficit when the patient is awakening from anesthesia should point to intraoperative stroke, whereas new symptoms preceded by a normal anesthetic recovery period should point to risk factors, such as aortic atherosclerosis or atrial fibrillation, that were present before or after surgery.[3]

The inclusion of a simple neurologic assessment in the routine evaluation is essential to identify important changes that occur in stroke. The sudden onset of a neurologic deficit is the core feature of the stroke syndromes (Table 15.2). Any discrete change over a short period should stimulate more

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Table 15.1. Stroke in the critical care unit.

Stroke as a complication of critical illness	Stroke accompanying the primary critical illness	Primary stroke in the ICU
Surgical complication: cardiac bypass, carotid endarterectomy, fat embolism after hip replacement surgery, neurosurgical complication, others	Type A aortic dissection involving vertebral and or carotid arteries	Thrombolysis or post-thrombolysis management
Hypotension in the ICU or operating room	Hypotension	Malignant ischemic brain edema
Air embolism via venous catheter	Infective or marantic endocarditis	Need for mechanical ventilation: Inability to protect airway, damage to respiratory centers, secondary airspace disease (aspiration pneumonia)
Carotid dissection after inadvertent puncture	TTP	Secondary hemorrhage into ischemic stroke
Stroke due to atrial fibrillation, cardiomyopathy, cardioversion	Trauma: cerebrovascular arterial dissection, fat embolism, hypotension in patient with large artery stenosis	Progressive stroke: Severe middle cerebral, carotid or vertebrobasilar stenosis due to atherosclerosis or dissection
Cerebral vasospasm after subarachnoid hemorrhage	Drug abuse: cocaine, amphetamine, injection of talc and other particulate matter	
Stopping chronic anticoagulation in patients with atrial fibrillation, prosthetic valves, cardiomyopathy, etc. because of increased bleeding risk in the context of critical illness	Myocardial infarction with mural thrombus	
Angiography: cholesterol emboli disease, catheter tip embolus		
Endocarditis after sepsis	Hypercoagulable state: DIC, anti-phospholipid antibody syndrome	

TTP thrombotic thrombocytopenia purpura; *DIC* disseminated intravascular coagulation.

Table 15.2. Distinguishing features of encephalopathy and stroke.

Encephalopathy	Stroke
Generally slow onset of neurologic change	Generally sudden or discrete, stepwise deterioration of neurologic function
No responsible focal lesion on imaging	Computed tomography scan, standard magnetic resonance imaging, or diffusion weighted magnetic resonance scan with evidence of infarct
Altered level of alertness prominent but may be combined with focal neurologic deficit	Focal neurologic deficit prominent with altered level of alertness occurring in bilateral stroke or high brainstem stroke or in combined stroke/ encephalopathy
Waxing/waning level of alertness common	More commonly monophasic change in neurologic condition
Electroencephalography with diffuse slowing, commonly frontal intermittent recurrent delta activity	Electroencephalography with asymmetric slowing

extensive clinical and imaging evaluation. Except in patients being treated with sedation and neuromuscular blocking agents, the ability to follow simple commands, move each extremity, count fingers presented in each hemifield (or blink to threat), and respond to a sensory stimulus can be charted by the ICU staff. Regular neuro-monitoring facilitates prompt investigation of changes. In the paralyzed and sedated patient, a neurologic injury may be impossible to recognize unless the patient is weaned from medications.

A working knowledge of the different stroke types is essential for making accurate diagnoses. In addition, the stroke type is a determinant of the long-term functional outcome. It is important to understand the latter when making risk/benefit decisions regarding the implementation of treatments that carry significant risk.

The most common stroke occurs in the middle cerebral artery (MCA) territory. Motor deficits predominating in the upper extremity with a gaze and head deviation contralateral to the hemiparesis is suggestive of MCA occlusion. Aphasia occurs in lesions of the dominant hemisphere, and hemispatial neglect occurs in lesions of the nondominant hemisphere. In intubated patients, manifestations of language impairment include the inability to mouth words or follow simple commands. In the chronic phase, anterior lesions in the dominant hemisphere preferentially affect the language output. Posterior or complete MCA territory strokes are devastating because they can destroy the ability to comprehend and reason (receptive or global aphasia). The ability to mimic movements performed by the examiner is often retained except with the most severe aphasia. Patients with hemispatial neglect attend only to stimuli on one side (usually the right) of the bed. Malignant brain edema leading to a fatal increase in the intracranial pressure occurs predominantly in complete MCA strokes.

Motor deficits predominating in one lower extremity suggest an anterior cerebral artery (ACA) occlusion, especially if there is an accompanying grasp reflex. ACA infarcts may also manifest as abulia. These patients behave as if they have lost interest in their surroundings and require much prompting to respond and follow commands. After sufficient coaching, patients can reveal more cognitive function than initially expected. Significant recovery can occur in unilateral ACA stroke, although the lower leg may remain plegic.

Patients with hypotension and low cerebral blood flow may suffer from an ischemic injury at the border zone region

between the anterior and middle cerebral arteries. Stroke in the ACA/MCA border zone causes proximal limb weakness (the man-in-the-barrel syndrome). Bilateral stroke in the MCA/posterior cerebral artery (PCA) distribution causes an unusual visual-spatial disturbance, resulting from disconnection of the visual cortex from the language and spatial processing cortex (e.g., inability to recognize faces [prosopagnosia], misreaching, defective visual exploration, and unawareness of blindness [Anton's syndrome]).

PCA occlusions are less common and more difficult to recognize because most of the occlusions do not cause motor deficits. PCA occlusions may be unilateral or bilateral because they originate from the basilar artery. Thus, patients often present with unilateral visual field impairment. If the visual field impairment is bilateral, there can be "cortical blindness" characterized by complete amaurosis with intact papillary reflex. It is noteworthy that patients with cortical blindness who are awake often are not aware of any abnormality, so identifying the deficit requires specific testing by the staff. Unilateral PCA occlusion may not result in permanent severe disability. Bilateral PCA occlusion, usually with a top of basilar embolus, can cause permanent severe deficits in alertness and memory due to bilateral thalamic involvement.

Vertebrobasilar occlusions are a major diagnostic challenge when patients develop coma and quadriparesis immediately postoperatively. Close attention to the following signs is helpful in making the diagnosis: abnormal extraocular movements, such as nystagmus and/or ocular misalignment; absent or asymmetric corneal reflexes; and asymmetric grimacing to painful stimuli. Gaze preference in brainstem lesions, as opposed to supratentorial lesions, is toward the hemiparetic side. Most patients, however, present with a decreased level of arousal because of dysfunction of the brainstem/diencephalic reticular activating system, vertigo, nausea, ataxia, hemiparesis or quadriparesis, and cranial nerve deficits.[4] Embolus to the top of the basilar artery is especially difficult to diagnose because it often causes a poor responsive state (abulia), with loss of upgaze and convergence or visual loss as the only focal findings. Acute basilar artery occlusion is usually fatal.

Stroke Mimics

Many other causes of acute focal or global neurologic deficits are present during the postoperative period. Hypoglycemia can present as stroke and the blood glucose level should be checked in any critically ill patient who develops acute neurologic deterioration. Hypoglycemia is a likely cause of neurologic change in patients receiving insulin or oral hypoglycemic agents, in those who have had parenteral nutrition abruptly stopped, or in those who have had a hepatic failure. Sedation, hypoglycemia, hyponatremia, uremia, and surgery itself may all cause impaired mental status and precipitate either reappearance or worsening of old deficits.[5] Therefore, these should be excluded by appropriate laboratory and imaging tests. Modern neuroimaging is extremely valuable in making a positive diagnosis but normal imaging studies alone, however, do not exclude a vascular etiology. In one study, 28 of more than 700 patients had a normal initial diffusion weighted magnetic resonance imaging (MRI) during stroke-like deficits. More than half of the 28 were considered to have acute ischemia as the underlying etiology.[6]

Seizures are an uncommon cause of acute focal deficit immediately after the postoperative period, but they should be suspected in patients with a previous history of epilepsy. Transient paralysis of one or more limbs is usually preceded by a motor seizure (Todd's paralysis). Postictal electroencephalogram may demonstrate asymmetric slowing or subclinical seizure activity in the affected hemisphere.

Migraine is typically suspected in young women with a history of recurrent pulsatile headache or a family history of migraine. Symptoms are usually progressive (e.g., from visual scotomas to paresthesias and then aphasia with hemiparesis). Headache usually follows but may be absent, along with photophobia, phonophobia, nausea, and vomiting. Imaging studies have been unrevealing.

A syndrome of reversible posterior leukoencephalopathy has been described.[7] Patients are hyponatremic or mildly to severely hypertensive because of eclampsia, renal disease, postoperative SIADH, or the due to the effects of medications for liver transplantation; and they subacutely develop severe headaches, seizures, visual symptoms, and focal motor deficits.[7,8] Computed tomography (CT) shows low density and MRI shows a typical hyperintense signal on T2-weighted images predominating in bilateral occipital lobes. Diffusion-weighted imaging is initially normal, and differentiates this abnormality due to predominantly vasogenic edema from acute infarct in which DWI is hyperintense.[9] Rapid control of the hypertension (and hyponatremia) in these patients is associated with complete resolution of symptoms and imaging abnormalities in most cases.

Some patients who undergo carotid endarterectomy (CEA) for symptomatic severe carotid stenosis develop a "hyperperfusion syndrome" characterized by severe headache, irritability, focal neurologic signs contralateral to the site of endarterectomy, and seizures. The patient is often considered to have had a massive hemispheric stroke on the side of the endarterectomy. Imaging studies show patent blood vessels, hyperemia on angiogram (direct angiogram or magnetic resonance angiography), and edema of the affected hemisphere. Transcranial Doppler study shows high velocity blood flow. Patients may present immediately or up to 17 days after surgery. The incidence of hyperperfusion syndrome has been reported to be 0.4–2% of all endarterectomies, with a 30–80% mortality rate.[10] Fatal hemorrhaging sometimes occurs, but is a reversible condition. Treatment should include rapid normalization of blood pressure and the coagulation system.

Tumors are usually a cause of progressive neurologic deficits along with headache. However, some patients may present with acute and sometimes reversible neurologic deficits.[6,11]

Potential causes of these deficits include hemorrhage in the surgical site, vascular damage, seizure, and mechanical effects resulting from localized high intracranial pressures.

Etiology

Strokes are classified according to the mechanism into cardioembolic, low-flow, large-vessel atherothrombosis (carotid and basilar artery), small-vessel disease (lacunar-type strokes), other defined causes, and unknown.[12,13] Criteria for each subtype of stroke have been recently revised.[14] Cardioaortic embolism is suspected in patients with major territorial infarctions (MCA, ACA, or PCA) in whom a high-risk cardiac or aortic source is present (Table 15.3).[14] Severe atherosclerotic stenosis or occlusion in the extracranial cerebral arteries is a common source of embolus to the intracranial circulation. This is the more common stroke mechanism in out-of-hospital, large-vessel, atherosclerotic stroke, but low-flow strokes are typically seen with severe stenosis in the carotid in patients who become hypotensive intraoperatively or in the ICU. Under these circumstances, infarction develops in the border zone between the major vascular territories (MCA–ACA, MCA–PCA, or ACA–PCA). Lacunar infarcts are deep, nonembolic cortical lesions seen in patients with chronic hypertension. They are rarely seen in postoperative patients. Because the postoperative period is associated with a transient increase in the procoagulant and a decrease in the fibrinolytic activity,[15–17] there is an increased risk of venous but not arterial thromboembolism.[18]

Table 15.3. Cardio-aortic sources for emboli.[14]

Sources with high primary risk for ischemic stroke (> 2% annual risk of stroke)
Sources of embolism of thrombotic origin
Left atrial thrombus
Left ventricular thrombus
Atrial fibrillation
Paroxysmal atrial fibrillation
Sick sinus syndrome
Sustained atrial flutter
Recent myocardial infarction[51,52] (within 1 month)
Rheumatoid mitral or aortic valve disease
Bioprosthetic and mechanical heart valves
Chronic myocardial infarction together with low ejection fraction less than 28%
Symptomatic congestive heart failure with ejection fraction less than 30%
Dilated cardiomyopathy
Non-bacterial thrombotic endocarditis
Sources with embolism not predominant of thrombotic origin
Infective endocarditis
Papillary fibroelastoma
Left atrial myxoma
Sources with low or uncertain primary risk for ischemic stroke (<2% annual risk of stroke)
Cardiac sources of embolism
Mitral annular calcification
Patent foramen ovale
Atrial septal aneurysm
Atrial septal aneurysm and patent foramen ovale
Left ventricular aneurysm without thrombus
Isolated left atrial smoke (no mitral stenosis or atrial fibrillation)
Aortic sources of embolism
Complex atheroma in the ascending aorta or proximal arch

Table 15.4. Rare causes of stroke in the post-operative period.

Syndrome	Specific setting	Clinical features
Arterial dissection	Trauma, general surgery	Delayed onset of focal deficit T1 MRI with wall hematoma Angiography with intracranial occlusion
Air embolism	Cardiac surgery, neurosurgery, central line removal	Intraoperative hypoxia, hypotension, fall in end-tidal carbon dioxide Echocardiogram with hyperechoic "bubbles"
Fat embolism	Trauma, hip and knee replacement	Respiratory distress, petechiae, mental status change MRI with multiple infarcts
Cholesterol embolism	Angiography; cardiac, aortic and carotid surgeries; Coumadin; thrombolysis	Purple toes, renal failure, ischemic bowel, eosinophilia MRI with multiple infarcts

Some less frequent causes of stroke are more common after certain types of surgery (Table 15.4). Spontaneous arterial dissection has been reported after neck manipulation during positioning for general surgery or cardiac surgery.[4] Dissection is a serious complication of both major and minor neck injuries. Axial T1 MRI with fat saturation pulses combined with MRA is the initial study of choice to document the arterial occlusion or subocclusion with the characteristic crescent-shaped hematoma in the vessel wall.[19,20] CT angiography may be more practical in the work up of the emergent trauma patient. A CT angiogram (CTA) or conventional angiogram may show either subocclusion with a double lumen (most specific sign) or a gradual narrowing followed by a complete occlusion (more common "string sign"). Most dissections are extracranial, but unlike atherosclerotic plaques that typically occur near the carotid bifurcation, carotid dissections occur above the bifurcation, and vertebral dissections most commonly occur in the high cervical segment. Treatment to prevent artery-to-artery embolic stroke in extracranial dissections most commonly consists of intravenous (IV) or low-molecular-weight heparin followed by a short course of warfarin. Intracranial dissections, especially intradural vertebral dissections, can potentially rupture into the subarachnoid space and may be a contraindication to anticoagulation. The patient with progressive low-flow stroke may require a high-risk angioplasty/stent or bypass surgery. Cerebral artery dissections that are not totally occlusive frequently heal, and flow patterns return to normal over months. Permanent deformation of the vessel leading to pseudoaneurysm formation or arterial webs can also occur. Therefore, all patients with dissections require follow-up MRA or CTA after 3–6 months to document vessel patency and lack of complications.

Cerebral air embolism has been described as a complication of cardiac surgery,[21] neurosurgery performed with the patient in the sitting position,[22] or simple removal of central venous lines.[23] The incidence may be as high as 30% of patients undergoing neurosurgery in the sitting position, although most are inconsequential with early recognition and treatment. Patients present intraoperatively with acute hypoxia, hypotension, and a fall in end-tidal carbon dioxide. Immediate diagnosis and treatment consists of assuming a head-down position and aspiration of the right atrium via a central venous catheter. Intraoperative precordial Doppler ultrasound improves the detection of air embolism in high-risk patients.[22] Some authors have recommended hyperbaric oxygen as a primary therapy, but no controlled studies have been undertaken.[21] Some patients have permanent neurologic deficits, but the exact morbidity and natural history is poorly understood.

Cerebral fat embolism occurs in 0.9–2.2% of patients with traumatic long bone fractures[24] and in 0.1% patients after hip and knee replacements.[25] The mechanism of embolization seems to be an increase in the intramedullary pressure associated with either surgery or trauma, with the release of fatty bone marrow into the systemic circulation. Emboli reach the brain by intracardiac shunts or by deforming through pulmonary capillaries.[26] Patients present with a triad of acute respiratory distress, petechial rash, and global neurologic dysfunction after a seemingly uneventful anesthetic recovery. Intracellular fat globules can be detected by bronchoalveolar lavage,[27] but are nondiagnostic. Some patients develop transient or permanent focal neurologic deficits. Imaging studies show multiple small lesions in the deep white matter, basal ganglia, brainstem, and cerebellum. MRI is more sensitive for detecting these lesions.[24] Mortality varies from 13 to 87% and has improved with modern intensive care.[28] Most survivors have a good long-term prognosis without specific treatment.

Cholesterol embolism occurs in patients with generalized atherosclerosis from disruption of ulcerated atheromatous plaque material into the systemic circulation.[29] Typical settings in which this occurs include following invasive angiographic procedures, aortic manipulation during cardiovascular surgery, treatment with vitamin K antagonists, carotid manipulation, and thrombolytic therapy.[29–31] Clinical manifestations include "purple toes" (painful ischemia of extremities with preserved arterial pulses), acute renal failure, ischemic bowel, livedo reticularis, and eosinophilia. Fundoscopy may reveal retinal cholesterol emboli. Imaging characteristics are similar to those for fat embolism because small cholesterol crystals impact the terminal branches of major arterial territories (Fig. 15.1). The prognosis depends on the extent and location of the cerebral infarcts. Antiplatelet agents are usually recommended.

Diagnosis

In acute stroke evaluation, neuroimaging is used to exclude intracranial hemorrhage, identify the vascular territory responsible for the neurologic deficit, and estimate the extent of tissue injury. New imaging techniques can discern tissue that has been irreversibly damaged from ischemic tissue that is still salvageable. Selection of each imaging modality depends on the availability and specific clinical indication.

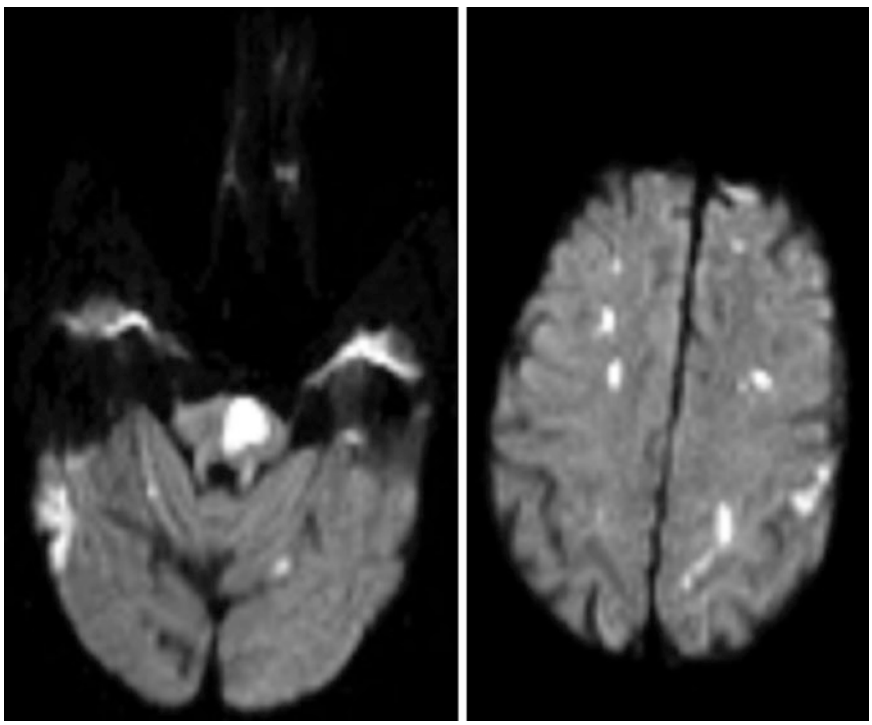

FIG. 15.1. Diffusion-weighted MRI of cholesterol emboli after combined coronary artery bypass grafting and aortic valve replacement. The patient was slow to awake with right hemiparesis, right gaze deviation, purple toes, and renal failure. The preferential distribution of emboli to distal vascular territories can be seen.

Computed Tomography

The main advantages of CT include widespread availability and speed of acquisition. CT excludes intracranial hemorrhages and provides information about major territorial infarctions. Early reports of the technique's low yield for infarcts during the first 24 h after the insult have changed because of the availability of better quality scanners, appropriate window levels, and improved recognition of early signs of infarction. The current sensitivity of CT during the first 6 h varies from 45 to 85%.[32–36] Subtle early signs include loss of the insular ribbon, hyperdense middle cerebral artery, local brain swelling, and parenchymal hypodensity (Fig. 15.2). Window and level settings of about 20–30 Houndsfield units provide a high-contrast image that allows greater perspicuity of early stroke.

Most spiral CT scanners now have angiographic capabilities. Portable CT scanners are now available for use in ICUs to avoid transport of critically ill patients. While the patient is in the scanner for the noncontrast CT, a CTA can be acquired within 40 s (Fig. 15.2). This allows large intracranial artery occlusions to be identified immediately, with a sensitivity of 89%.[37] Further, parenchymal contrast enhancement in the whole brain axial slices obtained with the same bolus of dye is proportional to the volume of blood reaching the tissue. Thus, areas of hypoperfusion can be seen acutely[38] and are highly predictive of the region affected. CTA is a practical means to emergently identify patients with a large artery occlusion who may be candidates for IA reperfusion therapy (see below).

Magnetic Resonance Imaging

New MRI techniques are more sensitive (88–100%) and specific (95–100%) than CT for detecting acute ischemic injury.[36,39–41] Diffusion-weighted imaging (DWI) demonstrates hyperintensity when there is an area of restricted water diffusion.[42] In acute ischemia, energy failure causes dysfunction of transmembrane pumps with increased intracellular fluid (cytotoxic edema). Because water motion is more restricted intracellularly, acute ischemia is detected rapidly when using DWI (Fig. 15.1).

By tracking the amount of contrast reaching the tissue by serial scans every 1–2 s for 1–2 min, MRI can also be used to construct perfusion-weighted images (PWI). With ultrafast MRI scanners, a complete study including MRA, DWI, PWI, and standard MRI sequences are completed in 30 min. This allows immediate assessment of the site of the arterial occlusion (MRA), the tissue damage that is irreversible (hyperintense on diffusion-weighted imaging), and the tissue that is ischemic but still viable (hypoperfused on perfusion-weighted imaging but still normal on diffusion-weighted imaging). Studies have correlated PWI and DWI with the extent of clinical deficit and outcome.[43] In addition, early reperfusion either spontaneously or with chemical thrombolysis has been correlated with saving tissue at risk identified by MRI.[44–46]

Diagnostic Ultrasound

Ultrasound is a useful method to noninvasively study extracranial and intracranial arterial vessels. Carotid Doppler duplex ultrasound scanners combine B-mode imaging and pulsed Doppler to produce both anatomical and hemodynamic data on extracranial carotid and vertebral vessels. Its usefulness to serially follow patients with progressive carotid stenosis is established, but is rarely used in the acute stroke setting, mainly because it is not immediately available in most centers.

Transcranial Doppler, which has been used successfully in the acute stroke setting,[47,48] can identify the site of vascular occlusion with a sensitivity of 88% and specificity of 89%,[48]

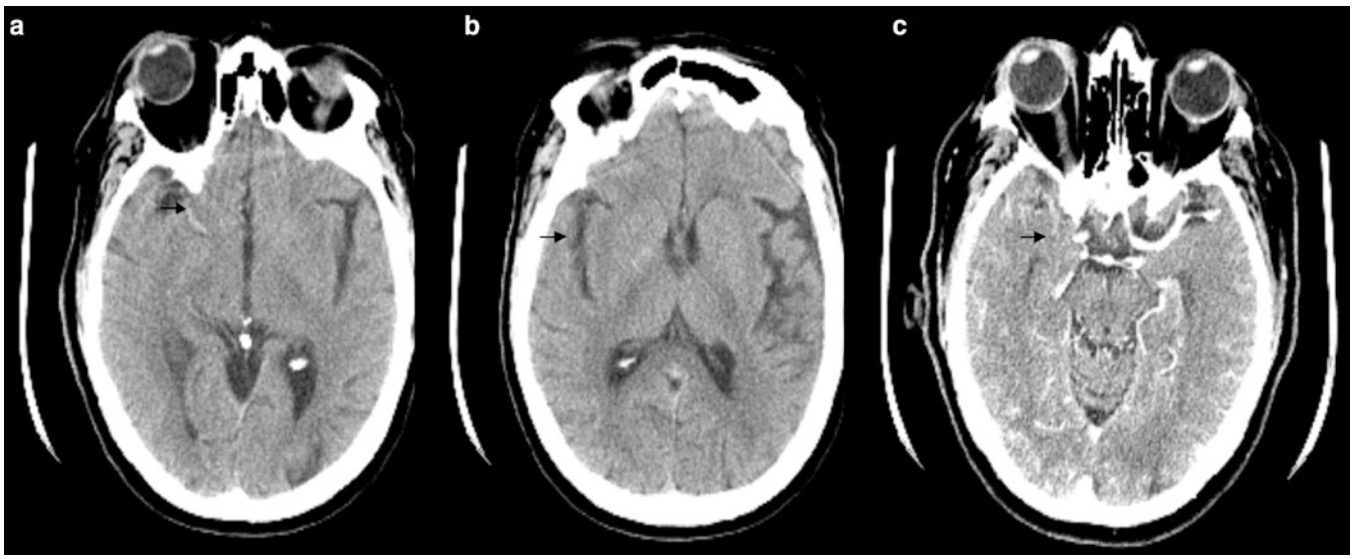

FIG. 15.2. Early CT signs in acute stroke. CT performed 1 h after onset of left hemiparesis. (**a**) Hyperdense MCA (*left*, *arrowhead*) and (**b**) loss of insular ribbon (*middle*, *arrowhead*) are shown on non-contrast CT. (**c**) MCA occlusion detected on CT-angiogram (*right*, *arrowhead*).

and can also monitor the recanalization after thrombolytic therapy.[49] Recent studies have documented a possible role of transcranial ultrasound monitoring in increasing arterial recanalization rates, which may be an avenue for post-operative stroke.[50,51] Limitations include examiner-dependence, a 15% incidence of absent windows for insonation, and a lower sensitivity for posterior circulation occlusions.[52] The use of intravascular ultrasound contrast considerably improves the ability to obtain flow signals in patients with poor bone windows of insonation.

Treatment

The initial goals of acute stroke management include stabilizing the medical condition, preventing progression of the ischemic injury, and potentially reversing the ongoing ischemia. Effort should be made to unravel the cause and extent of stroke in order to guide the initial and subsequent therapy.

General Treatment

Medical stabilization involves securing the airway, establishing adequate oxygenation and ventilation, correcting any hemodynamic instability, and aggressively treating fever. Patients with vertebrobasilar or bihemispheric stroke are at increased risk for aspiration because of a decreased level of arousal. The Glasgow Coma Scale alone should not be used as an indication for intubation because patients who are aphasic may be able to adequately protect their airway despite not being able to speak. A deteriorating level of consciousness, hypoxia, hypoventilation, absent or impaired gag reflex, and vomiting are general indications for endotracheal intubation.

Blood pressure levels in the acute care setting usually rise as an acute physiologic response to either stroke or hospitalization. Normally, autoregulation allows maintenance of constant blood flow, with mean arterial pressures varying between 50 and 150 mmHg. However, in acute arterial occlusion, the vascular bed distal to the occlusion is maximally dilated, and blood flow to an ischemic territory may vary directly with blood pressure. One study identified a subset of patients who respond to pharmacologic increases in blood pressure and worsen after decreases in blood pressure.[53] Decreasing blood pressure in the first 24 h of stroke onset has been correlated with poor outcome.[54,55] Consensus guidelines recommended not treating hypertension in the first 24 h unless it is associated with signs of end-organ damage (cardiac failure, aortic dissection) or if the diastolic blood pressure is above 120 mmHg and/or the systolic blood pressure is above 220 mmHg.[56] Increasing the blood pressure with phenylephrine may improve neurologic deficits in some patients. In contrast, strict blood pressure control is recommended for patients undergoing thrombolysis. In this case, the threat of hemorrhage becomes the overriding concern. In patients treated with angiographic, IA thrombolysis with direct visualization of the obstruction, it is possible to maintain hypertension until the vessel is recanalized. After the flow is restored, blood pressure can be controlled at a lower level to avoid hemorrhage.

In order to optimize the cerebral blood flow, most patients should be maintained normovolemic. Patients with volume depletion should be fluid resuscitated to establish normal filling pressures. Hypoosmolality should be avoided because it contributes to ischemic brain swelling. Administration of 5% dextrose and normal saline, or simply normal saline is recommended. The combination of hypertension, hypervolemia, and hyperosmolality is the standard of care in the treatment of brain ischemia resulting from vasospasm after subarachnoid hemorrhage.

Fever has been shown to worsen ischemic injury both experimentally and clinically.[57,58] Patients with stroke and early fever have larger infarcts, higher mortality levels, and worse long-term outcome.[59] Even changes of a few degrees in temperature have a significant effect on outcome. Induced hypothermia decreases the mortality and infarct size experimentally, but the only clinical study performed did not have a control group to allow firm conclusions to be drawn.[60] The available data recommend aggressive treatment of fever when it develops.

Though somewhat counterintuitive, animal and human studies demonstrate that hyperglycemia also aggravates the infarct size and brain swelling after stroke and worsens the clinical outcome. This may be related to hyperglycemia, anaerobic glycolysis, and worsening of the lactic acidosis in the ischemic area secondary to an increased catecholamine response.[61] However, a recent study failed to demonstrate a benefit in intravenous glucose–insulin–potassium infusion aimed at maintaining strict glucose levels (80–110 mg/dl) in the first 24 h after stroke onset.[62] Maintenance of a normal blood glucose level should therefore be the goal.

Thrombolysis

Treatment of stroke has gained momentum in the past decade after IV and intra-arterial (IA) thrombolysis were shown to be effective. The NINDS trial showed that 0.9 mg/kg of IV recombinant tissue plasminogen activator (rt-PA) given within 3 h of symptom onset improves the functional outcome by 30% at 3 months. This occurred without an increase in mortality, despite a small but definite risk (6%) of symptomatic intracranial hemorrhage.[63] The major contributors to success in the trial were early treatment and strict inclusion/exclusion criteria, which controlled the factors associated with increased risk of hemorrhage postthrombolysis. Recently, a randomized controlled clinical trial demonstrated efficacy of IV thromolysis in the 3 to 4.5-hour time window.[64,65]

The PROACT II trial examined the benefit of 9 mg of IA pro-urokinase and low-dose IV heparin for MCA strokes within 6 h of onset.[66] No mechanical dissolution of the thrombus was allowed by study design. This study also showed 58% improvement in 3-month outcome despite a 10% risk of intracranial hemorrhage in the treated group compared to 4% in the placebo group. There was no increase in mortality in the treated group.

For postoperative strokes, IV chemical thrombolysis is contraindicated because of the increased risk of systemic bleeding from recent surgery. The dose of rt-PA for IA lysis (10–30 mg) is considerably lower. In devastating large-vessel stroke, relatively small doses of rt-PA can be combined with mechanical clot disruption, either using a thin wire to repeatedly impale the clot or by inflating a low-pressure angioplasty balloon inside the clot. Ongoing studies are examining the catheter-based therapies to lyse and remove clots using pure mechanical, laser light, or ultrasound means. The NINDS IMS3 trial is now testing the IA thrombolysis in patients treated with intravenous tPA who have persistent large intracranial vessel occlusion. Recently, a corkscrew-type device has been approved in the United States for intra-arterial clot retrieval.[67] Such devices may improve the safety of emergent clot removal in patients in whom thrombolytic drugs are contraindicated because of the risk of bleeding. They may also increase the time window during which the clot removal can safely be undertaken.

Revascularization

A difficult issue that often arises in patients who have had a stroke because of carotid disease is the most appropriate timing of CEA.[68–70] When the patient's symptoms result from a low-flow state (watershed distribution of infarct on brain imaging) or a fluctuating or progressive stroke syndrome, then immediate CEA should be considered. However, most strokes that occur because of carotid stenosis occur when a thrombus generated at the site of carotid stenosis embolizes into the MCA. The major concerns surrounding early CEA are: (1) the contribution of higher perfusion pressure after CEA to the risk of secondary hemorrhage into the infarct (more than 40% of patients with MCA occlusion have hemorrhagic conversion of the infarct)[67]; (2) the potential for surgery to cause clinical worsening or impede the early recovery process that occurs after stroke; and (3) the inability to assess whether CEA offers any functional benefit in patients with severe neurologic deficits. The major concerns surrounding postponing surgery are the potential for complete occlusion or a second stroke occurring in the interim.

One approach is to perform CEA early in patients with transient ischemic attack, low-flow syndrome, or minor stroke (small infarct on brain imaging). These patients likely have a low risk of symptomatic brain hemorrhage. In contrast, patients who have had a major stroke (large infarct on brain imaging) can be re-evaluated 3–4 weeks later. If brain swelling and brain hemorrhage are absent at this time and if the patient has neurologic function that could be lost from a second stroke ipsilateral to the tight stenosis, then CEA should be considered. Patients who do not recover from maximal deficits in the internal carotid artery territory may have little to gain from ipsilateral CEA. Anticoagulation may help prevent carotid occlusion during the interval between stroke and CEA but it also carries some risk of hemorrhage.

Angioplasty and stenting of critical cerebrovascular lesions have recently been introduced into the clinical armamentarium.[71–73] Endovascular treatment of carotid stenosis, when compared to endarterectomy in randomized clinical trials has similar efficacy, but some show slightly higher complication rates.[74–76] The reported incidences of major stroke, death, bradycardia, minor stroke, and other angiographic complications after stent/angioplasty in the carotid vary partly because of the evolving technology[77] and the level of expertise. Carotid stent/angioplasty with a protection device is approved in the US in patients who have recent symptoms secondary of severe carotid artery stenosis and who are high-risk surgical candidates. In addition, angioplasty for patients with symptomatic intracranial stenosis or vertebral/basilar stenosis refractory to medical treatment is often the only intervention that can prevent further stroke.[72,73] Procedural complications related to intracranial angioplasty are higher than for extracranial disease; fatal arterial rupture, symptomatic vasospasm, dissection, and embolic stroke are the most feared. A NIH trial is in progress to compare intracranial stent vs. medical therapy in patients with symptomatic disease. External carotid to MCA bypass surgery has a long history and should be considered in those patients with progressive ischemia resulting from low flow distal to extracranial vessel occlusion(s).[78]

Pathophysiology-Based Therapy

Efforts should be made in the acute care setting to identify the stroke mechanism and help define the best management course. In general, patients with high-risk cardioembolic sources such as a mechanical prosthetic valve, a recent myocardial infarction, or an intracardiac thrombus are at higher risk for recurrent stroke and probably should receive IV heparin acutely if the risk of systemic hemorrhage from surgery is low. Exceptions to the rule include patients with imaging tests suggesting other mechanisms (e.g., low flow, lacunar) and patients with cholesterol emboli. In cholesterol embolization, the embolic event is directly related to the manipulation of atherosclerotic plaques in the aorta or carotid arteries, and the risk of recurrence is considered low.

Acute large-vessel atherothrombosis is typically encountered in patients with previous carotid artery stenosis undergoing general surgery or CEA. Acute re-exploratory surgery may be an option in this setting, and its management is discussed under "CEA."[79]

The risk of stroke in large-vessel atherothrombosis is stratified by arterial patency: Chronic complete occlusions are associated with lower intraoperative stroke risk and lower risk of recurrence than severely stenotic vessels.[80] A recent study showed that double antiplatelet therapy with aspirin and clopidogrel decreased the embolization rate in patients with large vessel stenosis, suggesting this therapy may be beneficial.[81] Adding clopidogrel to aspirin has not been shown to be beneficial in broad studies of chronic stroke prevention. No good well-designed studies have evaluated the efficacy of heparin in acute stroke.

In the TOAST study of a low-molecular-weight heparinoid, patients who had had a stroke were treated after a considerable delay. Benefit was seen in the 3-month outcome only in patients with carotid artery stenosis as the cause of stroke. There was a nonsignificant trend toward the benefit in patients with stroke from large vessel atherosclerosis but not from cardioembolism or small-vessel stroke.[82] A European study showed no benefit with unmonitored use of subcutaneous heparin.[83] In the only randomized study of intravenous heparin in hyperacute (<3 h) stroke, a benefit was demonstrated at the expense of more frequent intracerebral hemorrhages, without increased mortality rates.[84]

Some practices now limit the use of heparin in patients with submaximal infarcts in the territory supplied by a diseased artery. This requires rapid evaluation of the vascular lesion to determine if there is stenotic disease in the parent vessel supplying the intact brain tissue. Fluctuating brainstem symptoms due to threatened basilar thrombosis is perhaps the strongest indication for heparin. Administering large doses of heparin should be avoided in patients who have had an acute stroke. A weight-based nomogram for dosing, with frequent check of the partial thromboplastin time (PTT) should increase the safety of heparin use.

Malignant Ischemic Brain Edema

Brain infarcts swell progressively over the first 2 days and sometimes up until a week from onset. Swelling is worsened by fever, hyperglycemia, and hypoosmolality. In patients who have had a large stroke, osmolality should be monitored and maintained over 280 milliosmols and higher if swelling with a mass effect is detected on CT scan. The blood sugar level should be maintained in the normal range and the fever treated aggressively. Hemorrhage into a large swollen stroke also introduces a mass effect with disastrous clinical deterioration, so anticoagulation may be dangerous once a mass effect is observed.

In cerebellar stroke – especially that involving the posterior inferior cerebellar artery – cerebellar swelling may rapidly lead to fatal brainstem compression or compression of the IVth ventricle, thereby blocking the cerebrospinal fluid outflow and causing acute hydrocephalus. Decompressive surgery or ventriculostomy to relieve hydrocephalus is lifesaving in cerebellar stroke once the signs appear. Important signs to monitor include: (1) increased drowsiness, loss of upgaze, and convergence due to hydrocephalus that can be easily demonstrated on CT scan, or (2) cranial nerve palsies (V, VI, VIIth most commonly) as the cerebellum pushes against the brainstem. Decerebrate posturing is an ominous sign indicating that posterior fossa decompression is required immediately.

In MCA and internal carotid artery embolic stroke, brain edema can lead to a major mass effect with compression of the midbrain and a fatal herniation syndrome. The first sign is often an increased drowsiness associated with a new headache. The pupils decrease in size because of thalamic compression or hydrocephalus secondary to compression at the foramen of Monro. Thereafter, deterioration may occur suddenly as a result of transient jumps in the intracranial pressure (so-called plateau waves). One or both pupils dilate, the patient becomes unresponsive, and then decerebrates on one side and then bilaterally. Brain death ensues if the process cannot be stopped. Hyperosmolar therapy, intubation, and hyperventilation may temporarily reverse the process. However, in many cases only decompressive surgery can prevent death. Best results are observed in young (<60 years old) patients with nondominant hemisphere strokes who undergo surgery in the first 48 h of stroke onset.[85] After initial imaging shows a large infarct (>80 ml or >50% of the MCA territory), close observation and repeat imaging is critical to identify patients who will benefit from decompressive surgery before malignant edema becomes life threatening. Recovery requires months of rehabilitation, but return to independent function is common. Older patients fare less well after major stroke, and patients with permanent global aphasia from dominant hemisphere stroke have a difficult battle to function independently.

Postoperative Stroke in Specific Settings

CEA

The risk of stroke after CEA has lessened with better surgical techniques and intraoperative monitoring, and has been reported to be 3.4–6.0% for symptomatic stenosis[86] and 1.5% for asymptomatic stenosis.[87] Patients with concurrent carotid siphon stenosis (“tandem” lesion), intraluminal thrombus, diabetes, previous stroke, or transient ischemic attack, and uncontrolled hypertension have an increased risk of postoperative stroke.[87,88] The patient who awakens with a deficit most likely suffered intraoperative stroke. The patient who develops a deficit after awakening is more likely to have an acute occlusion, secondary to platelet thrombus formation at the denuded vessel wall, or a dissected flap. Returning to the operating room for exploration is the usual practice in the latter instance.[80] Administration of antiplatelet agents (dextran, aspirin, and clopidogrel) may be necessary to prevent thrombus formation in some cases. Some institutions use transcranial Doppler postoperatively to monitor the frequency of embolic signals in the MCA as a sign of thrombus formation and an indication for dextran therapy. If the carotid is patented, then the problem may be embolic intracerebral artery occlusion, the diagnosis of which requires vascular imaging (intraoperatively: CTA, color flow transcranial Doppler, or direct angiogram). Platelet thrombi in the patient who has undergone CEA not infrequently cause severe immediate neurologic deficits, but improve markedly over the ensuing hours. It is critical to control blood pressure in these patients because of the role of hypertension in the development of post-CEA intracranial hemorrhage, and the hyperperfusion syndrome (see section “Stroke Mimics”).

Coronary Artery Bypass Grafting

Stroke occurs after 1.4–5.8% of coronary artery bypass grafting (CABG).[1,88,89] Factors associated with a higher risk of stroke include advanced age, concurrent aortic or carotid atherosclerosis, history of stroke, diabetes or hypertension, and bypass time.[1,90,91] Several models are available to estimate stroke risk after CABG.[92] Stroke is associated with higher mortality, morbidity, and increased use of hospital resources.[1] One study stratified patients by time of stroke occurrence, whether early (immediately after surgery) or delayed (after a seemingly uneventful recovery period).[3] The causes varied accordingly: Early stroke was associated with longer bypass times, while delayed stroke was associated with postoperative atrial fibrillation and a decreased cardiac output. Atherosclerotic risk factors increased the risk of both early and delayed strokes. Embolic debris generated from cross-clamping the severely atherosclerotic aorta is considered the prime culprit, while hypoperfusion represents only 9% of etiologic mechanisms.[93]

Cognitive changes are much more common than stroke in the postoperative period, with rates up to 75% 8 days after surgery and 30% 1 year later.[94] Possible explanations include metabolic encephalopathy, global ischemia during bypass, or microemboli during surgery. Intraoperative monitoring with transcranial Doppler or electroencephalography may identify some patients at risk.[95,96]

Patients with greater than 70% carotid stenosis are a subgroup with a potentially preventable cause of stroke before undergoing CABG. One study randomized patients with unstable coronary artery disease and asymptomatic carotid stenosis to receive either CABG followed by CEA or a combined CEA/CABG procedure.[97] Patients who underwent CABG followed by CEA had a 14% stroke rate, as compared to 2.8% for the combined procedure. However, whether or not to perform combined CEA/CABG or staged CEA followed by CABG procedures is still controversial because no randomized trials have been performed. Proponents of the combined procedure cite low perioperative mortality (3.5–5.8%), stroke risk (4.0–5.8%), and decreased hospital costs.[89,98]

Spinal Cord Stroke After Aortic Surgery

Spinal cord stroke is a devastating condition, most common after aortic disease but also described after thrombosis of spinal arteriovenous malformations, global ischemia, hematomyelia, epidural hematoma, celiac plexus block, lupus erythematosus, coagulopathy, and decompression sickness.[99] Overall, it affects 16% of patients after aortic aneurysm repair,[100] with risk related to the extent of the aneurysm, clamp time, low cardiac output after clamping, and reason for operation (higher in cases of rupture and aortic dissection).[101,102] The common pathophysiologic mechanism is the lack of blood supply because of various conditions that decrease the blood flow through the vertebral arteries or the radicular arteries arising from the aorta, which supply the spinal cord.

Spinal cord stroke is suspected in patients who present with bilateral lower extremity weakness after aortic surgery. Spinal MRI is sometimes diagnostic in the post-acute phase; a hyperintense signal on T2-weighted images is seen at the affected level. Some patients also develop vertebral body infarction, due to common vascular supply from the aorta.[103] Some authors have suggested epidural cooling, naloxone, and cerebrospinal fluid drainage as spinal cord protection strategies during surgery, but no controlled studies have been conducted.[101,102] High-dose steroids have been administered based on traumatic spinal cord injury studies, but there is no proof that they are efficacious.[104]

Type A Aortic Dissection

Stroke is described as a complication in 6% of type A aortic dissections.[105] For patients present with acute chest pain (85%), a physical examination may disclose a murmur of aortic insufficiency (44%) or asymmetric pulses (19%). A high index of suspicion is necessary to make a correct diagnosis. Plain chest radiography may show mediastinal widening in 63% of cases, whereas a definite diagnosis can be made on either thoraco-abdominal CT or echocardiography. Surgical or endovascular treatment is indicated and may prevent extension of the dissection into the origin of the carotid or subclavian arteries. Surgical risk is even higher in the patient with stroke because of the need for aggressive anticoagulation at the time of cardiac bypass.

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16
Hemorrhagic Stroke

Jamary Oliveira-Filho and Walter J. Koroshetz

Hemorrhagic stroke comprises 10–20% of all strokes. Intracerebral hemorrhage (ICH) occurs much more frequently than subarachnoid hemorrhage (SAH).[1] Both ICH and SAH are associated with high initial mortality and long-term morbidity. Various treatment strategies are available to minimize and prevent the ongoing neurologic injury. For these treatments to be effective, they must be instituted while the injury is still reversible. Thus, early recognition is essential. This chapter discusses the etiology, clinical manifestations, and critical management of intracerebral and subarachnoid hemorrhages.

Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) is still a devastating condition with a mortality rate that is estimated to be 44–51%. Half of all deaths occur in the first 2 days after onset.[2] Most cases of ICH are attributed to a hypertensive vasculopathy in small penetrating brain arteries or subcortical vessels in patients with amyloid angiopathy. In hypertensive patients, the small penetrating vessels originating at a right angle from large arteries in the circle of Willis and basilar artery are at risk for rupture. These vessels can acutely thrombose, causing small subcortical and brain stem infarcts, or rupture and cause ICH. Other causes of ICH are primary vascular malformations, amyloid angiopathy, anticoagulant or thrombolytic use, venous sinus thrombosis, vasculitis, Moyamoya disease, aneurysm rupture with injection of intracerebral blood, mycotic aneurysms, myxomatous aneurysms, hemorrhage into tumor, and sympathomimetic drug abuse.[3]

Etiology

The etiology of ICH differs according to the bleeding location. Hemorrhages located in deep structures within the brain are typically caused by systemic hypertension. These hypertensive hemorrhages occur most frequently at the putamen, thalamus, pons, and cerebellum (Fig. 16.1); they are attributed to the rupture of small arteries originating from the basilar artery, middle cerebral artery, and posterior cerebral artery – the same vessels involved in hypertensive occlusive disease (lacunar disease).

The etiology of lobar hemorrhages varies according to the patient's age. Younger patients (<45 years) more frequently have underlying vascular malformations, cerebral venous thrombosis, or sympathomimetic drug use as the cause of hemorrhage. Amyloid angiopathy, a chronic deposition of congophilic material in brain vessels, is the most common cause of lobar hemorrhage in older patients (>55 years). Lobar hemorrhage in the elderly has a high 2-year recurrence rate (21%) and has been correlated with the presence of a particular apolipoprotein E genotype.[4]

Primary intraventricular hemorrhages are rare, representing only 1–9% of all cases of ICH.[5] Some of the hemorrhages are the result of small ICH deep within the brain parenchyma. The ICH in this case is related to hypertension.[6] Other causes of intraventricular hemorrhages are tumors and vascular malformations in the brain or spinal cord.[5,7]

ICH rarely occurs in patients who have undergone intravenous (IV) thrombolysis for myocardial infarction (0.22–0.70%),[8] but occurs more often in those who have undergone acute stroke thrombolysis. Most hemorrhages are single and lobar (46%), but can also occur in the basal ganglia, subdural space, or multifocally.[9] Mortality rates for thrombolysis-related ICH vary from 48 to 74%. Predictors of increased mortality are depressed level of consciousness, volume of hemorrhage, and short length of time from thrombolysis to ICH.[8]

Symptoms and Signs

Patients with ICH typically present with acute headache, vomiting, a progressive focal deficit, and a depressed level of consciousness. These symptoms are more common in hemorrhagic stroke than in ischemic stroke.[10] However, no combination of symptoms can be used to differentiate between these two

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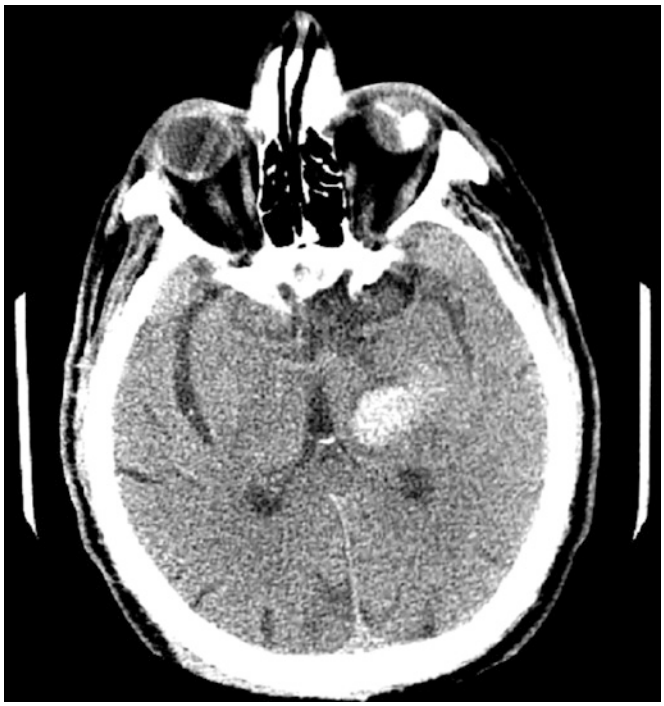

FIG. 16.1. Noncontrast computed tomography of a thalamic hemorrhage.

stroke subtypes with 100% certainty. Brain imaging is essential for making the diagnosis. The constellation of symptoms depends on the location and extent of the presenting hemorrhage. Small thalamic hemorrhages are less likely to cause headache or a change in mental status, thus mimicking ischemic stroke.

Hemorrhages in the putaminal region are most commonly associated with hypertensive ICH. Clinical signs of putaminal hemorrhages are rapidly progressive hemiparesis and sensory deficit in the face, arm, and leg; depressed level of arousal; and gaze deviation contralateral to the hemiparetic side. Aphasia may occur in patients with dominant hemisphere lesions. The gaze in patients with nondominant hemisphere lesions may neglect toward the contralateral side. In addition, homonymous hemianopia occurs frequently in patients with putaminal hemorrhages. The pupils of these patients are equal and symmetric, unless uncal herniation occurs.

Thalamic hemorrhages also present with sensorimotor deficits involving the face, arm, and leg. Useful diagnostic signs that distinguish thalamic from putaminal hemorrhages are more frequent oculomotor deficits (typically upward gaze palsy and miotic pupils) and less frequent headache.[11] If horizontal ocular deviation is present, it is usually contralateral to the hemiparetic side, but, in some cases, the eyes deviate toward the hemiparetic side. Aphasia and neglect can also occur in thalamic hemorrhages.

Cerebellar hemorrhages are characterized by acute onset of nausea, vomiting, headache, dizziness, and gait disturbances. Diagnostic signs include ipsilateral ataxia of the limbs, horizontal gaze palsy, and facial palsy involving upper and lower facial muscles ("peripheral-type" palsy).[12] Hemiparesis is rare at presentation unless a patient has suffered severe brain stem compression and is in coma.

Pontine hemorrhages are characterized by early coma, miotic pupils, and horizontal gaze deviation toward the hemiparetic side. Symptoms may also include absent horizontal ocular movement, similar to the doll's eye maneuver, and ocular bobbing (brisk conjugate ocular depression followed by slow return to mid-position).[13]

Diagnosis

CT scan is the initial modality of choice for diagnosing ICH because it quickly differentiates between ischemic stroke and hemorrhagic stroke, excludes other causes of acute focal deficit such as subdural hematomas or tumors, and provides immediate assessment of location and extension of the hemorrhage. Prognostic factors such as hydrocephalus, intraventricular extension, and hematoma size can also be assessed.

Conventional angiography is indicated to exclude the underlying sources of intracranial bleeding. Vascular malformations, tumors, aneurysms that rupture into the brain substance, Moyamoya disease, vasculitis, and venous sinus thrombosis are causes of ICH that can be excluded using this technique. One study of 206 patients with ICH undergoing angiography found that hypertensive patients older than 45 years with putaminal, thalamic, pontine, or cerebellar hemorrhages do not need to undergo an angiogram because hypertension is most likely the cause.[14] Similarly, elderly patients with lobar hemorrhage are rarely subjected to angiography because of the high incidence of amyloid angiopathy as a cause of lobar hemorrhage in this age group.

Magnetic resonance imaging (MRI) has been used recently as a screening method in acute stroke management. Newer MRI techniques using susceptibility-weighted sequences have shown excellent sensitivity for blood detection in the acute setting.[15] Although the use of MRIs is promising, the lack of widespread availability and patient-related contraindications limit its general use in evaluating patients for ICH.[16] MRI with susceptibility sequences sensitive for iron deposition often shows multiple small asymptomatic hemorrhages in patients with amyloid angiopathy. A tangle of flow voids on T2 and flair images may identify arteriovenous malformations (AVM) as the source of hemorrhage. MRI and magnetic resonance angiography (MRA) can identify large aneurysms. A follow-up MRI with contrast enhancement is sometimes needed in the chronic phase to determine if a tumor was concealed by the blood signal on the CT or MRI in the acute phase. MRI demonstrates a "popcorn-like" structure composed of rings of hemorrhage of different ages in patients with cavernous angiomas.

Management

Initial management goals for ICH include stabilizing the medical condition, supporting failing organ systems, and preventing further neurologic injury with medical or surgical treatment. Patients who show signs of ventilatory insufficiency and have

deteriorating mental status should be intubated emergently. Seizures are estimated to occur in 6% of patients acutely and should be aggressively managed with IV anticonvulsants.[2] However, a recent study using continuous electroencephalographic monitoring showed a 31% incidence of subclinical seizures, which were associated with poor outcome.[17] While the use of prophylactic anticonvulsants is controversial, many practitioners believe that they should be administered to patients with lobar hemorrhages and increased intracranial pressures (ICP), whose risk for herniation is increased when coupled with a major motor seizure.[18] Routine laboratory tests should include complete blood count, renal and liver function tests, electrolytes, and coagulation studies. Any coagulation abnormality should be corrected to decrease the likelihood of rebleeding.

Blood pressure management remains controversial. Ideally, antihypertensive medications should be titrated to achieve the lowest mean arterial blood pressure (MAP), while maintaining an adequate cerebral perfusion pressure (CPP = MAP − ICP) above 70 mmHg. The controversy stems from the potential benefit of a lower blood pressure to prevent hematoma expansion versus the risk for decreasing global or local perfusion around the hematoma site. Studies showing the adverse effect of high blood pressure on outcome have been flawed by worse baseline characteristics in hypertensive patients.[19,20] Evidence from experimental and clinical studies has shown no sign of ischemic tissue surrounding the hematoma, even after the blood pressure is lowered by 15–20%.[21,22] However, other studies have correlated the rate of blood pressure decline in the first 24 h with increased mortality.[23] In the absence of randomized, controlled data, consensus guidelines suggest maintaining a MAP below 110 mmHg[18] if no ICP monitoring is available.

The management of intracranial hypertension is discussed elsewhere in this chapter. Therapy should be considered for any comatose patient who demonstrates deteriorating mental status, believed to be due to increased ICP.[18] Up to 38% of patients experience a more than 33% growth in the initial hematoma size in the first 24 h.[24] Hematoma growth has been associated with increased mortality and poor functional outcome.[25] The condition of patients surviving the first 24 h may worsen in the next 2 or 3 weeks as a result of delayed cerebral edema.[26] Surgical decompression should be considered for patients whose condition continues to deteriorate secondary to the intracerebral hemorrhage. Mannitol is the first-line of medical therapy, followed by hyperventilation and pentobarbital. Steroids have no beneficial effect on the management of ICH; they are no more effective than mannitol and are associated with increased risk for infections and complications associated with hyperglycemia.[27] Fever should be treated aggressively.

Based on the relation between hematoma growth and increased mortality, studies using activated factor VIIa have been conducted in an attempt to decrease the hematoma growth. In the phase II NovoSeven study, promising results showed both decreased hematoma growth and mortality rate in one of the factor VIIa dosages used.[28] However, the NovoSeven phase III results did not gain significance for the primary endpoint.

Hydrocephalus is an ominous sign in ICH.[29] Although ventriculostomy placement has not been shown to change the outcome,[29] it is usually indicated to improve symptoms and to help manage increased ICP. The benefit of instilling a thrombolytic agent into the ventricle to aid clot removal by the ventriculostomy is under investigation.

Surgery in supratentorial hypertensive ICH is a highly debated subject. In the largest randomized, controlled clinical trial to date, no benefit was observed with surgical clot evacuation within 96 h of symptom onset.[30] Based on subgroup analysis from the same trial, current guidelines recommend evacuating lobar hematomas within 1 cm of the surface.[18] In patients with lobar hemorrhage, surgical evacuation and decompression is also considered appropriate if there is neurologic deterioration due to worsened hemorrhage or mass effect.

In contrast, there is greater agreement about surgery in infratentorial ICH. Based on the case series compared with historical controls, cerebellar hematomas greater than 3 cm in diameter or associated with significant mental status impairment (Glasgow Coma Score < 14) are usually evacuated acutely.[12,31,32] Cerebellar hemorrhages greater than 3 cm in diameter are commonly associated with brain stem compression or hydrocephalus from compression of the fourth ventricle. Surgical evacuation can prevent rapid neurologic deterioration after cerebellar hemorrhage. Functional outcome can be good if there is no major secondary brain stem injury. Hypertensive hemorrhage into the brain stem is nonoperable and usually fatal.

Prognosis in ICH has been related to the level of consciousness on admission, the size of hematoma, the presence of intraventricular extension and hydrocephalus, and contrast extravasation on CT angiography (CTA). Hematoma size is one of the most powerful predictors of ICH and can be easily estimated by CT scan performed on admission. One study showed that deep hematomas greater than 60 ml are associated with a 93% 30-day mortality, as compared with 23% for hematomas less than 30 ml.[33]

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is a common cause for admission to a critical care unit. While one-quarter of patients with SAH die before hospital admission, survivors are still subject to risks for rebleeding, delayed ischemia due to vasospasm, hydrocephalus, and various systemic complications.

Etiology

Most cases (~80%) of SAH are due to ruptured saccular aneurysms. These aneurysms typically form at the bifurcation of intracerebral arteries. Common locations include the junction

between the anterior communicating artery and the anterior cerebral artery, the junction between the posterior communicating artery and the internal carotid artery, and bifurcation of the middle cerebral artery. Posterior circulation aneurysms are less common and usually located at the top of the basilar artery.

Risk factors related to either hemodynamic stress or wall fragility have been studied in the genesis of intracranial aneurysms, which are present in up to 8% of the population in autopsy series.[34] Hypertension, estrogen deficiency, older age, smoking, hereditary factors, and collagen deficiency disorders have all been related to increased risk for intracranial aneurysm in case-control studies.[35–39]

Signs and Symptoms

Most patients (97%) who suffer a SAH present with the sudden onset of headache, usually described as "the worst headache of my life."[10] Some patients awake from sleep with a headache, a pattern rarely observed in ICH. About 30-50% of patients have a "sentinel headache" 6–20 days before the SAH. This is thought to represent a minor leak from the aneurysm prior to the rupture. Nausea, vomiting, and neck stiffness also frequently occur. The level of consciousness is variable and has prognostic implications: disoriented and unconscious patients tend to have a poorer prognosis. Various scales exist to grade SAH. The most frequently used is that of Hunt and Hess, which has a good correlation with outcome (Table 16.1).

Diagnosis

Non-contrast CT is the cornerstone of imaging in acute stroke diagnosis (see Fig. 16.2). Sensitivity decreases from 93% in the first 24 h to 73% after 5 days,[40] as acute blood clears from the subarachnoid space. CT also gives pertinent information regarding the possible aneurysm location, severity of the hemorrhage, and presence of early hydrocephalus. The amount of blood in the basal cisterns and subarachnoid space has been correlated with risk for vasospasm.[41,42] Table 16.1 shows the Fisher scale, which segregates patients into groups based on initial CT findings and the correlation with risk for vasospasm.

Patients with a suspicious history and a negative CT scan should undergo cerebrospinal fluid (CSF) analysis. Absent xanthochromia in the CSF supernatant 24 h after the event excludes SAH. In the acute phase, the presence of red blood cells in the CSF after removal of successive CSF samples should lead to an angiogram. A compulsive approach to such patients is important because of the high frequency of a sec-

Table 16.1. Scales used in subarachnoid hemorrhage.[42,60]

Hunt and Hess Scale (clinical grading on admission)
1. Asymptomatic or mild headache
2. Moderate to severe headache, nuchal rigidity, with or without cranial nerve deficits
3. Confusion, lethargy, or mild focal symptoms
4. Stupor and/or hemiparesis
5. Comatose and/or extensor posturing
Fisher Scale (CT groups on admission)
1. No blood on CT. No spasm predicted
2. Diffuse SAH without vertical layers of blood greater than 1 mm. Intermediate risk for vasospasm
3. Dense collection of blood forming vertical layers greater than 1 mm or localized clots greater than 3 by 5 mm. Severe vasospasm predicted
4. Intracerebral or intraventricular clots in the absence of significant subarachnoid blood. No vasospasm predicted

Focal signs are less frequent than in ischemic stroke or ICH. If present, the symptoms represent either intraparenchymal extension of the hemorrhage (most frequent in middle cerebral artery aneurysm ruptures), cranial nerve abnormalities from aneurysmal compression (e.g., third nerve palsy from posterior communicating artery aneurysm), or increased ICP (typically sixth nerve palsies).

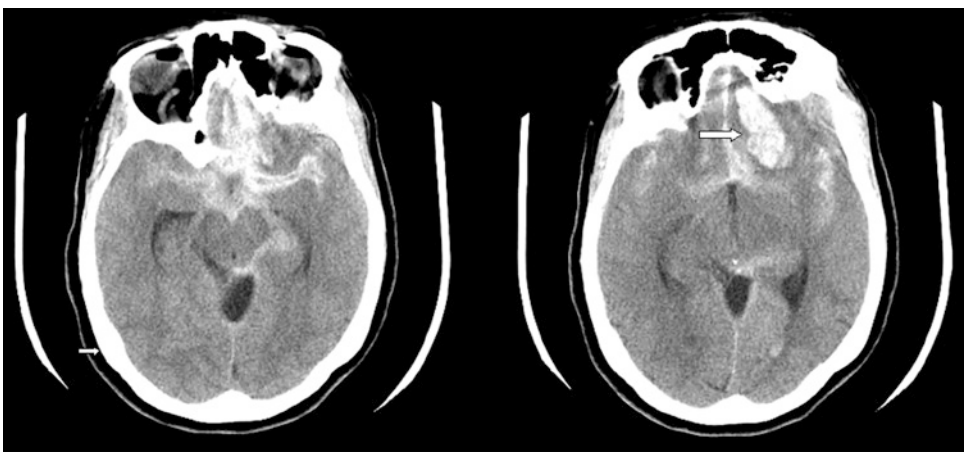

Fig. 16.2. Noncontrast CT of a Fisher group 3 subarachnoid hemorrhage. An intraparenchymal hematoma in the left frontal lobe (*arrow*) can be seen, suggesting anterior communicating artery aneurysm rupture.

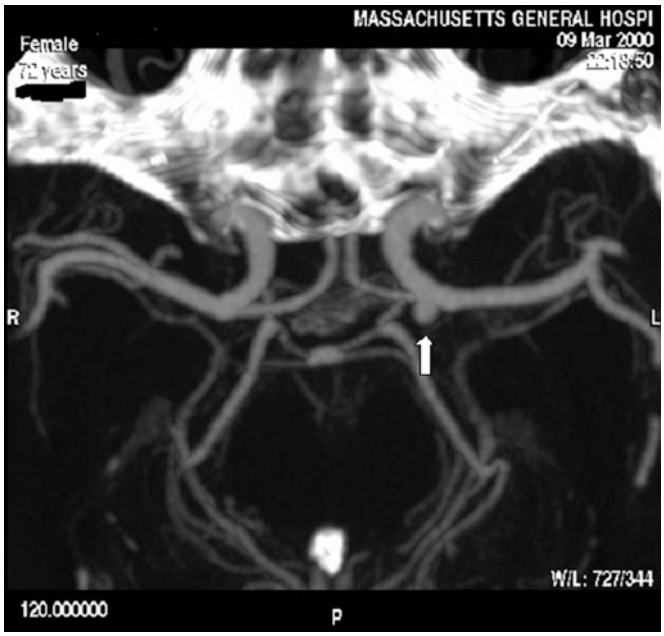

FIG. 16.3. CTA shows aneurysm in the junction of left posterior communicating artery with the internal carotid (*arrow*).

ond fatal rupture within days of onset of the sentinel bleed. Some patients with a typical history, negative CSF exam, and no other reason for the acute headache may require angiography, CTA, or MRA to exclude the presence of an expanding aneurysm as the cause of pain.

While cerebral angiography remains the "gold standard" for identifying an aneurysm, its diagnostic role has recently been challenged by noninvasive technology. CTA can be performed in 10 min while the patient is undergoing a noncontrast CT and can accurately provide information about the relation between the aneurysm and bony structures (Fig. 16.3). Both the CT and MR angiographies have been compared with conventional angiography, and can detect aneurysms greater than 3–5 mm.[43]

In 15–20% of patients, no aneurysm is found on the angiogram.[44,45] These patients are stratified according to the hemorrhage pattern found on the initial CT. A perimesencephalic pattern is associated with no rebleeding risk and excellent outcome, while a more diffuse SAH is linked to an increased likelihood of rebleeding and death.[44] Because of this dichotomy, patients without a perimesencephalic pattern and a negative angiogram should receive a second angiogram 1–2 weeks later and be closely monitored for the same complications as SAH patients. Some have advocated surgical exploration in selected cases of negative angiograms to look for microaneurysms.[46]

Preoperative Management

In this phase, management includes securing the airway, stabilizing blood pressure, reversing coagulation abnormalities, and treating hydrocephalus. Airway management is discussed in Chap. 2. Blood pressure should be titrated to the lowest possible MAP while maintaining an adequate CPP (above 70 mmHg). In the only controlled study of preoperative blood pressure reduction, the decreased risk for rebleeding was offset by an increased risk for ischemia.[47] Early surgery allows for the maintenance of higher blood pressures without the risk for rebleeding and less risk for ischemia secondary to low flow states.

Hydrocephalus occurs in 16% of patients within 24 h of bleeding.[40] Patients may also develop hydrocephalus at any time during the course of the illness. Ventriculostomy allows for decompression along with ICP monitoring, making it the most attractive option for symptomatic patients.

Surgical and Endovascular Treatment

Treatment decisions in the acute phase depend on the severity of the initial hemorrhage and aneurysm characteristics. Patients with good clinical grades (i.e., Hunt and Hess grades I--III) benefit from early surgery or coiling (within 4 days of the hemorrhage) because the first 2 weeks are associated with a 12% risk for rebleeding and a 30% risk for delayed cerebral ischemia.[48] The ability of the ICU physician to treat vasospasm is much enhanced if the ruptured aneurysm is definitively treated by surgery or endovascular techniques. When compared with historical controls,[49] improvements in critical care and early surgery as well as better management of vasospasm have been implicated with better outcomes.

Patients with poor grades previously were managed conservatively. Early interventions were not thought to change long-term outcomes. However, studies in large referral centers have shown that patients subjected to an aggressive protocol achieve good outcomes in 47–54% of cases.[50,51] This protocol includes a triage based on CT findings, early ventriculostomy with ICP treatment, early clipping or coiling if ICP is controlled, and postoperative hypertensive hypervolemic therapy. No clinical variables accurately identify patients with poor grades who will benefit from this therapy.[52] Therefore, all patients without vital brain destruction on CT or poor filling on angiogram should undergo initial aggressive management.

The choice between surgical and endovascular treatment is subject to debate. There is much more data on long-term safety and efficacy of surgical clipping than on coiling procedures. In the largest randomized, controlled trial to date, patients who were thought candidates for both procedures were allocated to either clipping or coiling of the relevant aneurysm.[53,54] Results showed increased survival without disability at 1 year, favoring endovascular treatment at the expense of a small but significantly greater risk of rebleeding. However, certain clinical scenarios are more suited for surgical treatments, while others are better suited for endovascular treatments. For example, basilar artery aneurysms are usually more easily treatable by endovascular methods, whereas middle cerebral artery bifurcation aneurysms with intraparenchymal hematomas are better off being treated by surgical clipping with concomitant hematoma evacuation.[55]

Postoperative Management

Patients admitted to the ICU generally undergo serial neurologic examinations for signs of new focal or global neurologic deficits, ICP monitoring with a ventriculostomy or intraparenchymal catheter, and daily transcranial Doppler (TCD) studies to monitor the developing vasospasm. A variety of treatable neurologic and systemic complications may occur during the postoperative period. These include rebleeding, vasospasm, seizures, hyponatremia, fever, and cardiac injury. All patients should receive pneumatic boots for deep venous thrombosis prophylaxis.

Rebleeding of untreated aneurysm occurs at a rate of 12% in the first 2 weeks,[48] then at a rate of 2.2–3.5% per year.[56,57] Rebleeding is associated with a high mortality rate (67–78%). In a study of 150 patients with SAH, 70% of rebleedings occurred within 6 h, and 87% occurred within the first 24 h.[58] This stresses the importance of early surgery or coiling, if possible, to decrease the high mortality and morbidity associated with this catastrophic event.

Vasospasm is a focal narrowing of a blood vessel thought to be caused by various substances released from the subarachnoid clot.[59] Angiographic vasospasm occurs in 60–75% of patients with SAH.[59] Delayed cerebral ischemia due to vasospasm occurs in 14–40% of patients, presenting as an acute focal deficit starting no earlier than 4 days after the initial bleed, usually peaking around days 5–9 and lasting no longer than 21 days.[60] The calcium-channel blocker nimodipine has been shown to decrease the incidence of delayed cerebral ischemia and should be administered daily until 21 days after onset of SAH.[61,62]

Daily monitoring with TCD ultrasound can detect vasospasm before symptoms develop. Vessel narrowing is detected as an increase in TCD velocity in the affected vessels.[63] However, patients with vasospasm in distal vessels (segments not insonated by TCD) may not change the TCD velocities. Furthermore, increased TCD velocities may represent hyperemic flow and not the vasospasm. Therefore, TCD is another method to diagnose delayed cerebral ischemia, which remains a diagnosis of exclusion after CT shows no other cause for the new focal deficit.

Once the diagnosis of delayed cerebral ischemia is made, treatment with induced hypertension, hypervolemia, and hemodilution ("triple-H" therapy) can be instituted. The fundamental principle is augmentation of cerebral blood flow through a narrowed vessel by increasing the blood volume (hypervolemia), blood pressure (hypertension), and improving rheologic properties (hemodilution). Various studies have demonstrated that focal defects can be reversed[64–66] and that the therapy has a good safety profile.[67] Hypervolemia and hemodilution are usually accomplished by increasing IV fluids and titrating therapy to achieve normal to high central venous or pulmonary artery occlusion pressures. Both colloids and crystalloids have been used without a clear advantage of one over another. If there is no improvement with hypervolemia, induced hypertension can be accomplished with vasoactive amines, preferably phenylephrine. Congestive heart failure is a common complication of the treatment. Many of these patients have intrinsic heart disease and, as discussed below, even young patients with a severe clinical grade are at an increased risk for myocardial injury.[68] All patients should preferentially undergo central venous pressure monitoring or pulmonary artery catheterization before triple-H therapy is instituted.

Patients who are refractory to triple-H therapy should be considered for endovascular treatment of vasospasm. Proximal blood vessels can be angioplastied with balloons and smaller distal vessels treated with selective intra-arterial papaverine. Experts believe that angioplasty yields more permanent results,[69] with clinical improvement in 61–72% of patients.[70,71] Papaverine infusions improve the angiographic vasospasm in 66–78% of patients, but only 26–33% clinically improve and vasospasm may recur.[72,73] ICP monitoring should be instituted during papaverine infusions, because a significant increase in ICP may occur in up to 46% of patients.[74]

Seizures occur in 10–25% of patients with SAH.[60] Because of the potential risk for hypertension, increased ICP, and rebleeding during a seizure, prophylactic anticonvulsants are usually recommended.

Causes of hyponatremia in SICU patients are discussed in another chapter. Hyponatremia occurs in 30–40% of patients with SAH.[75] Initially thought to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH), patients with SAH have a different hemodynamic pattern as they are usually hypovolemic due to salt wasting. Various natriuretic peptides – namely atrial and brain natriuretic peptides and digoxin-like peptides – have been implicated in the genesis of this salt-wasting syndrome, with secondary hypovolemia and, probably, aldosterone inhibition.[75–78] Treatment consists of fluid replacement to achieve euvolemia and sodium replacement with either sodium tablets or hypertonic saline. Osmotic therapy with urea has also been found to be effective. Recognizing this syndrome is important because the treatment program contradicts the fluid restriction instituted to treat SIADH.

Pyrexia is common in patients with SAH and is often multifactorial. Infections are common, as in any critically ill patient. A decreased level of arousal, which occurs frequently in SAH, is a known risk factor for aspiration pneumonia. Noninfectious causes of fever are present in one-quarter of patients and include drug-related fever, blood in the cerebrospinal fluid, and vasospasm.[79–81] Regardless of etiology, fever has been related to worse outcome in SAH.[79,80] Thus, as in any condition associated with brain ischemia, fever should be treated aggressively.

Cardiac abnormalities are common after SAH. The pathophysiology relates to local excess of catecholamines with elevated myocardial wall stress.[82] Electrocardiographic abnormalities are present in 25–75% of patients. T-wave inversions are the most common, but ST-segment depression or elevation and transient pathological Q-waves also occur.[68] These electrocardiographic abnormalities are not associated

with increased peri-operative mortality.[68] Patients may also develop elevated creatine kinase myocardial isoenzyme, troponin-I elevations,[68,83] and, as mentioned previously, left ventricular dysfunction.[68]

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17
Status Epilepticus

Andreas H. Kramer and Thomas P. Bleck

Prolonged or recurrent seizures can cause life-threatening systemic and neurological complications. Status epilepticus (SE) has traditionally been defined as more than 30 min of either continuous seizure activity or a series of seizures during which there is incomplete recovery of consciousness.[1] There are several reasons why a shorter duration might be more appropriate for an operational definition of SE.[2] First, the duration of a generalized seizure rarely exceeds 2 min, and spontaneous resolution becomes unlikely after 5–10 min.[3–6] Second, seizures become more difficult to abort pharmacologically over time.[6,7] Third, systemic complications frequently occur even after a few minutes.[8] Finally, the duration of time leading to neuronal injury is uncertain, and could conceivably be less than 30 min in certain cases. Longer seizure duration has been associated with worse outcomes.[6,9,10] It would be inappropriate and harmful to delay pharmacologic treatment of seizures for 30 min. Consequently, recent large clinical trials assessing management of SE have employed durations of only 5–10 min in their inclusion criteria.[11,12] Another approach that has been advocated to remain consistent with the previous definition is to define seizures lasting 10–29 min as "impending SE."[13]

Classification

Seizures are usually classified according to the terminology of the International League against Epilepsy.[14] All types of seizures can become prolonged and meet criteria for SE. Although there is no universally accepted classification scheme specifically for SE, it is common to specify the following:

1. Is the seizure activity generalized (involving most of the brain) or partial (limited to certain regions)?
2. If the seizures are partial, is consciousness preserved (simple partial) or lost (complex partial)?
3. Is there any visible motor activity (convulsive vs. nonconvulsive)?

It is not uncommon for the categorization to change over time. For example, seizures that are initially partial may "secondarily generalize;" or generalized convulsive SE may progress to nonconvulsive SE.

Refractory SE is defined as persistent seizure activity even after the administration of conventional first-line pharmacotherapy.[15,16] There is some disagreement among authors about whether one, two, or three categories of drugs must be administered without success prior to considering SE to be refractory. Given the frequent lack of response to a second and third conventional agent when the first one has failed,[12] we favor defining refractory SE based on failure of no more than two agents to control seizures.

Epidemiology

In population-based studies from North America and Europe, the incidence rate of SE ranges from 7 to 41 cases per 100,000 per year.[17–21] There are more than 100,000 cases annually in the United States. Given that it has only recently been recognized that a large proportion of acutely brain-injured patients have NCSE,[22] more widespread use of electroencephalography (EEG) in critical care units may reveal an even higher incidence.

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The case fatality of SE is 7–22%, with the main risk factor for death being the prognosis of the underlying condition. For example, studies that include patients with anoxic brain injury consistently have a higher death rate.[23] SE is refractory about 20–40% of the time, in which case it is associated with higher mortality, longer intensive care unit (ICU) stay, worse functional outcome, and more frequent subsequent development of epilepsy.[15,24–26,102,115]

Etiology

Successful management of SE requires a systematic search for potential etiologies. A known history of epilepsy is present in about one-third of patients. In this case, contributing factors typically include low antiepileptic drug (AED) levels or recent changes in therapy.[8,17,27] Other chronic conditions that may present with seizures include tumors, traumatic brain injury, or previous infarcts.

SE resulting from acute processes is often more difficult to control and associated with higher mortality.[9,24,26–28] Seizures complicate 15–25% of cases of bacterial meningitis and are predictive of a worse outcome.[29,30] The incidence of seizures with encephalitis varies from relatively infrequent with West Nile Virus encephalitis, to more than one-third of patients with herpes simplex virus encephalitis and 85% in children with Japanese encephalitis.[31–33] A diagnosis of viral encephalitis is the strongest risk factor for refractory SE.[24] Central nervous system infections are also a particularly common cause of nonconvulsive SE, which occurs in more than 25% of patients monitored with continuous EEG.[22]

Metabolic derangements are often responsible for new onset seizures in intensive care units (ICUs).[34,35] Hyponatremia is the most common abnormality, and has been identified as a risk factor for refractory SE.[24,35,36] It is unusual for seizures to develop until sodium levels decrease below 125 mEq/L.[35] Hypoglycemia, hypocalcemia, and hypomagnesemia must also be excluded. Uremia may predispose to seizures, and can increase levels of potentially epileptogenic drugs.[37] Seizures are a relatively common complication of acute liver failure, where they may worsen cerebral edema.[38,39]

Withdrawal-related seizures occur at some point in about 3% of chronic alcoholics.[40] Without treatment, recurrent seizures complicate as many as 60% of cases, although SE occurs less than 4% of the time.[41,42] Still, ethanol withdrawal remains one of the most common overall causes of status epilepticus in some series.[17,27] Alcohol-related seizures do not necessarily always occur in the classic 6–48 h time frame following cessation of ethanol consumption.[43] Benzodiazepines are highly effective in preventing and treating these seizures, and patients usually have a favorable prognosis[44,45] (Table 17.1)

Most seizures caused by overdoses are brief and self-limited. Tricyclic antidepressants used to be the predominant toxicologic cause of SE, but have become less common with more widespread use of selective serotonin release inhibitors (SSRIs). Other drugs implicated include stimulants (cocaine, amphetamines), antihistamines, and lithium.[46] Seizures and other forms of neurotoxicity are increasingly being reported with the use of methamphetamine (Ecstasy), which has emerged as one of the most common drugs of abuse.[47]

Approximately 50% of patients with brain tumors develop seizures at some point during their illness, and a small proportion of these will develop SE. Seizures are slightly more common with primary tumors than with metastases.[48] There remains controversy about the need for prophylaxis in patients with brain tumors who have not yet had seizures, but the best evidence suggests AEDs should not be used.[48,49]

Seizures are diagnosed within 5 years in 10% of patients who have sustained severe traumatic brain injury (TBI), with the risk persisting for many years.[50] Studies using continuous EEG have found the true incidence to be considerably higher, since more than 50% of seizures in this setting are nonconvulsive (Fig. 17.1). The overall incidence of SE in severe TBI was found to be more than 6% in one study, and some patients develop refractory SE.[51,52] Phenytoin is effective at reducing seizures in the first 7 days after TBI, but not thereafter.[53]

Strokes are among the most common cause of SE, occurring especially with larger, more disabling, and cortical (vs. deep) insults.[17,20,54,55] Early seizures occur in 2–6% of patients with ischemic strokes, 3–19% with intracerebral hemorrhage (ICH), and 3–16% with subarachnoid hemorrhage (SAH).[55–57] As many as a quarter of early seizures progress to SE, which in turn develops in about 1% of strokes overall.[55,58] The risk of seizures and SE is particularly high in patients with cortical ICH, such that prophylaxis with AEDs is reasonable in this setting.[55,59,60] Seizure prophylaxis for SAH was recommended in the past, but has become more controversial with the demonstration that the risks may outweigh the benefits.[61,62] Nonconvulsive seizures are common in ICH, and have been associated with neurological deterioration.[63] With SAH, NCSE occurs in about 8% of patients, is difficult to treat, and is a strong predictor of poor prognosis.[64] Seizures are very common with cerebral venous thrombosis, occurring in as many as 40% of cases.[65]

Pathophysiology

As SE increases in duration, it becomes self-sustaining, less likely to spontaneously abate, and more refractory to therapy.[66] This phenomenon is thought to involve alterations in the function of inhibitory and excitatory neurotransmitters, most notably γ-aminobutyric acid (GABA) and *N*-methyl-D-aspartate (NMDA), respectively.[13] Ongoing seizure activity induces structural alterations in GABA receptors and causes them to become internalized into postsynaptic neurons, such that their concentration within synapses decreases.[7,67,68] These changes have important therapeutic implications, since several AEDs exert their effect by binding to GABA receptors.[13,16] In contrast, with prolonged seizures, the concentration of synaptic

Table 17.1. Etiology of status epilepticus.

Etiology		Relative frequency (%)
Chronic epilepsy	± Non-complianceLow anti-epileptic drug levels	29
Ethanol related		21
Drug Effect	Sympathomimetics (e.g., cocaine, methamphetamine)	10
	Tricyclic antidepressants	
	Anticholinergics, antihistamines	
	Carbon monoxide, cyanide	
	Iron	
	Theophylline	
	Salicylates	
	Antibiotics (e.g., imipenem, β-lactams, fluoroquinolones)	
	Baclofen	
	Chemotherapeutic agents	
	Opiates (especially meperidine)	
	Withdrawal syndromes (e.g., benzodiazepines, opiates)	
Stroke/Vascular	Intracerebral hemorrhage Subarachnoid hemorrhage	8
	Cerebral infarct	
	Cerebral vein thrombosis	
	Arteriovenous malformation	
	Cerebral hyperperfusion syndrome	
	Posterior reversible encephalopathy syndrome	
Infection	Bacterial meningitis Brain abscess	7
	Subdural empyema	
	Viral meningoencephalitis	
	Systemic infection lowers “seizure threshold”	
Metabolic Disturbance	Hyponatremia Hypoglycemia	5
	Hyperosmolar state	
	Hypocalcemia	
	Hypomagnesemia	
	Acute liver failure (with cerebral edema)	
	Uremia	
Tumor	Risk varies with location and type	5
Trauma	Especially with intracranial blood	4
Anoxic Injury	Frequently myoclonus	4
Other	Demyelinating diseases	7
	Cerebritis, vasculitis	
	Postneurosurgery	

Relative frequencies based on combined data from references[8] and [27].

NMDA receptors increases. Activation of NMDA receptors by glutamate increases intracellular calcium concentrations, which may contribute to neuronal injury and promote further seizures.[69] Blockade of NMDA receptors is therefore a promising approach to the management of prolonged, refractory SE.[70–72]

Animal studies have consistently demonstrated that sustained seizures can cause neuronal damage, especially in vulnerable regions of the brain such as the hippocampus and thalamus. This effect is observed even when convulsions are prevented with neuromuscular blockade, arguing that nonconvulsive SE may have similar injurious effects. Damage is observed even when potentially harmful systemic effects of SE, such as hypoxemia, hyperthermia, and acidemia, are prevented.[73–75] Neuronal loss has been documented in autopsy series of patients who died with SE.[76] Elevated levels of neuron-specific enolase (NSE), a marker of neuronal injury, can be demonstrated following SE, including complex partial SE and nonconvulsive SE.[77] MRI studies initially show hyperperfusion in seizing areas of the brain, followed by diffusion abnormalities, consistent with cytotoxic edema.[78,79] These changes probably occur because prolonged ictal activity raises metabolism to a degree not matched by increased flow, although the mechanism may be more complex.[80,81] MR spectroscopy has similarly demonstrated the accumulation of lactate and evidence of anaerobic metabolism.[82] The radiographic defects are sometimes transient, but permanent changes – often with increased temporal T2 signal consistent with hippocampal sclerosis – may ensue.[83] It is probably partially for this reason that patients who survive SE are at substantially increased risk of subsequent seizures.[84]

Manifestations

Generalized convulsive SE is associated with several serious medical complications, which in turn can contribute to secondary brain injury.[8] Because cerebral blood flow autoregulation becomes impaired, subsequent hypotension

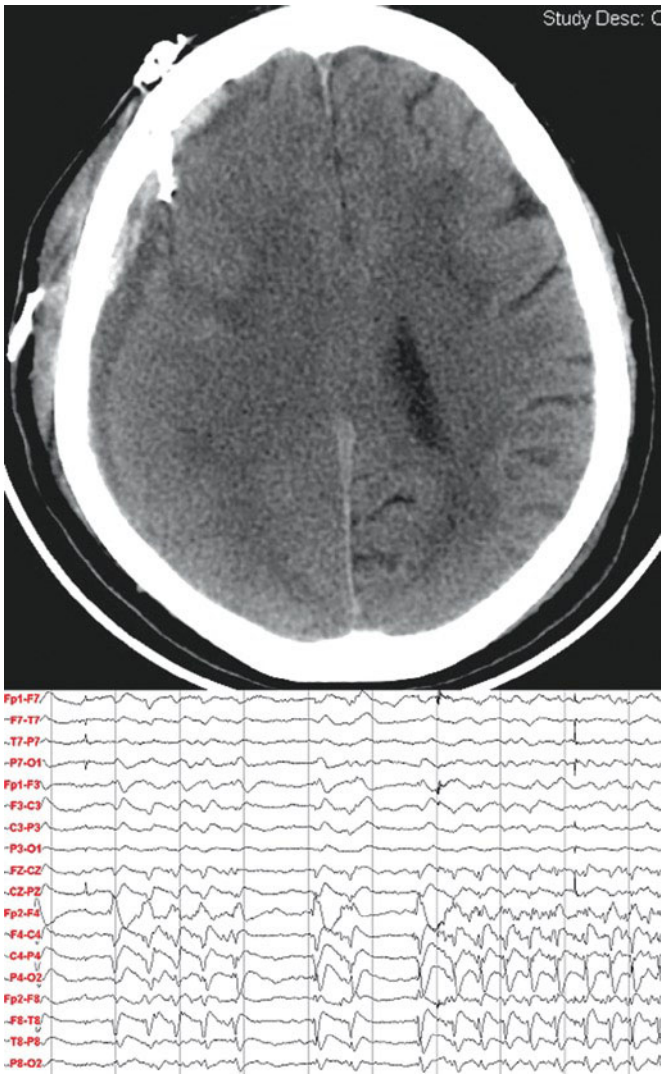

FIG. 17.1. A 70-year-old man was admitted to the neurointensive care unit after a fall, and was found to have an acute or chronic right subdural hematoma. Because of a persistently depressed level of consciousness, an EEG was obtained. Frequent spike-wave complexes arising in the right frontal region repeatedly evolved into focal, and then secondarily generalized, seizures. There were no accompanying clinical manifestations other than stupor.

can be particularly deleterious. When a seizure is prolonged, ventilation is ineffective, and patients develop both hypercapnia and hypoxemia. Therapy for SE causes further respiratory depression, and the combination of hypercapnia with the development of lactic acidosis can induce profound acidemia.[85] It is possible that acidemia may actually have some protective anticonvulsant effects.[86]

Normal airway protective reflexes are impaired during a seizure, and patients are vulnerable to aspiration of oral and gastric contents. The development of bilateral pulmonary infiltrates and hypoxemic respiratory failure is most commonly due to either aspiration pneumonitis or neurogenic pulmonary edema. The pathogenesis of neurogenic pulmonary edema is thought to involve acute pulmonary venoconstriction, although some degree of "increased permeability" is also present.[87,88]

Increased sympathetic tone initially causes hypertension, but there are several reasons why patients with SE ultimately become hypotensive. As with other causes of acute brain injury, patients with SE may develop acute neurogenic cardiac dysfunction. Animal models and autopsy series have suggested that the mechanism involves massive catecholamine release, with the formation of myocardial contraction bands adjacent to sympathetic nerve endings.[89,90] Electrocardiographic abnormalities are very common, although the clinical importance of some of these changes is unclear.[91] Several of the drugs used in the management of SE have important hemodynamic effects.

Hyperthermia is common, probably contributes to the development of secondary brain injury, and should therefore be treated.[8,92] Rhabdomyolysis can be severe enough to induce acute renal failure. Ensuring adequate intravascular volume and blood pressure while minimizing the use of nephrotoxins, including intravenous contrast, may be important.[93]

The natural history of refractory generalized convulsive SE that cannot be pharmacologically halted is for patients to eventually develop "electro-mechanical dissociation," such that there are ongoing electrographic seizures with only minimal, if any, clinical correlate. Thus, the clinician should not be misled into believing that the cessation of overt convulsive activity means that the seizures have stopped. Studies have shown that 15–20% of patients continue to have electrographic seizures even after control of visible convulsive activity.[94] Consequently, unless a patient quickly regains consciousness, an EEG should be obtained emergently to rule out the possibility of nonconvulsive SE.[95]

The diagnosis of nonconvulsive SE requires a high index of suspicion, and should be considered in any patient with an altered level of consciousness not clearly explained by another cause. Some patients may have subtle motor or ocular movements that should further raise suspicion,[96] but these are more often absent (Fig. 17.1). In one series, 8% of patients with previously unexplained coma were found to have nonconvulsive SE when an EEG was performed.[97]

Diagnosis

The initial priority in the management of SE is to ensure physiologic stability and rapid seizure cessation. However, clinicians must at least be considering potential etiologies as they are attending to the patient. Treatable metabolic derangements should be rapidly excluded. If there is a history of epilepsy, AED levels need to be determined. If there is a suspicion of meningitis or encephalitis, antimicrobial therapy must be initiated prior to performing a lumbar puncture. A toxicology screen should be obtained if drug abuse is a possibility. Cerebral imaging with CT or MRI is important, but should

not interfere with proper attention to the patient and urgent treatment of seizures.

By definition, nonconvulsive SE can only be confidently diagnosed with an EEG. Unfortunately, a routine 20–30 min EEG is insufficient, having a sensitivity of less than 50%.[22] Because seizures come and go, at least 24–48 h of continuous monitoring is required to rule out nonconvulsive SE as a contributing cause of an altered or depressed level of consciousness. Even with an EEG, it may be difficult for interpreters to determine whether frequent epileptiform discharges are truly seizures, rather than simply representing the electrographic changes caused by an injured brain. In such cases, one can administer a test dose of benzodiazepine (e.g., 2 mg midazolam): If there is definite clinical and electrographic improvement, then the diagnosis is clear. However, more often there will be no change, or the epileptiform discharges will be abolished without any clinical improvement, such that the diagnosis remains in doubt.

Treatment

Similar to the management of other conditions in neurocritical care, patients with SE should be approached with the philosophy that "time is brain." Throughout the management of SE, the need for endotracheal intubation must repeatedly be assessed (Table 17.2). As long as the airway can be kept patent, most patients will not require it immediately. If a seizure continues beyond 2 min, it should be treated pharmacologically. Benzodiazepines are first-line therapy and work by binding to the GABA receptor complex, thereby increasing inhibitory neurotransmission. They are relatively effective, as long as

Table 17.2. Management algorithm for status epilepticus.[13,167]

1. First 5 min
   - Do not panic! Most seizures subside spontaneously after no more than 1–2 min
   - Attention to ABCs, minimize risk of aspiration, establish IV access, physiologic monitoring
   - If seizure persists beyond 2 min, administer 2 mg lorazepam
   - If no IV access, alternatives include diazepam 20 mg pr or midazolam 10 mg intranasally, bucally or IM
2. 5–10 min
   - If still seizing, administer 2 mg lorazepam q1–2 min to a maximum of 0.1 mg/kg (typically ~8 mg)
   - Consider possible etiologies, send appropriate bloodwork; rapidly determine blood glucose
   - Administer D50W and thiamine if appropriate
   - If CNS infection is suspected, administer ceftriaxone 2 g IV ± acyclovir 10 mg/kg
   - If space-occupying lesion and mass effect is suspected (e.g., pupillary dilatation), give 0.5 g/kg mannitol
3. 10–20 min
   - If still seizing, options include:
     - Phenytoin 20 mg/kg (1 g is insufficient for most patients!) at rate not exceeding 50 mg/min. If still seizing after ~10 min, consider proceeding to step 4 prior to completion of infusion
     - Valproate 20–30 mg/kg over 5–10 min (advantage over phenytoin is that it can be administered more rapidly and avoids delays in proceeding to step 4)
     - Proceed directly to step 4
4. 10–60 min
   - An intensivist, emergency physician or anesthesiologist should participate in care at this point
   - If still seizing, patient requires endotracheal intubation. The medications described below can be part of the induction dose to facilitate laryngoscopy
   - Administer a fluid bolus. Concomitant use of an alpha agonist (e.g., phenylephrine, 100 µg increments) may be necessary to promptly treat hypotension during airway management
   - If neuromuscular blockade is required, use short acting nondepolarizing agent (e.g., rocuronium, cis-atracurium) rather than succinylcholine. Be aware that the patient may still be seizing despite absence of visible convulsions
   - Initiate arrangements for emergent continuous EEG monitoring
   - If still seizing, options include the following:
     - Midazolam: Load with ~0.1 mg/kg, and repeat as necessary q3–4 min until seizures abolished. Use of very large doses (as high as 2 mg/kg!) has been described in the literature, although we have found it unusual for doses greater than 30–40 mg to be effective. If effective, begin infusion at 0.1 mg/kg/h. If higher dose is required, give another 0.1 mg/kg bolus prior to increasing infusion rate. Infusions as high as 2–3 mg/kg/h have been described
     - Propofol: Load with 1–2 mg/kg. Begin infusion at 50 µg/kg/min (3 mg/kg/h). If higher dose is required, give another 0.5–1 mg/kg bolus prior to escalating infusion. Infusion should not exceed 80–85 µg/kg/min (5 mg/kg/h) for more than a few hours to avoid risk of propofol infusion syndrome
5. ≥60 min
   - If still seizing, options include the following:
     - Pentobarbital: Load with 5 mg/kg at rate of 50 mg/min, and repeat ~q15 min as necessary until seizure abolished, to maximum load of ~25 mg/kg. Begin infusion at 1 mg/kg/h, and titrate to seizure suppression
     - Combine midazolam and propofol
   - If stage 4 or 5 is reached, most patients will require arterial and central venous catheterization
   - Optimize volume status, and if necessary, begin infusion of vasopressor
   - Once patient sufficiently stable, obtain necessary diagnostic tests (e.g., lumbar puncture, imaging)

they are administered early in the course.[7,27,98] Diazepam has the advantage of high lipid solubility, such that it reaches the CNS quickly. However, its duration is short because of rapid redistribution to adipose tissue, and patients may be at risk of recurrent seizures.[99] Lorazepam has a slightly slower onset, but may bind more tightly to the GABA receptor complex and has a considerably longer duration of action.[100] Furthermore, diazepam may cause more respiratory depression, and increase the need for intubation.[101,102] Based on these observations and the findings of several clinical trials, lorazepam (maximum dose of 0.1 mg/kg, 2 mg/min) is favored as the initial drug of choice.[1,11,12,101,103–105] One approach is to load 8 mg into a syringe and administer increments of 2 mg every 1–2 min until seizures subside. If intravenous access is not immediately available, potential options, which have been best studied in children, include intramuscular, intranasal, or buccal midazolam.[106–109] The latter has been shown to be superior to rectal diazepam, which is another option in this setting.[107,110]

There should be no delay in progression to another agent if first-line therapy has failed. All of the drugs traditionally used in status epilepticus (lorazepam, diazepam, phenobarbital, phenytoin) are relatively ineffective as second-line agents.[12,15] In the large Veterans Affairs trial, only 7% of patients who continued to seize after lorazepam subsequently responded to phenytoin.[12] Nevertheless, phenytoin (~20 mg/kg) continues to be the most commonly used drug after the administration of benzodiazepines.[111] Because of its propylene glycol content, rapid infusion (more than 50 mg/min.) of phenytoin consistently causes hypotension,[112] and 20–30 min is required for the dose to be safely completed. The slow administration and limited efficacy of phenytoin can therefore cause critical delays in seizure control. The highly alkaline pH of phenytoin is responsible for a high incidence of phlebitis. Thus, phenytoin should ideally be administered through a relatively large intravenous catheter (≥18 gauge) in a proximal vein. In rare cases, probably because of extravasation, phenytoin causes severe skin sloughing and necrosis, a condition sometimes called the "purple glove syndrome."[113,114] Fosphenytoin is a phosphate ester precursor of phenytoin that is water soluble and can be infused considerably faster (up to 150 mg/min). Even though it has been shown to be efficacious,[115] the duration of time required for fosphenytoin to be metabolized prevents therapeutic levels of phenytoin from being achieved any faster.[116]

Given the high incidence of persistent nonconvulsive seizures after cessation of convulsions,[94] an EEG should be considered, even if patients have responded to first- or second-line therapy, especially if their mental status is slow to normalize. SE is most often defined as refractory after the failure of adequate doses of two first-line drugs, usually lorazepam and phenytoin. Because subsequent treatment involves deeply sedating drugs, patients with refractory SE invariably require endotracheal intubation. If neuromuscular blockade is required to facilitate airway management, we favor avoiding succinylcholine, since many patients have rhabdomyolysis and the risk of hyperkalemia may be higher than usual.[10] A short-acting, nondepolarizing agent (e.g., rocuronium) is preferred to avoid confounding the neurologic examination for too long, keeping in mind that the patient may still be seizing while they are paralyzed. Hypotension is common, and should be aggressively treated with fluids and vasopressors in order to ensure adequate cerebral perfusion. Continuous EEG monitoring is essential at this stage in order to guide further pharmacologic management.

There are no randomized trials comparing different regimens in the management of refractory SE, but the most commonly used agents include midazolam, propofol, and high-dose barbiturates. Because of the particularly elevated risk of adverse effects, and long duration of action associated with use of barbiturates, these are often reserved for cases where midazolam or propofol fail. Midazolam has the advantage of causing less hemodynamic compromise compared with the other agents. Relatively large doses (0.1–0.2 mg/kg load, 0.1–0.4 mg/kg/h infusion) are typically necessary to achieve seizure control.[118,119] In the largest series of patients, the success rate was over 80%, but breakthrough seizures occurred in 47–56%.[119,120]

Compared with other benzodiazepines, propofol has the advantage of more rapid awakening after prolonged infusion, a property that is potentially advantageous in neurocritical care patients.[121–123] While benzodiazepines and barbiturates exert their effects exclusively on GABA receptors, propofol has additional antiseizure properties, including NMDA receptor blockade and modulation of calcium influx.[124] Conversely, there have been reports of possible proconvulsant effects and seizure-like phenomena.[125,126] Accumulating evidence does show propofol to be an effective agent in refractory SE, with success rates ranging from 63% to 100%,[127–131] although it is not uncommon for seizures to recur when propofol is weaned.[127,129] One small study suggested that the risk of death might be somewhat higher with propofol than midazolam, although the results did not reach statistical significance, and the doses used were relatively large.[131] It has recently been recognized that infusions of propofol should not be administered at doses exceeding 5 mg/kg/h for more than a few hours because this increases the risk of developing the potentially life-threatening propofol-infusion syndrome.[132,133]

There are several case series using high-dose pentobarbital (5–10 mg/kg at 50 mg/min; then 5 mg/kg every 30–60 min if necessary to abolish seizures, for maximum dose of 25 mg/kg; 0.5–2 mg/kg/h infusion) [134–136] and thiopental (5–10 mg/kg, 3–5 mg/kg/h infusion)[130,137] in refractory SE. Although these agents are very effective at controlling seizures, a large proportion of patients require hemodynamic support[138] and develop infections.[130,139] Barbiturates have numerous deleterious effects on immune function, including impairment of cytokine release, chemotaxis, and phagocytosis.[140,141] In a systematic review of case reports, barbiturates were found to be more likely to control seizures than midazolam or propofol, but also to have a greater risk of complications.[142] At present

there is no conclusive evidence of a difference in outcomes between the three categories of drugs.[142,143]

Some authorities prefer to use intravenous valproic acid instead of, or in addition to, phenytoin prior to moving on to more deeply sedating drugs. The typical loading dose is 15–30 mg/kg, which can be infused safely at rates as fast as 6 mg/kg/min,[144–146] such that the entire load can be administered in less than 10 min. This represents a major advantage over phenytoin, in that little time is wasted prior to moving on to more aggressive therapy if a patient does not respond. Furthermore, valproate can be continued as an infusion at a dose of 1–5 mg/kg/h.[147,148] Preliminary data, including a small pilot randomized controlled trial, suggest that valproate may be more effective than phenytoin in SE when benzodiazepines have failed.[147–150]

Recognition that excitatory amino acids play an important role in sustaining seizures has generated interest in the use of NMDA receptor antagonists for refractory SE.[71,151] One such drug, that is readily available, is the anesthetic agent ketamine, which has the additional advantage that it does not cause hypotension. Preliminary reports have suggested that ketamine is sometimes effective for refractory SE when other agents are not.[152,153] However, the safety of using ketamine, at high doses for extended periods of time, has not been established.[154] There has traditionally been a reluctance to use ketamine in neurocritical care because of concerns about raising intracranial pressure, although this effect has probably been overstated.[155]

Topiramate has multiple antiepileptic properties, one of which is antagonism of glutamatergic transmission. Although it cannot be given intravenously, it has been used as rescue therapy in cases of refractory SE.[156–158] Levetiracetam is another newer AED that works by a variety of mechanisms and has relatively few adverse effects. Several cases of success in the treatment of SE have been reported.[159–161] Use of this agent will likely increase in the future, particularly with the recent development of an intravenous formulation. Drugs like topiramate, levetiracetam, and valproate can be especially helpful to avoid seizure recurrence as general anesthetic drugs are being weaned.

Therapeutic decisions must always consider the overall context and prognosis of the patient. For example, patients with anoxic brain injury following cardiac arrest may demonstrate myoclonic status epilepticus (Fig. 17.2). Although aggressive treatment with sedatives may abolish the myoclonus, this intervention will not alter the outcome.[162] The same principle may also apply in other settings.

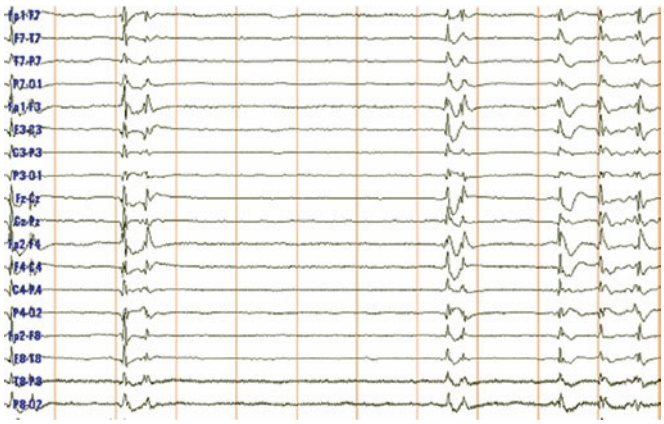

FIG. 17.2. An elderly man was admitted to the ICU following resuscitation from a prolonged cardiac arrest. Frequent myoclonus was observed clinically, and an EEG was obtained. Generalized, periodic epileptiform discharges were seen coinciding with myoclonic jerks. The patient never awakened.

Continuous EEG Monitoring

The purpose of cEEG monitoring in SE is primarily to ensure that patients are not having nonconvulsive seizures. In a stuporous or comatose patient being treated for nonconvulsive SE, it is difficult to appropriately titrate drug therapy without cEEG. Recurrence of electrographic or clinical SE with decreasing sedation is a strong predictor of poor outcome.[163] It is therefore possible that a period of more intensive suppression of EEG background activity could be beneficial in achieving lasting seizure control.[164] Consequently, some published protocols have adjusted sedation to achieve either a burst-suppression pattern or even a "flat" EEG.[128,129,134,142,165] The frequency of breakthrough seizures does appear to be less with a goal of burst suppression compared with simply eliminating epileptiform activity.[117] However, the routine use of such an approach remains of uncertain value,[142,143] while subjecting patients to additional risks associated with deeper sedation.[142,143,166] Furthermore, clinicians must not be deceived into believing that patients cannot have further seizures despite the presence of burst-suppression. Thus, regardless of which drug we choose to treat refractory SE, we prefer to adjust therapy simply to keep patients seizure-free; we only deliberately target a more suppressed EEG if patients repeatedly develop seizures with attempts to wean therapy. It is also good practice to ensure that patients are seizure-free for at least 12–24 h before attempting to decrease sedation. In cases where repeated attempts to reduce therapy have been unsuccessful, an even longer seizure-free period may be helpful.

Given the increasing recognition that nonconvulsive seizures and SE are common among patients with different forms of brain injury, the use of cEEG in the ICU should continue to increase.[22,51,63,64] It is obvious, but still important to emphasize, that cEEG is a diagnostic modality, and does not constitute therapy. Thus, in order to ensure that relevant electrographic changes are recognized and acted upon in a timely fashion, there must be regular, frequent communication between bedside clinicians and experienced EEG interpreters.

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18
Critical Illness Polyneuropathy and Myopathy

Galen V. Henderson

Critical illness polyneuropathy (CIP) and myopathy (CIM) are neuromuscular disorders that have been documented in critically ill patients admitted into intensive care units and are usually noted because of their failure to wean from mechanical ventilation.[1–3] As a result of the diseases, there are increases in hospitalization length of stay, morbidity, and costs.

Epidemiology

The development of weakness in intensive care unit patients has been increasingly recognized over the past few decades. Although the incidence of CIP and CIM in the critically ill varies considerably according to the diagnostic criteria, they are the most common causes of weakness in intensive care unit patients and their true incidence has been found to range from 33% to 57%.[2,4–6]

Pathophysiology

Critical Illness Polyneuropathy

The pathogenesis of CIP is uncertain. There have been no specific toxin, agent, or nutritional deficiencies that have been identified with this disorder. The current thoughts are that cytokines and free radicals associated with systemic inflammatory response syndrome (SIRS) adversely affect the microcirculation and produce distal axonal degeneration by neuronal hypoxia.[7] This view seems to be supported by the finding that critically ill patients with high Acute Physiology and Chronic Health Evaluation-III (APACHE-III) scores and SIRS are most prone to the development of this disease.[2,4,5]

Critical Illness Myopathy

Critical illness myopathy was first described in patients who had status epilepticus and were being treated with high-dose corticosteroids and neuromuscular-blocking agents.[8] CIM can occur in septic patients who have not received corticosteroids and/or neuromuscular blocking agents.[8] This process has also been called a "thick filament myopathy," due to a the loss of intramysial myosin fibrils. In some cases, it has been called a membranopathy of uncertain pathogenesis due to inexcitable muscle membranes, in which there may be no discernible histologic abnormality on muscle biopsy.[9,10] Rossignol et al.[11] have recently conducted experiments in an animal model of sepsis and found a reduction in the maximal sodium current conductance that could explain muscle membrane inexcitability. This occurred in the absence of any alteration in the resting membrane potential. Although Dr. Rossignol and colleagues point out that their model was one of sepsis and did not involve denervation or corticosteroid administration, the septic animals likely had increased cortisol from stress, and 10 days is enough time for the early development of critical illness polyneuropathy (these were not assessed in their model). It is likely that sodium channels in skeletal muscle membrane are regulated in a very dynamic manner and that these are altered by denervation, neuromuscular blockers, corticosteroids, and sepsis. Further research is needed to determine whether a unifying pathogenesis is possible or if a variety of mechanisms is causative.[12]

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Risk Factors

The identification of risk factors is an important step in understanding the pathogenesis and for the development of preventive or curative therapy. Studies have shown an association between systemic inflammation, medications such as corticosteroids and neuromuscular blocking agents (NMBAs), and hyperglycemia with CIP/CIM.

Diagnosis

In the intensive care unit, the typical patients with the potential for CIP/CIM are those with clinical features that include difficulty weaning from mechanical ventilation and those who have a symmetrical and flaccid tetra-paresis sparing the face with decreased tone, areflexia, muscle atrophy, and absence of pathologic reflexes. Serum creatinine kinases (CK) are normal or slightly elevated in most cases. Appropriate imaging (computed tomography, magnetic resonance imaging) may be necessary to exclude central nervous system (CNS) causes (Table 18.1[13]).

Electromyographic Studies

The diagnosis of CIP or CIM is usually established by nerve conduction and electromyographic studies performed within 2–3 weeks after initiation of mechanical ventilation.[2] There have been attempts to make the diagnosis of CIP/CIM earlier in a patient's clinical course. In a recent prospective study of patients with severe sepsis, Kahn et al. evaluated the prevalence, time of onset, and the cause of neuromuscular dysfunction by evaluating weekly neurologic examinations and nerve conduction studies (NCSs) within 72 h of developing severe sepsis until ICU discharge. Electromyography was performed if clinical weakness developed or if there was a significant reduction in nerve conduction response amplitudes. The study found that abnormal NCSs were present upon enrollment in 63% of patients (31/48). The presence of abnormal baseline NCS was predictive of hospital mortality (55% vs. 0% for patients with normal baseline NCS; $p<0.001$). The development of acquired neuromuscular dysfunction could be predicted by NCS performed on day 7. Twenty patients remained in the ICU long enough to have serial NCSs; 50% of these patients developed acquired neuromuscular dysfunction. Most patients with acquired neuromuscular dysfunction had electrophysiologic evidence of both critical illness myopathy and critical illness neuropathy. Changes in nerve conduction studies occur in the majority of patients early in the course of severe sepsis and predict the development of acquired neuromuscular dysfunction and mortality in intensive care unit patients. Most patients with acquired neuromuscular dysfunction after sepsis have both CIP and CIM.[14]

Since electrophysiological tests of peripheral nerves and muscles may be time-consuming, Latronico et al. evaluated a simplified electrophysiological investigation of only two nerves as an alternative to complete electrophysiological tests. He prospectively studied 92 ICU patients measuring unilateral action potential amplitude of the sural and peroneal nerves. After the first 10 days, complete electrophysiological investigations were carried out weekly until ICU discharge or death. At hospital discharge, complete neurological and electrophysiological investigations were performed. Electrophysiological signs of CIP/CIM occurred in 28 patients (30.4, 95% confidence interval [CI] 21.9–40.4%). A unilateral peroneal CMAP reduction of more than two standard deviations of normal value showed the best combination of sensitivity (100%) and specificity (67%) in diagnosing CIP/CIM. All patients developed the electrophysiological signs of CIP/CIM within 13 days of ICU admission. Median time from ICU admission to CIP/CIM was 6 days (95% CI 5–9 days). Multi-organ failure occurred in 21 patients (22.8, 95% CI 15.4–32.4%) and was strongly associated with CIP/CIM (odds ratio 4.58, 95% CI 1.64–12.81). At hospital discharge, diagnoses in the 15 survivors were CIM in six cases, CIP in four, combined CIP and CIM in three, and undetermined in two. A peroneal CMAP reduction below two standard deviations of normal value accurately identifies patients with CIP/CIM[15] (Table 18.2).

Table 18.1. Typical clinical features of critical illness polyneuropathy and myopathy.[13]

Disease	Abnormalities on neurologic examinations	Creatine kinase levels	Cerebral spinal fluid	Other features
Critical-illness polyneuropathy	Distal more than proximal limb weakness, rarely involving facial muscles Distal sensory loss Reduced or absent reflexes Preexisting or concomitant encephalopathy	Normal	Normal or slightly elevated protein	Associated with sepsis, multi-organ failure
Acute myopathy associated with myosin deficiency	Weakness either generalized or more prominent proximally. No sensory deficits Reduced or absent reflexes	Normal or slightly elevated	Normal	Associated with exposure to high-dose corticosteroids, with or without concomitant exposure to neuromuscular blockers

Table 18.2. Electrophysiologic and muscle biopsy finding associated with critical illness polyneuropathy and myopathy.[13]

Disease	Nerve conduction studies	Electromyography	Muscle biopsy findings
Critical illness polyneuropathy	Reduction in both CMAP and SNAP amplitudes without evidence of conduction block or slowing		
Myopathy associated with myosin deficiency	Reduction in CMAP amplitudes with relative preservation of SNAP amplitudes No evidence of conduction block or slowing	Little or no spontaneous activity Predominance of normally recruiting, normal appearing MUPs mixed with varying numbers of small, brief polyphasic MUP	Relative preservation of atrophic myofibers, with occasional angulated muscle fibers Myosin deficiency on lights and electron microscopy with relative preservation of actin filaments

CMAP compound muscle action potentials; *SNAP* sensory nerve action potential; *MUP* motor unit potential.

Differential Diagnosis

Guillan–Barré syndrome (GBS) is the most common neuromuscular disorder that requires admission to the ICU, as well as the most important differential diagnosis for CIP/CIM. GBS is typically a rapidly progressive, symmetric ascending paralysis, often after a viral illness or surgical procedure. Elevated CSF protein and electrodiagnostic findings clearly distinguish GBS from CIP/CIM.

Management

There is no specific treatment or management for CIP or CIM. In general, supportive care is essential because most of these patients will eventually recover despite neuromuscular study abnormalities. Prevention of CIP and CIM is feasible in part by avoiding risk factors and by aggressive medical management of critically ill patients. Medications that may increase the risk of CIP/CIM such as corticoids and NMBA should be used with caution. Sedation protocols designed to minimize the use of sedatives and to promote earlier wakefulness and permit earlier recognition of weakness are recommended.[16]

Although data supporting specific approaches to treat CIP/CIM are limited, strict control of glycemia by insulin has been shown to reduce the incidence of CIP. In the landmark prospective randomized, controlled clinical trial conducted by Van den Berghe et al. involving adults admitted to surgical intensive care units who were on mechanized ventilation, intensive insulin therapy (blood glucose <100 mg/dL or 6.1 mmol/L) reduced overall in-hospital mortality by 34%, and critical care neuropathy by 44%.[17,18]

Management of CIP/CIM requires a full multidisciplinary team that includes physiotherapy and psychological support. After discharge from the ICU, patients should enter an intensive rehabilitation program.

Prognosis

The prognosis of CIM/CIM is directly related to the prognosis of the underlying critical illness. Although complete recovery can occur within a few weeks, many patients will have persistent functional disabilities in activities, reduced quality of life, and restrictions in autonomy.[19,20]

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Part III
Cardiology

19
Management of Hypertension in the Perioperative Period

Nicholas P. Tsapatsaris and Durathun Farha

This chapter focuses on common clinical challenges in hypertension management faced by intensive care providers. They include the treatment of patients with preexisting hypertension who cannot take oral medications, the treatment of hypertensive urgencies and emergencies, and the use of specific antihypertensive medications. The challenge for the clinician is not the lowering of blood pressure with parenteral drugs, but rather the more difficult questions about in whom to use them and what goals to achieve. We have learned a great deal about the treatment of chronic hypertension and the attendant long-term reduction in cardiovascular morbidity and mortality associated with effective blood pressure lowering. Currently, the definition of hypertension, goals for treatment, and benefits of therapy have been established in numerous clinical trials, and widely disseminated in evidence-based consensus documents to practicing physicians. Unfortunately, these goals do not necessarily apply to acutely ill surgical intensive care unit patients, some of whom benefit and some of whom are harmed from blood pressure lowering. Thus, the management of hypertension in the intensive care unit is highly individualized. There are few, if any, prospective trials regarding choice of antihypertensive medications in this setting. Recommendations are generally on the basis of consensus opinion, customary use, extrapolation from animal models, and common sense application of physiologic principles.

The management of hypertension in the perioperative period remains a challenge despite an impressive array of effective antihypertensive medications. The need to reduce blood pressure while maintaining adequate end organ perfusion, and the various unavoidable factors that play a role in the postoperative period, make it easy to move from hypertension to hypotension with or without treatment.

Definition of Postoperative Hypertension

Acute postoperative hypertension is defined as a significant elevation in blood pressure during the immediate postoperative period that may lead to serious neurological, cardiovascular, or surgical site complications (Table 19.1).[1,2] Acute postoperative hypertension generally starts within 2 h after surgery in most cases, and usually lasts for about 4–6 h. Occasionally, the elevated blood pressure can persist for 24–48 h. True postoperative hypertension will persist despite adequate sedation and analgesia. Complications are higher if the elevated blood pressure lasts longer than 3 h.[3] Invasive arterial-pressure monitoring is indicated for major procedures, and the arterial pressure should be actively managed to target blood pressure reduction to 20% below pretreatment baseline and to avoid major excursions in mean arterial pressure.

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Table 19.1. Complications of uncontrolled postoperative hypertension.[2]

Site	Complication
Brain	Stroke, seizure
Eye	Hemorrhage, exudate
Heart	Myocardial ischemia or infarction, left ventricular dysfunction or failure, arrhythmia
Kidney	Acute renal failure, proteinuria, hematuria, increased creatinine level
Vascular anastomoses	Hematoma, hemorrhage, anastomotic disruption (at surgical sites)

Definitions of hypertension applied in clinical trials of postoperative hypertension include the following[3]:

- (Most commonly) an increase in systolic blood pressure or diastolic blood pressure of greater than or equal to 20% above the preoperative baseline, or
- Greater than 30 mmHg increase in systolic blood pressure above the preoperative baseline, or
- A fixed blood pressure value of greater than 160/90 mmHg on three consecutive measurements, or a MAP of >110 mmHg, especially in patients with no known history of hypertension.

Blood Pressure Targets in Various Postoperative States

The targeted blood pressure values differ with various procedures, especially with respect to neurological and cardiovascular surgeries. With cardiovascular surgery, blood pressure is usually targeted to a lower level. Recommended thresholds for treatment are a blood pressure of greater than 140/90 mmHg or a mean arterial pressure of 105 mmHg or greater. However, there seems to be no consensus for this recommendation.[3] With neurosurgical procedures such as carotid endarterectomy, most studies quote a blood pressure of higher than 160/100 mmHg as the target at which to start treatment.[4,5] In stroke patients, however, the recommendation is not to lower the blood pressure precipitously and consider treatment only if the blood pressure is higher than 180/110 mmHg. In subarachnoid hemorrhage antihypertensive agents are advocated for a blood pressure of greater than 140/90 mmHg. It is recommended to maintain systolic blood pressure in the 90–140 mmHg before aneurysm treatment, and then allow some increase in blood pressure to keep systolic blood pressure of less than 200 mmHg. This avoids central nervous system damage in the ischemic penumbra from reactive vasospasm.

Prevalence of Postoperative Hypertension

Postoperative hypertension is most commonly associated with neurosurgical, cardiothoracic, vascular, head, and neck surgeries. The frequency of postoperative hypertension with various surgical procedures is listed in Table 19.2.

Table 19.2. Frequency of Acute Postoperative Hypertension (APH) by surgical procedure.[3]

Procedure	Frequency of APH (%)
Carotid endarterectomy	9–64
Cardiac surgery	22–54
Abdominal aortic surgery	33–75
Radical neck dissection	10–20
Intracranial neurosurgery	57–91
Elective general surgery	3–9
Elective surgery (noncardiac)	20[a]
Release of flexion contractures	46

[a]Includes a mix of general, orthopedic, urologic, gynecologic, obstetric, neurologic, otolaryngologic, and minor vascular surgeries.

Pathophysiology

Acute (instantaneous) change in blood pressure is predominately mediated by the autonomic nervous system; while chronic changes (days to weeks) in blood pressure operate through the kidneys via the humoral system (renin angiotensin aldosterone system). The final common pathway leading to acute postoperative hypertension appears to be the activation of the sympathetic nervous system, as evidenced by elevated plasma catecholamine concentration. Activation of renin angiotensin aldosterone system contributing to acute postoperative hypertension (APH) is being studied; and plasma renin, angiotensin II, and aldosterone levels are not significantly different between hypertensive and normotensive patients, suggesting that the predominant mechanism is sympathetic activation.[3] The primary hemodynamic alteration observed in APH is an increase in afterload (sympathetic mediated vasoconstriction) with or without tachycardia. There is no difference in cardiac index, left ventricular stroke volume, or left atrial pressure compared to normotensive patients.[3]

Management of blood pressure should take into consideration the following basic principles:

- Blood pressure = cardiac output × vascular resistance
- Cardiac output = Heart rate × stroke volume

An increase in the heart rate (assuming no change in stroke volume), blood volume, blood viscosity, or peripheral resistance will result in an increase in the blood pressure. The autonomic nervous system, by inducing changes in heart rate, systemic vascular resistance, and venous tone, modifies blood pressure. Every time we manage postoperative hypertension, we should question ourselves whether we need to treat the central power station (hyper-dynamic heart) or peripheral network or both. Beta blockers, nondihydropyridine calcium channel blockers, and central acting alpha agonists predominately affect cardiac output. The vasodilating drugs nitroglycerin, nitroprusside, hydralazine, alpha blockers, and

dihydropyridine calcium channel blockers predominately reduce peripheral resistance.

Often combinations of medications are necessary because of individual drug activation of compensatory mechanisms to maintain blood pressure. A good example of this principle is the anti-impulse therapy for aortic dissection. Beta blockers are used in combination with vasodilators to blunt the reflex tachycardia induced by vasodilators.

Etiology

In most patients, postoperative hypertension is often a benign self-limited phenomenon, not associated with sequelae. Thus Gal and Cooperman,[6] in their study involving 1,844 recovery room patients, noted that two-thirds of the patients had associated precipitating factors. They suggested treating possible precipitating factors first, and if hypertension persists for more than 2 h or has associated complications, prompt treatment is warranted. Gal and Cooperman[6] in the same study analyzed the frequency (%) of the associated factors contributing to postoperative hypertension, listed in Table 19.3.

Several preoperative patient characteristics, as well as operative, and postoperative factors, may precipitate increased sympathetic activity and result in or exaggerate postoperative hypertension, as listed in Table 19.4. It is recommended that in all patients these factors be reviewed and treated prior to the use of antihypertensive medication. Patients with preoperative hypertension are at increased risk because 50% of these will develop postoperative hypertension, and half of these will develop complications as a result. Atherosclerotic vessel changes and increased systemic vascular resistance associated with aging can predispose elderly patients to postoperative hypertension. Surgical factors, such as prolonged surgeries with major fluid shifts and vascular manipulations, can result in postoperative hypertension.

Pain and anxiety during emergence from anesthesia are the most common contributors of postoperative hypertension. Preoperative counseling and adequate analgesia/sedation in the postoperative period is essential to preventing the development of postoperative hypertension. Anesthetic emergence with hypothermia and shivering is especially common in patients receiving inhalation anesthetics and can result in blood pressure elevation. Hypoxemia and hypercarbia can result from inadequate ventilation or respiratory insufficiency. Tracheal airway responses to endotracheal tube, overinflated cuff, or suctioning should be corrected and treated with adequate sedation. Bladder distension from an occluded urinary system can increase blood pressure.

Both hypervolemia and hypovolemia can cause acute elevation in blood pressure and can be managed easily with diuretics or fluid administration as appropriate. Drug interactions and use of vasoactive agents during anesthesia should be suspected and treated appropriately. Antihypertensive withdrawal, as discussed later in the chapter, can be prevented by continuing antihypertensives until the morning of surgery and reinstituting at the earliest as tolerated. Rarely, postoperative hypertension is

TABLE 19.3. Frequency of factors contributing to postoperative hypertension.[6]

Factor	Present in patients (%)
Pain	36
Emergence excitement	17
Reaction to endotracheal tube	15
Hypercarbia	2
Excess fluid administration	7
Hypothermia	7
Hypoxia	17
Hypertension by history	58
Uncertain	17

TABLE 19.4. Factors associated with acute postoperative hypertension.[3]

Preoperative factors
Hypertension (especially if poorly controlled)
Diabetes mellitus
Extent of vascular disease
Advanced age
Renal disease
Operative factors
Type of surgery
Vascular
Cardiothoracic
Neurosurgery
Head and Neck
Anesthesia technique
Anesthesia agents
Pancuronium
Acetylcholinesterase inhibitors
Opiate antagonists
Operative technique
Duration of procedure
Postoperative factors
Pain
Anxiety
Hypothermia, shivering
Anesthesia emergence, excitement
Hypoxia
Hypercarbia
Endotracheal tube placement
Bladder distension
Antihypertensive withdrawal
Hypervolemia
Hypovolemia
Myocardial ischemia
Drug interactions
Increased intracranial pressure
Pulmonary embolism
Vasopressor therapy
Bronchodilators

a result of secondary hypertension from pheochromocytoma, coarctation of the aorta, or renal vascular disease. If there is diagnostic or clinical evidence of myocardial ischemia, increased intracranial pressure, or pulmonary embolism, treatment should be directed at these conditions.

Patients with Preexisting Hypertension

Howell et al. have recently reviewed the literature regarding hypertension, hypertensive heart disease, and perioperative cardiac risk.[7] Their systematic review and meta-analysis of 30 observational studies including 12,995 patients demonstrated an odds ratio for the association between hypertensive disease and perioperative cardiac outcomes to be 1.35. They felt this association, while statistically significant, was not clinically relevant. They also felt that there is little evidence for an association between admission blood pressures of less than 180 mmHg systolic or 110 mmHg diastolic and perioperative complications. Patients with blood pressure above this range may be more prone to perioperative ischemia, arrhythmias, and cardiovascular lability, but there is no clear evidence that deferring surgery reduces perioperative risk. Finally, they concluded that anesthesia and surgery should not be canceled on the grounds of elevated blood pressure, and that intraoperative blood pressure should be maintained within 20% of the best estimate of preoperative blood pressure, especially in patients with markedly elevated blood pressures.

The American College of Cardiology/American Heart Association guidelines comment that stage 1 and 2 hypertension are not independent risk factors for perioperative complications. They do suggest that BP > 180/110 should be controlled before surgery.[8] In the postoperative period, the clinician can expect significant lowering of blood pressure as a nonspecific response to surgery and bed rest. This lowering can persist for months, but expect a gradual return to preoperative levels.[9] Chronic untreated hypertension alters the autoregulatory threshold so that higher mean arterial pressures are needed to maintain target organ blood flow. Thus, a decision may be made to manage these patients at a higher range of mean arterial pressure in the perioperative period.

It is generally recommended that patients take their usual antihypertensive medications with sips of water the morning of surgery. If the patient cannot take oral medications after surgery, their parenteral or transdermal equivalents can be administered. For example, patient on diuretics may receive intravenous furosemide or bumetanide; beta-blockers esmolol, labetalol, or metoprolol; ACE inhibitors like enalaprilat; and calcium channel blockers, such as Nicardipine.[10] Any patient on beta-blockers should continue through the perioperative period to avoid unmasking preexisting heart disease and to reduce the risk for postoperative atrial fibrillation.[11]

Hyperadrenergic States Associated with Acute Postoperative Hypertension and Hypertensive Crisis

Medication withdrawal rebound hypertension is rare, but can be associated with acute severe elevation in blood pressure (Table 19.5). It is most common with abrupt withdrawal of beta blockers and clonidine. It is less likely to happen with other antihypertensives and when the medication is continued until the morning of surgery. Medication withdrawal hypertension is best treated by reinstituting the same medication orally, intravenously, or transdermally. Beta blockers can be replaced with IV labetalol/esmolol/metoprolol, and oral clonidine can be administered transdermally.[12]

Patients taking both beta-blockers and clonidine are at increased risk for bradycardia and rebound hypertension after withdrawal of either. The transdermal patch may contain metal, for example aluminum, so it is recommended that the patch be removed prior to MRI as a result of the potential for altered electrical conduction. The transdermal patch should also be removed before cardioversion or defibrillation. Transdermal clonidine may take several days to achieve adequate drug levels.

For patients who experience an intraoperative hypertensive crisis, suspect pheochromocytoma. The management includes an alpha-blocker-like phentolamine with or without a beta-blocker. In view of the hypertensive risk of unopposed alpha adrenergic receptor stimulation, beta blockers should not be initiated until adequate alpha blockade is established. Nitroprusside and nicardipine can also be used in this setting. Serum and urine catecholamines, metanephrines, and VMA can be checked to help with diagnosis.

Assessment of Patients with Acute Postoperative Hypertension

Blood pressure should be checked in both arms. The brachial, femoral, and carotid pulses should be verified. A careful cardiovascular and neurological examination should be

Table 19.5. The following conditions can cause hypertensive crisis.[13]

Adrenal crisis from pheochromocytoma, Medication withdrawal hypertension
Drug overdose from cocaine, amphetamines.
Encephalopathy
Intracranial hemorrhage
Coarctation of aorta
Renal failure
Toxemia of pregnancy
Vasoconstrictor overdose
Thyroid crisis
Paraplegia
Burns

Table 19.6. The following diagnostic aids are helpful in diagnosing the etiology of postoperative hypertension.[13]

Pulse rate
Blood pressure
Urine output
Urine concentration and electrolytes
Central venous pressure
Pulmonary artery pressure
Pulmonary artery capillary wedge pressure
Cardiac output
Hematocrit
Serum electrolytes, blood urea nitrogen, serum creatinine
EKG
BNP

BNP brain natriuretic peptide.

conducted. Funduscopic examination should be done to detect any hemorrhage or papilledema. Lastly the abdomen has to be auscultated for renal bruits (Table 19.6).

Future Trends in the Management of Postoperative Hypertension

For many years there has been ongoing research for an ideal drug in the management of hypertension in the operative, postoperative/surgical ICU, and emergency room setting (Table 19.7). This agent should be an intravenous drug that has rapid onset and short duration of action. In addition, the drug should have no effect on heart rate, cardiac function, and myocardial oxygen demand. It should also have a benign adverse effect profile.

Clevidipine is a novel, intravenous, ultra-short-acting, vasoselective dihydropyridine calcium channel antagonist that is structurally related to felodipine. Clevidipine acts by selectively dilating small arteries and arterioles, without affecting heart rate or cardiac output and without the risk of rebound hypertension on discontinuation. Clevidipine has an ester group incorporated into the drug molecule that leads to rapid hydrolysis of the drug by red cell esterases, which is responsible for its short duration of action and makes it safe for use in patients with end organ dysfunction. It has been shown to have high clearance and small volume of distribution resulting in a short half-life of less than 1 min. The cardioprotective effect of clevidipine during late ischemia and early reperfusion is mediated via bradykinin and nitric oxide-related mechanism and by preserving coronary endothelial function.[15–25]

ECLIPSE (evaluation of cLevidipine in the postoperative treatment of hypertension assessing safety events) studies involved 1,964 patients and compared clevidipine with sodium nitroprusside, nitroglycerine, and nicardipine.

The study concluded that the primary end points for rate of death, stroke, heart attacks, and kidney dysfunction were similar between the clevidipine and the other three agents.

The studies also assessed blood pressure control by calculating the magnitude and duration of episodes when patients' blood pressures went above or below predetermined acceptable ranges, on the basis of the area under the blood-pressure-monitoring curve (AUC) that was outside the upper or lower limits of the range during surgery and for 24 h afterward.

The first two ECLIPSE studies found that patients treated with clevidipine experienced significantly improved blood pressure control over those who received nitroglycerin (6.02 vs. 14.88 AUC) or nitroprusside (8.94 vs. 17.28 AUC) ($p<0.05$ for both studies). The third study found no significant difference in blood pressure control between clevidipine and nicardipine (5.27 vs. 5.67 AUC). The safety outcomes were similar for all medications. In a separate but supporting study, the same research team found that a higher AUC in cardiac surgery patients is a significant indicator of increased 30-day mortality.

Most common side effects were headache and flushing. The ease of use and reduction in mean arterial pressure were similar to those of the comparable drugs. Unfortunately, a clevidipine phase III safety trial was suspended because interim analysis of the study population showed that atrial fibrillation was more frequent among patients randomized to clevidipine than in patients randomized to the comparator drugs. Further investigation is in progress to clarify this, and use of this ideal intravenous antihypertensive is at the present time on hold. However, the trials of this agent are a paradigm for studies of future investigational agents for postoperative hypertension.

Conclusion

In summary, acute postoperative hypertension is a relatively common problem in the surgical ICU. It is common in patients with prior history of hypertension and those undergoing cardiovascular and neurosurgical procedures. Postoperative hypertension is often multifactorial. It is important to first rule out associated precipitating factors prior to considering antihypertensives.

Postoperative hypertension is often short-lived. Complications are higher if the elevated blood pressure lasts longer than 3 h. Continuous blood pressure monitoring is recommended. A blood pressure of 20% above the baseline when associated with increased risk of complications is an indication for treatment. The goal of treatment is to lower blood pressure to no more than 20–25% below a pretreatment baseline.

Intraoperative hypertensive crisis can be associated with pheochromocytoma and should be treated accordingly. Acute medication withdrawal hypertension is rare, and is best treated by reinstituting the same preoperative medication. Generally, a combination of vasodilators and beta blockers works best in a given patient (Table 19.8).

Table 19.7. Preferred parenteral drugs for selected hypertensive emergencies in the order of preference.[14]

Emergency	*Preferred drugs	Drugs to avoid
Postoperative hypertension	Nitroglycerine	
	Nitroprusside	
	Labetalol	
	Nicardipine	
	Fenoldopam	
Hypertensive encephalopathy	Labetalol	
	Nicardipine	
	Nitroprusside	
	Fenoldopam	
	Enalaprilat	
Cerebrovascular accidents	Labetalol	
	Nicardipine	Hydralazine
	Nimodipine (in SAH)	Nitroglycerine
	Enalaprilat	Nitroprusside (may increase intracerebral pressure)
	Nitroprusside (use with caution)	
Myocardial infarction and unstable angina	Nitroglycerine	
	Labetalol/Esmolol	Hydralazine
	Nitroprusside (use with caution)	Nitroprusside (increase heart rate, myocardial oxygen demand)
	Nicardipine (in unstable angina)	
Congestive heart failure	Nitroglycerine	Labetalol/Esmolol(decreased cardiac output)
	Enalaprilat	
	Loop Diuretics	
Aortic dissection	Esmolol	
	Labetalol	Hydralazine
	Nitroprusside (always use with beta blocker)	Nicardipine
Renal disease	Nicardipine	
	Fenoldopam	
Adrenergic crisis	Phentolamine	Labetalol (in cocaine crisis)
	Nitroprusside	
	Labetalol	
Preeclampsia, eclampsia of Pregnancy	Hydralazine	Nitroprusside
	Labetalol	Enalaprilat
	Nicardipine	

IV intravenous; *SAH* subarachnoid hemorrhage.

Table 19.8. Agents commonly used to treat acute postoperative hypertension.[3]

Agent	Typical dosage	Time to onset of action	Duration of action	Potential adverse events	Comments
Intravenous agents					
Sodium nitroprusside	0.5–5 μg/kg/min (max 10 μg/kg/min) (can be titrated to onset of headache or nausea)	<1 min	1–3 min	Tachycardia hypotension Rebound hypertension Increased intracranial pressure Myocardial ischemia Pulmonary V/Q mismatch	Requires continuous monitoring Sodium thiosulfate (10:1) prevents cyanide toxicity Monitor cyanide and thiocyanate levels
Nitroglycerin	5–300 μg/min	<1 min	5–10 min	Tachycardia hypotension Rebound hypertension Increased intracranial pressure Peripheral edema	Methemoglobinemia and tolerance
Labetalol	Bolus dose: 10–20 mg, then 10–40 mg q10 min Infusion: 0.5–4 mg/min (Max – 300 mg)	<5–10 min	3–5 h	Bradycardia hypotension Left ventricular dysfunction Bronchospasm	
Esmolol	Bolus: 500 μg/kg Infusion: 25–200 μg/Kg/min	<6–10 min	<20 min	Bradycardia Left ventricular dysfunction Bronchospasm	

(continued)

Table 19.8. (continued)

Agent	Typical dosage	Time to onset of action	Duration of action	Potential adverse events	Comments
Nicardipine	10 mg/h initially, increased by 2.5 mg/h q5–15 min to a max of 15 mg/h maintenance: start at 3 mg/h initially	10–15 min	15–20 min	Tachycardia hypotension Myocardial ischemia Peripheral edema	Caution in CHF and idiopathic hypertrophic subaortic stenosis Contraindicated in advanced aortic stenosis
Hydralazine	5–20 mg q6 h	15–30 min	4–6 h	Tachycardia hypotension Cardiac ischemia Increased intracranial pressure Peripheral edema	Usually used with diuretics (causes fluid and salt retention) not routinely recommended Contraindicated in coronary disease
Fenoldopam	0.1 μg/kg/min initially, increased my 0.05–01 μg/kg/min q15–20 min maximum – 1.6 μg/kg/min	20–40 min	15–30 min	Tachycardia hypotension Angina increased intracranial pressure Elevated intraocular pressure	Avoid in glaucoma
Enalaprilat	0.625–1.25 mg (repeat if needed)	15–20 min	>4 h	Hypotension Renal dysfunction Hyperkalemia Angioedema	Contraindicated in renal artery stenosis Caution in aortic stenosis

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Postoperative Myocardial Infarction

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Incidence

Postoperative myocardial infarction (PMI) was first described in 1952.[1] Approximately, 7–8 million noncardiac surgical patients are at the risk of cardiac morbidity or mortality annually.[2] The reported incidence of PMI in the literature varies between 0.0 and 0.7%,[2] and is as high as 37% in patients who have surgery within 3 months of a myocardial infarction (MI).[3] Approximately, 50,000 patients annually have a PMI, of which 20,000 are fatal.[2] There is now a better understanding of the factors that lead to the development of PMI, but many areas of controversy remain. The relationship between perioperative ischemia and PMI is uncertain. The factors leading to PMI in a cardiac surgical population may be different from the noncardiac group, and within the noncardiac group there appears to be varying degrees of risk depending on many factors, including the type of surgical procedure.[3–10] One undisputed fact is the existence of certain patient populations with increased risk of PMI.[11] The following discussion focuses predominantly on PMI in the noncardiac surgical population.

Pathogenesis

The classic theory of imbalances in myocardial supply and demand leading to coronary ischemia is well established. Factors that cause increased myocardial oxygen demand include tachycardia, increased cardiac contractility, and increased afterload. Reduced myocardial oxygen supply may be due to a coexisting pulmonary disease, hypotension and decreased coronary perfusion, or decreased oxygen-carrying capacity resulting from anemia.[12] The most significant factor limiting the myocardial oxygen supply is reduced coronary blood flow resulting from coronary artery disease (CAD). In addition, coronary vasoconstriction further reduces blood flow and oxygen delivery.

Supply/demand imbalances may occur in the perioperative period, which can lead to ischemia in patients with CAD. The stress response to surgery may be one of the initiating factors that precipitates ischemia, but the exact relationship between perioperative events and the development of PMI is still difficult to explain. Most patients who die from MI in a nonsurgical population have thrombosis of the artery supplying the affected area. The precipitating factor for thrombosis appears to be the rupture of a coronary atherosclerotic plaque.[13–15] It is likely, therefore, that the pathology of PMI is the same; but this is difficult to confirm because surprisingly few autopsies are performed on patients who died from PMI. Some patients may be considered as having had PMI without any enzymatic, electrocardiographic, or postmortem confirmation. These patients, who often have known ischemic heart disease or risk factors of CAD, may have died from an ischemic arrhythmia that was precipitated by postoperative coronary supply/demand mismatch.

Slogoff and Keats showed that perioperative tachycardia and hypertension in a cardiac surgical population lead to a significantly increased rate of PMI.[16] Although perioperative events play a role in the development of PMI, a clear cause-and-effect relationship is hard to establish. A prolonged supply/demand imbalance would cause the ischemia to progress to infarction. A situation such as this occurring intraoperatively with any degree of frequency is hard to imagine, and this would tend to lead to detectable PMI immediately postoperatively. This is usually not the case.[17] The development of intraoperative signs of cardiac ischemia – such as ST-segment depression on electrocardiogram (ECG), increased pulmonary capillary wedge pressure (PCWP), or new wall-motion abnormalities on transesophageal echocardiography (TEE) – leads

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to the initiation of aggressive intraoperative therapy with nitroglycerin and beta-blockers to prevent PMI. Again, the causal relationship between these events and PMI has to be questioned. Many patients undergo rigorous diagnostic exercise ECG testing, often with positive results and profound ST-segment changes that may persist for some time after the test is complete. These changes are much more obvious than those that tend to occur intraoperatively, but they almost never result in a MI two days later. Patients who undergo "off-bypass" coronary revascularization tolerate total occlusion of diseased vessels for a significant period of time. Clearly, very close monitoring and hemodynamic control are provided for these patients, but the tolerance for intraoperative ischemia is probably quite high, even for patients with severe CAD.[18] This tends to imply that postoperative factors such as paroxysmal hypoxemia and hypercoagulability may also be involved in the genesis of PMI. In general, the intraoperative period is relatively quiescent with regard to myocardial demand. Studies have shown significant reductions in oxygen consumption with both general and regional anesthetic techniques,[19–21] and it is tempting to suggest that the vasodilator properties of anesthetic agents may have some beneficial effects by reducing the afterload, provided they do not compromise the diastolic coronary perfusion. These factors, however, must be balanced against elements of stress response[22]; the effect of catecholamine surges alone may be substantial.[23]

It has been postulated that coagulation changes in the perioperative period predispose to coronary occlusion, and certainly a hypercoagulable state does exist after surgery.[24–26] Attention has also been focused on the role of post-operative hypoxemia in the genesis of PMI.[27] In one study, 50% of patients spent prolonged periods with an oxygen saturation (SpO_2) of less than 85% during at least one of the first five nights following major abdominal surgery.[28] The causes of this episodic desaturation include post-anesthetic pulmonary atelectasis and respiratory depression from narcotic analgesia administration. The effect of this hypoxemia, and possibly accompanying hypercarbia, on myocardial function may be significant.

It is likely that the plaque rupture leading to coronary thrombosis is the precipitating factor in PMI, but what accelerates this process remains unclear.[29] There has been extensive research on the genesis of plaque rupture and thrombosis causing MI in a nonsurgical population, and some excellent reviews on the subject have been published.[15,30–33] One particularly interesting area relates to changes that may occur in plaque structure and function in the perioperative period. Atherosclerotic plaques are not inert lesions; they have an extensive blood supply and the vasa vasorum in the region of plaques is more highly developed than in areas of normal coronary arteries.[34,35] Plaque metabolism is likely to be high and microsphere studies have shown the intimal flow rate in diseased vessels to be 10 times that in normal vessels. As long ago as 1969, Chapman postulated that venous and/or lymphatic obstruction within plaques may lead to rupture. Coronary artery spasm leading to constriction of the vasa vasorum and plaque ischemia has also been implicated as a precipitant for plaque rupture.[36] An inflammatory hypothesis for plaque degeneration has also been proposed and a variety of inflammatory mediators can be found in abundance in diseased coronary vessels.[31] These include thromboxane A2, serotonin, and platelet-derived growth factor.[15] Their roles in promoting platelet aggregation and thrombosis may be significant. Increases in some of these mediators in the perioperative period may play a role in the genesis of PMI. Even an infective etiology has been postulated.[37,38] It is interesting to speculate that some intraoperative and/or postoperative factors initiate changes in plaque structure and function. Obstruction of the vasa vasorum and the veins draining the plaques and increased vessel wall tension may all be implicated. Changes in blood coagulability[24–26] and platelet aggregation[26] too subtle to cause coronary luminal thrombosis may still affect plaque microvasculature. These changes, coupled with hemodynamic stress on the plaque, increases in inflammatory substances, and paroxysmal postoperative hypoxemia, may lead to plaque instability and subsequent rupture. This pathologic process takes time, which may explain the well-recognized occurrence of PMI 24 h or more after surgery.[17,39] There is also evidence that plaques may exist in different forms – unstable and stable – and that they may change from one form to another depending on a number of factors. Stable plaques are quiescent and may be observed in patients with diabetes, impaired left ventricular function, and angina. They have a low lipid content, they show varying degrees of occlusion on coronary angiography, and tend to coexist with increased coronary collateralization. Under increased stress, however, such as prolonged perioperative tachycardia, they can lead to myocardial damage, which may not amount to a full-thickness myocardial infarction. This would explain the preponderance of a non-Q wave infarction under these circumstances. Unstable or vulnerable plaques tend to be inflamed, lipid-laden, and may appear benign angiographically. These plaques are prone to sudden rupture with coronary thrombosis and occlusion, and a full thickness Q-wave infarction. As increasingly sensitive testing methods have emerged for measuring myocardial damage, there now appears to be a spectrum of myocardial injury that can occur in the perioperative period. Le Manach and colleagues considered 1,136 patients undergoing repair of abdominal aortic aneurysm. Of the 57 patients with cTnI levels always greater than 1.5 ng/ml, who were considered to have a perioperative MI, approximately half were diagnosed within a mean of 37 h. The other half had troponins that did not reach myocardial infarction criteria until a mean of 74 h; and, more importantly, this so-called "delayed MI group" had a progressive troponin leak in the preinfarction period.[40] One can postulate that the early group represents acute plaque deterioration and coronary occlusion, while the latter group could represent ongoing ischemia that may be prevented or attenuated. The authors refer to this preinfarction interval as a "Golden Period" of opportunity for intervention.

Risk Factors

History and physical examination should always be the first line in any preoperative evaluation, and on the basis of this alone a preliminary risk assessment can be made. Exertional chest pain, previous MI, uncontrolled hypertension, carotid disease, and diabetes are just some factors that should alert the practitioner to the potential for increased risk.

There is an increased risk of PMI in certain well-defined groups. A study that evaluated coronary angiography in 1,000 patients before peripheral vascular surgery found significant coronary disease in 60%, many of whom had a normal resting ECG.[41] Goldman et al. devised a cardiac risk index that assigned points to a variety of factors including markers for ischemic and valvular heart disease.[4] The higher the points scored for an individual patient, the higher the risk of perioperative morbidity and mortality. Later studies further modified the risk index based on preoperative testing methods[6,42] and by assigning greater importance to factors such as angina and aortic stenosis.[7,43]

After initial clinical risk assessment, screening investigations may be indicated to further identify high-risk patients. The type, extent, and value of these investigations are the subjects of many publications and reviews, but considerable controversy remains regarding the ultimate value of many of these tests. Coronary angiography is the gold standard for identifying CAD, but the procedure is not without risk and expense and is rarely justified as a first-line investigation. The resting ECG is a valuable screening tool and has been an important component of a number of risk stratifications.[4,6,7,44] The presence of Q-waves provides clear evidence of a prior MI, and frequent premature atrial contractions correlate with increased cardiac risk in elderly patients during major surgery. A patient with an abnormal ECG has a threefold increase in perioperative cardiac events including PMI. These abnormalities may be subtle, such as ST changes and minor intraventricular conduction delays.[45] Significant (>2.5 mm), early, and sustained ST changes during an exercise ECG are highly suggestive of CAD, and patients who have these changes warrant further investigation. Unfortunately, many patients in "at-risk" groups cannot exercise to a level sufficient for a definitive result, making this test impractical.[46] Studies evaluating the use of exercise testing as a screening test for predicting adverse cardiac outcome after surgery have contradictory results.[47–49] Ambulatory ECG monitoring has been extensively studied in the perioperative period. In the at-risk groups, up to 40% of patients develop episodes of ischemia in the 48 h preceding surgery, and more than 75% of these ischemic episodes are asymptomatic – the so-called silent ischemia. Preoperative ischemia closely correlates with intraoperative and postoperative ischemia. Pre and postoperative ischemia precedes cardiac events in 88% of patients.[39] Postoperative cardiac events occurred in 38% of patients with silent ischemia, and 30% of these involved PMI.[50] The relative risk of suffering a cardiac event is 2.7 for patients with intraoperative ischemia, and is as high as 16 in patients with postoperative ischemia. A major limitation of both exercise and ambulatory ECGs is the presence of baseline abnormalities such as left ventricular hypertrophy and left bundle branch block, which make interpretation very difficult.

Dipyridamole-thallium-201 scintigraphy (DTS) uses an intravenous radionucleotide (thallium-201) that is taken up by myocardial tissue.[51] Dipyridamole is administered concurrently and acts as a coronary vasodilator. The vasodilation tends to "steal" blood flow away from areas supplied by stenosed and noncompliant diseased vessels. When the heart is scanned, these "cold areas" represent nonperfused myocardium. These areas could, however, also be scarred tissue from a previous MI and so, 4 h later, a second scan is performed without dipyridamole. If the cold areas have disappeared, these areas may be viable but under-perfused and thus can be considered to be at risk. These are termed areas of redistribution and may be predictors of PMI, especially when multiple cardiac segments are involved.[52–54] The absence of perfusion abnormalities indicates a low risk of PMI, but the role and sensitivity of DTS are the subjects of continued debate. It is thought that DTS is only useful when certain clinical markers such as angina and diabetes are present.[6] In one study, a significant number of patients with persistent defects on DTS suffered postoperative cardiac events. This raises questions about the benign nature of persistent cold areas on DTS.[55] It may be that some areas remain viable but are so poorly perfused that they remain cold for many hours; and in these cases the follow-up scan is too insensitive. To improve the sensitivity of DTS, a newer nucleotide, technetium 99m sestamibi, with better imaging characteristics has been introduced;[56] and adenosine is now used in some centers instead of dipyridamole with promising results.[57,58] Redistribution on DTS does not correlate with perioperative ischemia.[59] This is not surprising because DTS is a static, anatomic examination, whereas the development of perioperative ischemia is dynamic and multifactorial. In summary, therefore, DTS has a very strong negative predictive value for PMI, but the positive predictive value of the test is lower than was originally expected.

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are newer investigations used to detect ischemic heart disease. Both acquire information on the concentration of radionuclides introduced into the patient's body. These radioisotopes are incorporated into metabolically active tracer molecules such as glucose. The isotopes decay by positron emission, which can be detected by an array of sensors that surround the patient. PET has higher imaging resolution and sensitivity than SPECT. SPECT with thallium or technetium is being used with increasing frequency in preoperative evaluation, and it has been shown to provide significant prognostic value for cardiac events over that provided by clinical variables alone.[60] Cost constraints have so far limited the use of PET as a preoperative screening procedure, but when used to identify CAD in patients presenting with chest pain it appears to be the most sensitive of all noninvasive techniques.[61]

Echocardiography plays an increasingly important role in the preoperative evaluation and provides valuable information on ventricular wall-motion abnormalities, valvular disease, and ejection fraction. It is, however, of limited prognostic value.[62] The dynamic pharmacologic studies involving echocardiography appear to be very informative because they are designed to look for inducible ischemia. Dobutamine stress echocardiography is now regarded as one of the more cost-effective and valuable preoperative investigations. Increased inotropic and chronotropic workload is produced by intravenous dobutamine. As the dose of the drug is increased, patients with significant CAD develop regional wall-motion abnormalities that may not be apparent in the resting state. The doses of dobutamine range from 2.5 mcg/kg/min up to as much as 40 mcg/kg/min. If dysfunction is already present at rest, wall motion then sometimes improves and is augmented with low-dose dobutamine, but then worsens again with higher doses. This is thought to indicate significant disease. Dobutamine stress echocardiography is a useful method for identifying patients at low and high risk before major vascular surgery.[63] In some centers, atropine is added to provide a maximal heart rate response and this too has been shown to improve cardiac risk stratification.[42] Stress echocardiography is not as sensitive as PET for detecting the coronary disease, but it is more specific, which further illustrates the value of a negative test by this method.

Certain authors have focused on the left ventricular function at rest, and these include contrast studies and echocardiography. Increased risk of postoperative problems is present when the ejection fraction is less than 35%, but these events tend to be related to congestive cardiac failure rather than PMI.[64–66] A meta-analysis of dobutamine stress echocardiography, ambulatory ECG, radionuclide ventriculography, and DTS showed similar predictive values for adverse cardiac outcomes after vascular surgery.[67] The expertise of the local laboratory in identifying advanced coronary disease is probably more important than the particular type of test. In 1996, the American College of Cardiology and the American Heart Association published detailed guidelines on methods of cardiovascular evaluation and risk stratification before a noncardiac surgery.[68] This was revised and updated in 2007.[69] This work provides a step-wise approach to patient evaluation and should be a required reading for all involved in perioperative care. For those patients at intermediate risk, undergoing nonvascular surgery, there is no evidence that further testing adds any prognostic information. Patients at intermediate risk who are to have vascular surgery should undergo either dipyridamole nuclear imaging or dobutamine stress echocardiography. On the basis of these tests, some patients may then be considered high risk. Within this high-risk group, coronary angiography and revascularization procedures (both coronary artery bypass grafting and percutaneous transluminal coronary angioplasty) should be reserved for those patients in whom revascularization is indicated on the same clinical grounds that it would be in the absence of impending surgery. There is insufficient evidence to support prophylactic preoperative coronary revascularization. These patients can be aggressively managed with prophylactic beta-blockade and hemodynamic monitoring appropriate to the surgical procedure.[70] Coronary angiography may be considered as a first-line investigation for a small group of patients at very high risk, such as those who have had a very recent MI or unstable angina. A study by Lee et al.[71] tried to further simplify cardiac risk assessment. It is also worth noting that with rapid advancements in the field of genetic markers for disease, it may not be too long before patients at increased risk of adverse perioperative events can be identified with a simple blood test.

Presentation

A significant number of patients with PMI do not present with the classic symptoms of chest pain or pressure.[3,9,72,73] This may be explained by concurrent distracting surgical pain or the use of postoperative analgesics. While the most common presenting complaint is dyspnea,[74] the acute onset of cardiac failure or hemodynamic instability may be the first clue to the development of a PMI. Any change in the hemodynamic status in an at-risk patient, even in the absence of chest pain or ECG changes, should alert the clinician to the possibility of PMI. This is especially true for patients with diabetes who frequently have cardiac ischemia that is silent because of neuropathy.[75] In addition, ECG changes of PMI tend to be less well defined than those of infarctions occurring in the nonsurgical setting. Many infarctions are of the non-Q wave variety,[17] and the ECG changes can be subtle and often difficult to distinguish from nonspecific ST–T changes that can be seen with many conditions including LVH, electrolyte imbalance, digoxin therapy, and anemia. Up to 10% of MIs may produce no ECG changes.[76] CK-isoenzyme (CK-MB) was initially thought to be extremely valuable, but it is now known that this moiety is present in a number of other tissues and has also been detected in increased concentrations after peripheral and mesenteric vascular reconstruction.[77,78] CK-MB sub-forms are, however, the most efficient for early diagnosis (within 6 h) of MI. Cardiac troponins–I and T (cTnI and cTnT) may not be detectable for up to 6 h after onset of chest pain, but after this time they are highly cardiac-specific and particularly efficient for late diagnosis of MI.[79]

It is estimated that more than 30% of patients with chest pain who present without ST-segment elevation and would otherwise be diagnosed with unstable angina actually experience a non-Q-wave MI when assessed with cardiac-specific troponin assays. Elevated cTnI or cTnT levels, even in the presence of normal CK-MB levels, identify patients without ST-segment elevation who are at an increased risk of death. It should be noted that serum levels of cTnT and cTnI might be present for several days after MI. Therefore, the ability to diagnose recurrent infarction is highly compromised if the clinician relies solely on cardiac-specific troponins and fails to obtain a concomitant CK or CK-MB measurement within

the first 12–24 h after an MI. Handheld, rapid bedside assays are now clinically available for measuring cTnI, cTnT, and CK-MB.[80]

Management

The therapy of PMI is controversial. Some modalities that might be used in a nonsurgical patient following an acute MI may be contraindicated in the postoperative setting. The use of thrombolytic agents and anticoagulants may cause a hazardous increase in the postoperative bleeding after major surgery. Aspirin use is also controversial, but the enormous benefits of this simple therapy may outweigh the risks.[81] Decision should be made on a case-by-case basis after careful discussion between the cardiologist and the surgeon; in some situations, procedures that may significantly limit the infarction size may be justified. Patients diagnosed with PMI should be transferred to an appropriate setting for stabilization and monitoring. Depending on the postsurgical needs of the patient, this should ideally be a coronary care unit or a surgical intensive care unit. Detection and treatment of life-threatening arrhythmias are key goals in the early phase of PMI, and transferring the patient to a high-intensity setting is justified on the basis of this alone. Unless there are major contraindications, all patients should be treated with beta-blockers. Angiotensin-converting enzyme inhibitors are also being used with increasing frequency because they reduce the postinfarction ventricular remodeling,[82] a process that can lead to left ventricular enlargement and dysfunction.[83] The degree of invasive monitoring that these patients require depends on the extent of myocardial damage and dysfunction. After major surgery, when there may still be ongoing fluid shifts or the need for transfusion of blood products, the placement of a pulmonary artery catheter may greatly assist optimization of cardiac function. For unstable patients who are sedated and intubated, a TEE may be valuable for assessing the left ventricular performance in unstable patients, especially when fluid balance is a concern. Volume loading may occasionally be helpful and can be carried out with greater confidence with real-time visualization of ventricular cavity size and contractility. Serious disturbances of cardiac rhythm may require pharmacologic intervention, electrical cardioversion, or transvenous pacing. Atrial arrhythmias should be treated aggressively because the loss of an effective atrial contraction can lead to a significant fall in cardiac output. Worsening hemodynamic status may warrant insertion of an intra-aortic balloon pump,[84] and even urgent angioplasty or coronary artery bypass grafting may be indicated in a small group of suitable patients.

Prevention

In 1983, Rao et al. published a landmark paper in which the incidence of PMI in patients with a previous history of MI was significantly reduced by aggressive invasive perioperative monitoring.[9] Even though the methodology and some of the conclusions of this paper have been questioned, it paved the way for modern attitudes and approaches to the perioperative management of high-risk patients.

Patients with known cardiac disease should be given optimal pharmacologic treatment, and other important factors, such as ongoing congestive heart failure and anemia, must be identified and addressed. Strategies have been developed to manage high-risk patients. A few small studies have evaluated the use of a pulmonary artery catheter inserted the night before surgery in the ICU.[85] Fluid loading and/or inotropic agents are administered to maximize hemodynamic performance before undergoing surgery. The results with this approach have been disappointing and the procedure is not without complications, which include pneumothorax from placement of a central line and even inotrope-induced cardiac ischemia. The American Society of Anesthesiologists has practice guidelines for the use of pulmonary artery catheters that suggest that there is insufficient data for the use of preoperative pulmonary artery monitoring.[70] Prophylactic drug therapy is a more promising area of preoperative care. Recent studies have shown a significant reduction in perioperative cardiac events with the use of either orally or intravenously administered beta-blockers.[86–89] Mangano and colleagues treated patients undergoing noncardiac surgery who were considered at risk for coronary disease. Atenolol was administered throughout their hospital stay. The authors reported an 8% absolute reduction in mortality at 6 months and a 15% reduction in combined cardiac events including PMI.[86] The in-hospital mortality was, however, the same in both groups. Mangano's results were greeted with skepticism, as it was hard to explain how a perioperative drug regimen for only 7 days, which did not appear to affect in-hospital cardiac events, could impact mortality at 2 years. With the knowledge we now have regarding the low-grade troponin leaks and the spectrum of myocardial injury that occurs perioperatively, Mangano's findings now make more sense. The hypothesis is that the patients who received the atenolol were actually protected compared to the placebo group whose low-level myocardial damage went undetected at that time.

More recently, Poldermans et al. studied a group of patients scheduled for major vascular surgery who had positive results on dobutamine echocardiography.[88] Half of the patient population was randomized to receive the beta-blocker bisoprolol in the perioperative period. The incidence of death from cardiac causes or nonfatal MI was 34% in the untreated group and only 3.4% in the bisoprolol group. Unlike the study by Mangano et al., the in-hospital mortality decreased significantly, which may reflect the higher risk patient population, already preselected by noninvasive testing. Another significant factor in the success of this study is the fact that the beta-blocker therapy is started an average of 37 days (range 7–89) before surgery. The authors of this study not only recommend perioperative beta-blockade for high-risk patients, but also suggest that it may be acceptable in many cases for the prophylactic use of a beta-blocker to replace noninvasive testing. The mechanism

by which beta-blockers exert their protective effects is not clear, but it is probably related to a number of factors including reduction in heart rate, reduced myocardial oxygen demand, increased subendocardial perfusion, attenuation of the stress response, reduced platelet aggregation, and increased plaque stability. It should be mentioned, however, that the beneficial effects of beta-blockers in the low- and intermediate-risk patient groups is currently the subject of much controversy.[89] Although a number of studies are ongoing, many in the medical community are skeptical that such studies will ever have the statistical power to truly answer this question.

The intraoperative period has always been the subject of significant controversy. Slogoff and Keats showed that a high heart rate is detrimental, certainly in a cardiac surgical population, and it seems likely that this is also the case in a noncardiac setting.[16] The question arises as to how closely patients should be monitored for intraoperative ischemia and how relevant it is to PMI. The use of a five-lead ECG allows continuous monitoring of leads II and V5. This configuration can detect more than 90% of any ischemic changes that may occur.[91] Unfortunately, ECG changes may be a relatively late finding or may be absent during myocardial ischemia. Changes most commonly observed are ST-segment depression or elevation, but any new, onset arrhythmia is also a cause for concern. A rising pulmonary capillary wedge pressure (PCWP) has also been used as an indicator of ischemia, but its detection may be delayed during an ischemic episode because PCWP should not be continuously monitored. The transesophageal echocardiography (TEE) has been extensively used to detect regional wall-motion abnormalities indicative of ischemia and, although it seems to be very useful, there is a degree of operator dependence to this monitor; a stable short-axis left ventricular view must be maintained and the changes may be subtle. Some authorities have advocated that a second anesthesiologist be solely responsible for ischemic monitoring when a TEE is used, but this is frequently impractical.[92] When ischemia is detected, any obvious hemodynamic perturbations need to be corrected. Heart rate control using an intravenous beta-blocker should take priority. The development of anemia is often overlooked and significant blood loss should be treated aggressively.[12] This is especially the case when an apparently normal preoperative hematocrit is really a "dry" value and significant hemodilution occurs with crystalloid resuscitation. Nitroglycerin therapy has long been advocated for intraoperative ischemia, but its efficacy remains unproven.[93–95] It does, however, seem a reasonable therapeutic intervention, provided care is taken to avoid systemic hypotension, which results in reduced diastolic coronary perfusion and worsened ischemia.

While beta-blockers have become the mainstay of risk-reduction strategies, other drugs that also appear to improve the perioperative outcome have emerged. Wallace, a researcher who worked on Mangano's original atenolol study, went on to duplicate his results using the alpha-2-agonist clonidine instead of atenolol. This is good news for patients in whom beta-blockers are contraindicated.[96]

The statin group of drugs has also been studied extensively in this regard. When used, even for a short period perioperatively, they have been shown to significantly reduce both the perioperative mortality and the frequency of cardiac events. The plaque-stabilizing properties of these drugs may explain this beneficial effect.[97,98]

The choice of anesthesia is also the subject of debate. The use of regional anesthesia with its reduction in sympathetic tone and attenuation of the stress response has many protagonists. However, general anesthesia may provide close hemodynamic control, and recently it has even been suggested that the volatile anesthetic agents themselves may actually be cardioprotective.[99,100] Bode et al. compared general, spinal, and epidural anesthesia for high-risk patients undergoing peripheral vascular surgery.[101] These investigators used close hemodynamic monitoring for all patients in the perioperative period and recorded a low incidence of PMI. The type of anesthesia did not appear to influence the cardiac outcome. The use of a combined general/regional technique has also been advocated and may have benefits for some types of surgery, particularly when the regional technique can be extended into the postoperative period to provide good pain control.[102] Some prominent researchers believe that the most critical time for the myocardium at risk may well be toward the end of surgery and in the immediate perioperative periods. Patient emergence and endotracheal extubation, for example, can be particularly stressful. This, combined with issues of postoperative pain, relative hypothermia, and anemia, can all compound this problem. Indeed, tachycardia and signs of ischemia on continuous ECG monitoring during this time strongly correlate with the troponin leak and the incidence of perioperative MI.[103] In the postoperative period, pain, hypoxemia, inflammatory mediator activation, and major fluid shifts have all been recognized as causing cardiac instability. This has led to a heightened awareness of effective analgesia, oxygen therapy, and close monitoring after surgery.

It was originally thought that coronary artery bypass surgery (CABG) or other invasive cardiac interventions, such as percutaneous coronary angioplasty (PTCA) and stent placement, carried out prior to major vascular surgery may improve the outcome. In reality, the risk of either of these procedures combined with the vascular surgery itself leads to a worse outcome than if the vascular surgery was the only procedure performed, provided the patient is optimized and well beta-blocked.[104] Indeed, there has been much recent activity in the cardiovascular and anesthetic literature surrounding cardiac stents, and antiplatelet medications such as clopidogrel. Initially, a fear of excessive perioperative bleeding led most physicians to stop this medication 7–10 days preoperatively, but the acute withdrawal of antiplatelet agents is associated with a significant pro-thrombotic rebound effect. This has led in some studies to perioperative mortality as high as 86%.[105] These issues appear to be particularly important in the case of drug-eluting stents (DES) that are very dependent on antiplatelet therapy. The body of current evidence would suggest that

the risk of perioperative bleeding when continuing antiplatelet therapy, unless in closed-space surgery or where overly excessive blood loss is expected, is far outweighed by the likelihood of acute stent thrombosis and adverse cardiac outcome. Various management algorithms have been proposed in this regard.[106]

Conclusion

PMI remains a complication of a variety of surgical procedures in well-defined patient groups. Nevertheless, enormous progress has been made in risk stratification, and exciting new pharmacologic interventions seem to have an impact on the postoperative cardiac morbidity. The evidence for prophylactic drug therapy may even be strong enough to limit the use of expensive noninvasive cardiac testing in many cases in which increased risk is identified by clinical criteria alone. The etiology of PMI is probably multifactorial and the exact mechanisms of the condition remain elusive. Future developments in this area are likely to focus on the nature of coronary plaque instability in the perioperative period.

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21
Management of Postoperative Arrhythmias

Eugene H. Chung and David T. Martin

Cardiac arrhythmias in the perioperative period are common and a major source of morbidity. The most common sustained cardiac arrhythmia, atrial fibrillation (AF), occurs in 30–40% of patients after cardiac surgery, and in up to 4% of patients after noncardiac surgery.[1–3] Such arrhythmias are responsible for increased length of hospital stay as well as increased healthcare costs. This chapter will address the diagnosis and treatment of perioperative arrhythmias and will suggest simple, cost-effective strategies for evaluation and prevention. As many patients undergoing general and cardiac surgical procedures have implanted arrhythmia control devices (pacemakers and/or defibrillators), this chapter will also discuss the perioperative care of these patients.

Initiation of all cardiac arrhythmias requires trigger factors (such as premature beats) in the context of a susceptible cardiac substrate. The initiating factor in the postoperative patient may be a transient imbalance in electrolytes, myocardial ischemia or hypoxemia; however, the most prevalent condition in these patients is autonomic arousal and associated catecholamine surges related to stress and pain of surgery.[1] The overall incidence of postoperative arrhythmias peaks at two periods: in the operating room during induction of anesthesia and during days 2–7 after surgery.[2,4]

The patients at greatest risk of any cardiac arrhythmia have structural heart disease.[1] Previous myocardial infarction, hypertension, or valvular heart diseases are common in patients presenting for elective surgery and represent risk factors for the development of both atrial and ventricular arrhythmia. A patient with systolic or diastolic dysfunction or significant valvular disease may not be able to augment the stroke volume to maintain cardiac output if confronted with a prolonged bradyarrhythmia. The patient with long-standing hypertension and diastolic dysfunction who has AF or atrial flutter (AFL) postsurgery may have elevated pulmonary artery pressures. Tachyarrhythmias can decrease the diastolic filling time, the relative stroke volume, and thereby reduce the cardiac output, leading to hypotension and end-organ hypoperfusion.

General Approach

The first step is to maintain a clinical focus on the patient being treated, and not on the electrocardiogram (ECG) or telemetry monitor. It is important to determine whether the ECG matches the clinical picture and reflects a true arrhythmia or whether the artifact is present and obscuring a normal rhythm; such a scenario is very common in postoperative care environments. The evaluation should include a systematic review[5] of a 12-lead ECG and a telemetry strip. Following diagnosis of the arrhythmia, urgency of treatment must be determined by assessing the patient's symptoms, ventricular response, blood pressure, peripheral perfusion, duration of arrhythmia, and any evidence of ischemia. It is important to emphasize that during and after surgery many patients undergo cardiac monitoring for the first time ever; many intermittent arrhythmias observed in this environment may have been asymptomatically present for some time prior to admission and, therefore, do not represent an urgent call for clinical action. It is the consultant's role to assess the presence and clinical significance of such incidentally identified arrhythmias.

Postoperative arrhythmias are usually attributed to systemic problems leading to an increased catecholamine state. Predisposing factors include stress and pain, hypoxemia, pulmonary embolus, hypercarbia, myocardial ischemia, electrolyte, and acid-base imbalances (Table 21.1). Optimal management usually requires that the treatment be directed primarily to the

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Table 21.1. Common predisposing factors to postoperative arrhythmias.

Elevated catecholamines (e.g., stress, pain)
Hypoxemia
Hypercarbia
Electrolyte abnormalities
Acid-base imbalance
Volume overload
Ischemia
Pulmonary embolus
Surgical trauma (e.g., cannulation of atria)
Vagal stimulation (e.g., carotid or pelvic surgery)
Preexisting structural heart disease
Inflammatory processes

underlying trigger factors rather than to the arrhythmia itself, unless a hemodynamic emergency exists.

The clinical impact of any arrhythmia depends primarily on the ventricular rate, duration, and underlying cardiac function, as well as on fluid balance/cardiac loading conditions. If a patient is hemodynamically unstable, immediate cardioversion may be indicated for a tachyarrhythmia; temporary transvenous pacing may be indicated for a hypotensive bradyarrhythmia. Restoration of sinus rhythm may be needed to stabilize the patient, but the first objective is to stabilize hemodynamics and control ventricular response. Intermittent arrhythmias due to transient causes – such as periodic premature atrial or ventricular beats, or sinus tachycardia in the context of a fever – rarely require specific treatment.

ECG Diagnosis of Arrhythmias

Classification of Tachyarrhythmias

Tachyarrhythmias are classified by their anatomic location of origin, either supraventricular or ventricular. Tachyarrhythmias of supraventricular origin include sinus tachycardia, atrial fibrillation, atrial flutter, atrial tachycardia, multifocal atrial tachycardia, atrioventricular nodal reentrant tachycardias (AVNRT), junctional tachycardias, and accessory pathway reentrant tachycardias. Except for the latter, these tachyarrhythmias exclusively traverse the AV node, so that the ventricular rate can be controlled by agents that block conduction down the AV node. However, pre-excitation with antegrade conduction down an accessory pathway, such as occurring in Wolff–Parkinson–White (WPW) syndrome, can be worsened if an AV nodal blocking agent (e.g., beta-blocker, calcium channel blocker, digoxin) is administered.

Tachyarrhythmias: Supraventricular

Epidemiology

Atrial fibrillation is the most common and most studied postoperative arrhythmia. It can occur in up to 30% of patients following coronary bypass surgery and in up to 60% of patients following heart valve surgery.[1,2,6–8] The peak incidence occurs on the second and third postoperative days.[6,9] Data from the Framingham Heart Study show that increasing age is one of the strongest risk factors for atrial fibrillation in the general population.[10] Multiple studies have shown that with advanced age, the risk of postoperative atrial fibrillation increases.[7,9,11–13] Atrial fibrillation may be transient and benign, but chronic atrial fibrillation increases the risk of stroke, congestive heart failure, myocardial ischemia, and overall mortality. Atrial flutter is closely associated with atrial fibrillation, and although the management of flutter differs from atrial fibrillation, these arrhythmias are often grouped together since they frequently coexist. Up to one-third of atrial arrhythmias following open-heart surgery may be due to atrial flutter.[14] Overall, supraventricular tachycardias occurred in 4% of patients in a prospective registry of patients undergoing noncardiac surgery: 63% of these patients had atrial fibrillation or flutter.[15]

Postoperative arrhythmias can extend hospital stays and increase expenditures. Postoperative AF following coronary bypass graft surgery (CABG), for example, was associated in one study with approximately five additional hospital days and approximately an additional $11,000 in hospital costs per patient.[9] The incidence of postoperative events, including stroke and myocardial infarction (MI), and the mortality rate have been shown to be significantly increased in patients who develop AF after cardiac surgery.[16]

Diagnosis

Sinus tachycardia is very common following surgery and is manifested by normal P-waves and QRS complexes, and a heart rate greater than 100 bpm. It is usually due to a high adrenergic state induced by pain, stress, fever, anemia, hypovolemia, or hypoxia; and it may be considered to be a reflection of the need for management of such problems. Sinus tachycardia should not be the focus of specific cardiac management except in rare cases where myocardial ischemia is present.

Ectopic atrial tachycardia is initiated from non-sinus node foci, and on ECG is reflected by an unusual P-wave morphology and axis. The QRS complex remains the same as in the sinus rhythm. Usually, the heart rate gradually accelerates at the initiation of the tachycardia and gradually decelerates at the termination.

Multifocal atrial tachycardia (Fig. 21.1) is, as its name implies, a consequence of multiple atrial foci competing with the sinus node, and it usually occurs in the context of acute or chronic pulmonary disease. At least three different P-wave morphologies, each associated with a characteristic PR interval on ECG, are required for the diagnosis of this unusual arrhythmia.

Atrioventricular nodal reentrant tachycardia (AVNRT) (Fig. 21.2) is the most common sustained supraventricular tachycardia after atrial fibrillation and flutter. The P-waves are often hidden within the QRS complex as retrograde atrial

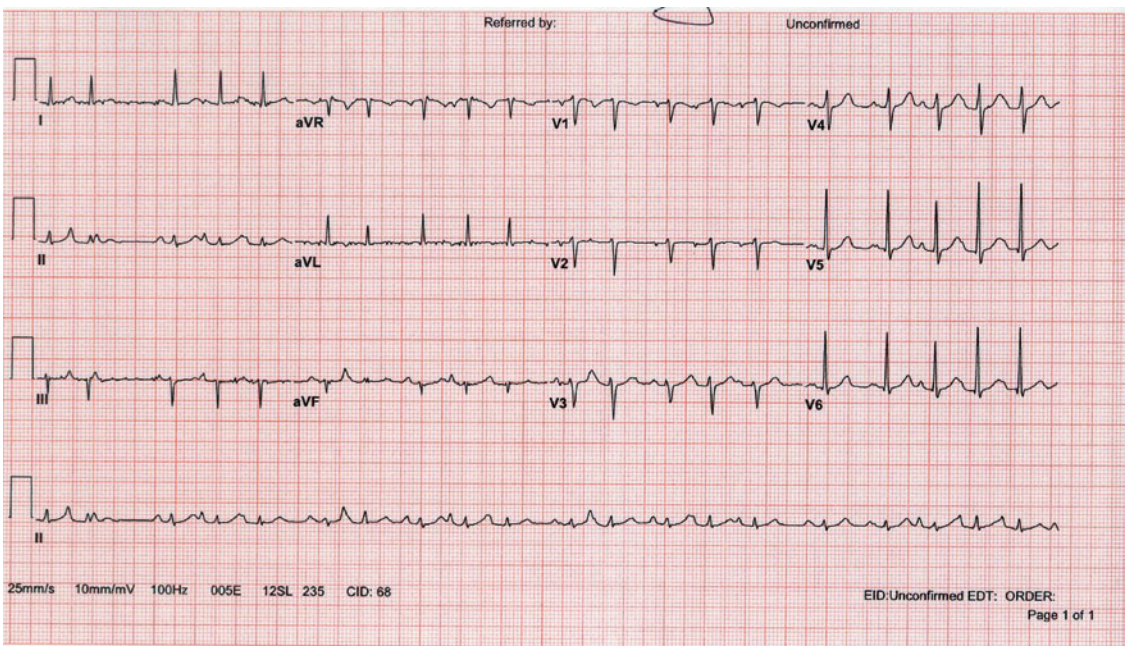

FIG. 21.1. Multifocal atrial tachycardia (MAT). The diagnosis is made by three or more ectopic (i.e., not all sinus) P-waves. The heart rate (approximately 100–140 bpm) may be variable due to the site of ectopy or non-conduction of certain P-waves. MAT is commonly observed in patients with chronic obstructive pulmonary disease.

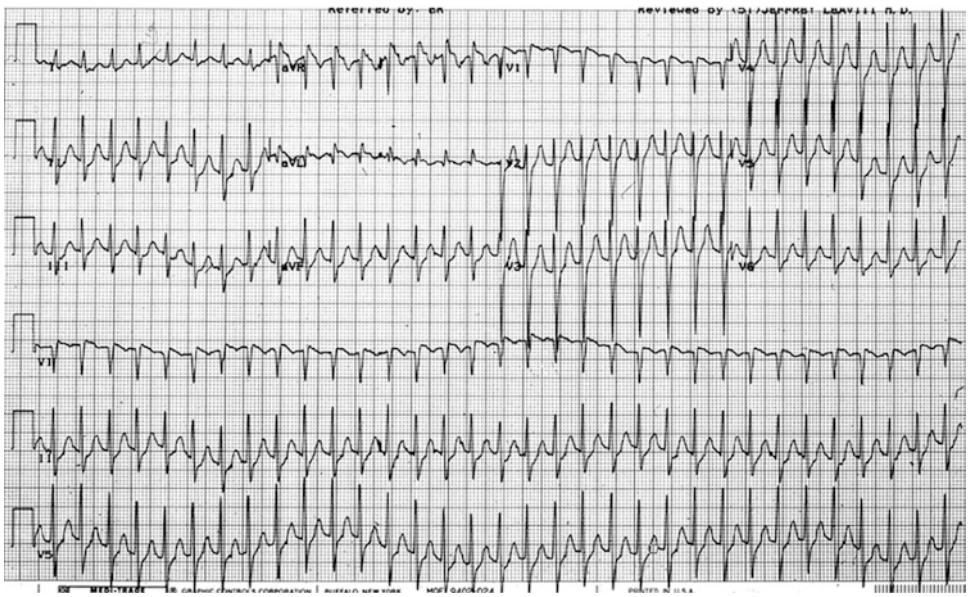

FIG. 21.2. Atrioventricular nodal reentrant tachycardia (AVNRT). In this regular narrow complex tachycardia, P-waves are often difficult to discern owing to nearly simultaneous activation of the right ventricle and atrium from the AV node. However, a "pseudo R prime" pattern, which is characteristic of AVNRT, is present in lead V1 and likely reflects P-waves at the end of the QRS. P-waves can also been seen after the QRS in the inferior (II, II, aVF) and lateral (I, aVL, V6) leads.

conduction overlaps with antegrade ventricular conduction. Dual AV nodal pathways with different conduction velocities and refractory periods provide the substrate for this reentry mechanism, which may be suggested on the ECG by a detectable increase in PR interval at the onset of tachycardia.

Atrioventricular reentrant tachycardia (AVRT) (Fig. 21.3) is mediated by a congenital accessory pathway between the atrium and ventricle that can conduct antegradely down the AV node and retrogradely up the bypass tract; this continuous circuit is also known as orthodromic AVRT. Such pathways

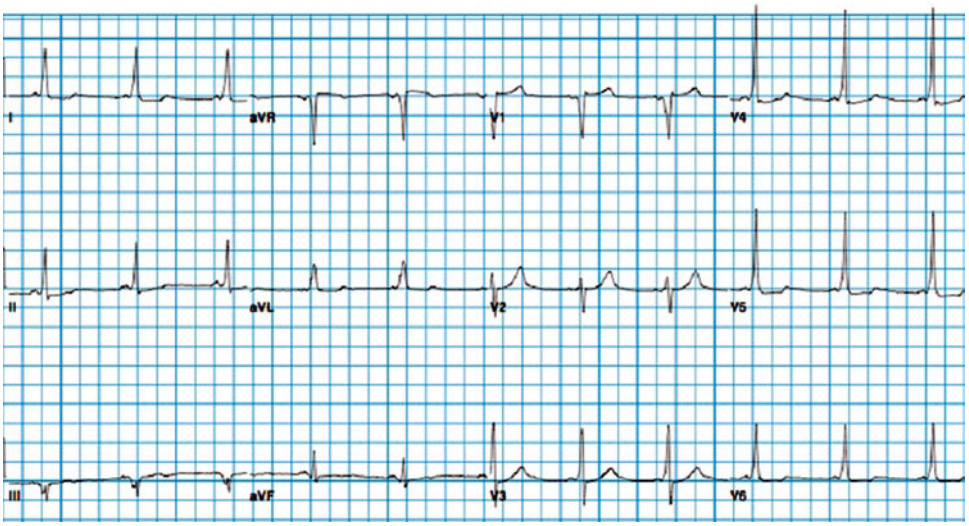

FIG. 21.3. Atrioventricular reentrant tachycardia. While this patient with Wolff–Parkinson–White (WPW) was not tachycardic, the ECG clearly demonstrates a short PR interval, positive delta waves in leads V2–V5, I and aVL, and a negative delta wave in III, all consistent with a postero-septal bypass tract.

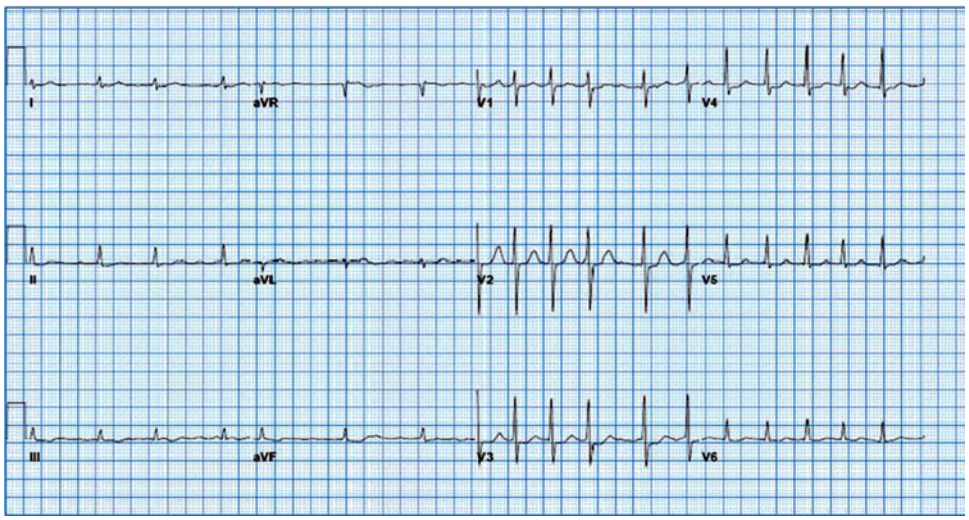

FIG. 21.4. Atrial fibrillation. This is an example of atrial fibrillation with a rapid ventricular response. The baseline shows oscillatory atrial activity, especially in lead III, but no discrete P-waves. Mild ST-depressions are seen in leads V2–6 and nonspecific T-wave abnormalities are present in multiple leads.

associated with the WPW syndrome rarely conduct antegradely down the bypass tract and retrogradely up the AV node, forming an antidromic AVRT. Orthodromic conduction usually manifests as a narrow QRS on EKG (unless bundle branch block is present) and antidromic conduction results in a wide QRS complex, which reflects the eccentric activation of the left ventricle via the accessory pathway.

Atrial fibrillation (Fig. 21.4) demonstrates fine or coarse atrial activity, or fibrillatory waves, on EKG, reflecting the nonuniform atrial depolarization. However, such atrial activity may not in some cases be discernable, and the irregular transmission to the ventricle is the hallmark of clinical and ECG diagnosis. Conduction over the AV node occurs randomly and results in the "irregularly irregular" ventricular response. In the absence of treatment, the ventricular rate may average 160–180 bpm.

Atrial flutter (Fig. 21.5) is typically a right atrial arrhythmia in which the reentrant wave front travels within and between the anatomic boundaries of the superior and inferior venae cavae, as well as the tricuspid annulus. Flutter is usually associated with very rapid and regular atrial rates close to 300 bpm. In the post-operative patient, AV conduction

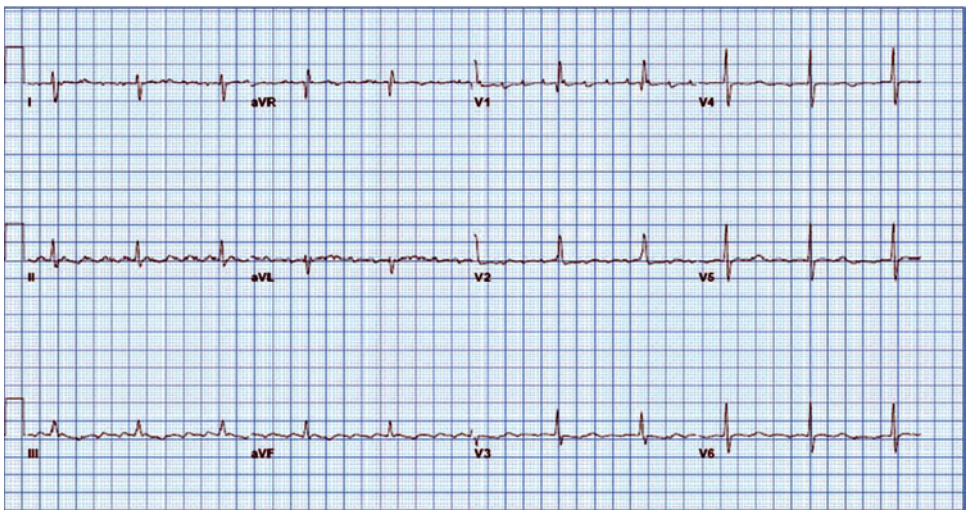

FIG. 21.5. Atrial flutter. The QRS complex is narrow, the atrial rate is approximately 300 bpm, and the ventricular response is 4:1. The flutter waves are most apparent in leads II and V1.

frequently occurs at a 2:1 ratio, resulting in a regular ventricular rate of 150 bpm. The ECG appearances are characterized by negative "flutter" waves in the inferior leads (a "sawtooth" pattern) and positive activity in lead V1.

Predisposing Factors

Predisposing factors for the development of perioperative atrial fibrillation combine the "preexisting substrate" and the "procedural substrate." The former includes clinical variables such as male gender, left atrial enlargement, prior atrial fibrillation, valvular heart disease (especially, of the mitral valve), hypertension, history of congestive heart failure, disease of the sinoatrial and/or AV nodes, alcoholism, and chronic obstructive pulmonary disease.[1,6,8] It is unclear how much reentrant conduction or focal phenomena contribute to the onset of arrhythmias.

The procedural substrate comprises conditions that are common in the postoperative state. Examples include blood pressure shifts, autonomic imbalance, increased circulating catecholamines, ischemia, trauma, cannulation of heart chambers, electrolyte imbalances, pericarditis/inflammation, cardioplegia and crossclamp times, and beta-blocker withdrawal.[6,8] One European study reported that 63% of patients with pericardial effusions had atrial arrhythmia compared with 11% of patients without effusions.[17] Elevated catecholamines increase the cellular potassium uptake and decrease the serum levels of potassium. Hypokalemia can provoke arrhythmias by altering the automaticity and conduction velocity of the atria. In a prospective case-control study of patients undergoing elective coronary bypass surgery, a serum potassium below 3.5 mEq/L increased the risk for serious peri-operative arrhythmias and postoperative atrial fibrillation or flutter by approximately twofold.[18]

Prophylaxis

Attempts have been made to identify patients at risk for postoperative arrhythmias via P-wave duration assessments on ECG or signal averaged ECG.[8,19] P-wave studies have shown that nonuniform atrial conduction is greatest on postoperative days 2 and 3, and longest atrial conduction time is on day 3.[20] These findings coincide with the peak incidence of atrial fibrillation observed on days 2 and 3 after surgery. However, the only moderate sensitivity and specificity of such testing has not warranted its widespread adoption as a screening measure.[8]

Beta-blockers, sotalol, amiodarone, and atrial pacing were compared in a 2004 meta-analysis of 58 randomized trials that studied more than 8,500 patients.[21] When active therapy with one of the four modalities was compared with placebo or routine therapy, the incidence of atrial fibrillation was reduced from 31--40% in controls to 18–22%. Multiple studies have verified the benefit of beta-blockers in preventing arrhythmias following cardiac surgery.[22–26] The benefit according to this meta-analysis is up to a 60–70% reduction in atrial fibrillation incidence (odds ratio 0.35) and is independent of the type of beta-blocker selected.[21] The 2004 American College of Cardiology/American Heart Association (ACC/AHA) guidelines gave beta-blocker therapy a Class I indication pre-operatively or immediately postoperatively in patients without contraindications.[27] Acute withdrawal of beta-blockers in patients chronically receiving them significantly increases the risk of postoperative tachycardia and atrial fibrillation, and is the subject of a "black box" warning for all beta-blockers issued by the FDA. Beta-blockers are also effective in controlling the ventricular response after the onset of atrial fibrillation.

Sotalol is a class III antiarrhythmic agent that exhibits beta-blocking activity. Studies have shown it to be as (but not more) effective as standard beta-blockers in preventing atrial fibrillation in CABG patients.[21,28–32] The Q–T interval must be

monitored for at least three hospital days as sotalol can induce torsade de pointes. It has been given a Class IIb recommendation in the 2004 ACC/AHA guidelines[27] for perioperative atrial fibrillation prevention.

Amiodarone administered orally for at least 7 days prior to surgery reduces the incidence of postoperative atrial fibrillation by 40–50% when compared with placebo.[21,33,34] A 2005 meta-analysis of 10 trials showed significant reductions in the rates of ventricular tachycardia, ventricular fibrillation, and stroke, as well as atrial fibrillation and atrial flutter[33] when this drug is employed. In the PAPABEAR study, a randomized trial of 601 patients undergoing elective coronary bypass or valve surgery, there was an approximately 50% reduction in perioperative atrial and ventricular arrhythmias.[35] In the ARCH trial, intravenous amiodarone given post-operatively significantly decreased the incidence of atrial fibrillation, although there was no significant improvement in length of hospital stay.[36] A combination of oral and intravenous amiodarone also showed a significant benefit.[37] However, it is important to emphasize that amiodarone, whether administered orally or intravenously, has not been approved by FDA for the treatment or prevention of atrial fibrillation. There is little data to suggest that this potentially toxic drug has efficacy for this purpose that is superior to standard beta-blocker therapy since these agents have not been directly compared in randomized controlled trials.

Digoxin may augment the effects of beta-blockers as prophylaxis, but it does not appear to prevent atrial fibrillation.[22,26] Similarly, calcium channel blockers such as verapamil and diltiazem, and Class I agents such as procainamide help limit atrial fibrillation once it starts, but do not reduce the incidence[26,38–40] when used prophylactically.

Epicardial right atrial or bi-atrial overdrive pacing has been used in cardiac surgery but has met with variable success.[12,40–46] It may be more effective in patients receiving beta-blockers. In one study of patients undergoing coronary bypass surgery, atrial pacing appeared proarrhythmic for the development of atrial fibrillation.[42] In the 2004 meta-analysis comparing beta-blockers, sotalol, amiodarone, and atrial pacing, pacing did significantly reduce atrial fibrillation, with an odds ratio (OR 0.57) that is similar to amiodarone.[22]

Treatment

Post-operative supraventricular tachycardias are often self-limiting. The general approach described previously should be applied. The primary goals are to control ventricular response, prevent thromboembolic complications, and restore sinus rhythm.

Sinus tachycardia is often observed in the postoperative state. Management should focus on the factors that increase the adrenergic tone (stress, pain, fever, anemia, hypoxia, hypovolemia). In atrial tachycardia, beta-blockers and calcium channel blockers can be used to control the heart rate, but short bursts do not require specific treatment. Multifocal atrial tachycardias often improve with treatment of the precipitating condition, such as hypoxemia, hypercapnia, and bronchoconstriction.[1] Beta-blockers and calcium channel blockers (in those with known bronchospasm related to beta-blockers) can also be used to control the ventricular rate.

In rapid supraventricular tachycardias where the diagnosis is uncertain, vagal maneuvers such as carotid massage or adenosine in 6–12 mg IV doses may slow conduction through the AV node enough to unmask the underlying atrial mechanism. In cases of hemodynamic embarrassment, urgent cardioversion may be required. AV nodal blockers can be given to slow the heart rate.

In the case of accessory pathway-mediated tachycardias, IV procainamide is the drug of choice, as AV nodal blockers such as verapamil, diltiazem, or digoxin could accelerate anterograde conduction down the accessory pathway.

Rapid ventricular rates from atrial fibrillation or atrial flutter result in loss of atrioventricular synchrony, decreased diastolic filling time, and decreased stroke volume. Hemodynamic instability (hypotension, ischemia, pulmonary edema) is unusual but, when present, requires synchronized cardioversion. Adhesive electrode pads placed in the anteroposterior right parasternal and left paraspinal positions are better for "atrial defibrillation" than the anterior–anterior positions classically used for ventricular defibrillation. Ibutilide, a class III antiarrhythmic available only in intravenous formulation, is a pharmacologic alternative for cardioversion in hemodynamically stable patients[47] since it is rapid in onset and has a short half-life. Associated QT prolongation requires continuous ECG monitoring and the risk of ventricular arrhythmia (torsade des pointes) may be as high as 4.3%.[48]

In clinically stable patients, the primary concern is control of the ventricular rate. Beta-blockers are preferred as first choice, especially during high-adrenergic states. IV diltiazem can be infused by a continuous infusion and should be considered if the ventricular rate remains rapid after administration of background beta blockade. Digoxin, which slows the AV nodal conduction by increasing vagal tone, has a delayed onset of action and is less effective in the acute post-operative setting. If a new atrial arrhythmia persists for more than 24 h, it is reasonable to consider electrical or pharmacologic cardioversion. When atrial fibrillation persists for more than 48 h, it is conventional to administer anticoagulation for stroke prophylaxis with IV heparin, if feasible from a surgical standpoint. A transthoracic echo may provide added information about structural heart disease if not previously known. If the atrial fibrillation or flutter is well tolerated, or the duration is uncertain due to its paroxysmal nature, the patient should be discharged on regimen of rate control and anticoagulation with warfarin, with 4–6 week follow-up. At that time, a long-term strategy of rate control and anticoagulation or rhythm control, which have been shown to be equally effective, can be determined[49]; such a decision is primarily based on the

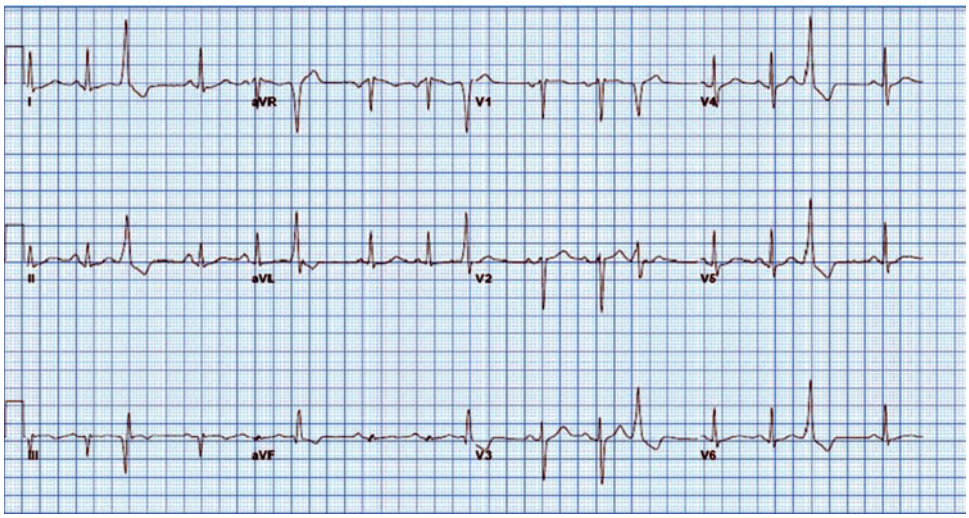

FIG. 21.6. Premature ventricular contractions (PVCs). This ECG shows sinus rhythm and occasional PVCs. The left bundle branch block morphology in V1 and the relatively narrow width of the QRS are suggestive of a septal origin in the right ventricle outflow tract.

patient's symptoms and hemodynamic condition. In a study of CABG patients prescribed a rate-control strategy, 90% had converted to sinus rhythm within 2–4 weeks of discharge from the hospital.[50] Patients with valvular heart disease, prior atrial fibrillation, left atrial enlargement, and advanced age are at highest risk for persistent arrhythmias. Additional guidelines have been recently published by the American College of Chest Physicians and the American College of Cardiology/American Heart Association/European Society of Cardiology.[51,52]

Tachyarrhythmias: Ventricular

Epidemiology

Sustained ventricular tachyarrhythmias are relatively uncommon after cardiac and non-cardiac surgery. Multiple studies have reported an incidence of ventricular tachycardia (VT) or ventricular fibrillation (VF) at 0.7–3.1% after cardiac surgery.[6,53–55] The associated mortality rate was as high as 44%.[55] Patients with prior myocardial infarction, depressed left ventricular function, and congestive heart failure were at highest risk for VT or VF. In one study, 72% of the events occurred within the first 48 h after surgery.[54] VT or VF after coronary revascularization surgery could be a sign of graft closure and should prompt urgent evaluation.[1]

Isolated premature ventricular contractions (PVCs) and non-sustained ventricular tachycardia (NSVT: 3 or more but less than 30 PVCs in succession without hemodynamic embarrassment) are rarely associated with sustained VT or sudden cardiac death in the post-operative period.[6,56,57] The incidence of NSVT has been reported to be up to 58% in post-CABG patients monitored in a hospital setting.[56,58]

Diagnosis

PVCs (Fig. 21.6) manifest on 12-lead ECGs as early, wide QRS complexes originating from the ventricle, often in a left bundle branch block (BBB) configuration. Aberrantly conducted premature atrial contractions (PACs) can have a wide QRS complex as well, but are preceded always by P-waves.

Ventricular tachycardia (VT) (Fig. 21.7) is characterized by A–V dissociation, positive QRS concordance, left axis deviation, QRS greater than 140 ms, fusion beats, and capture beats.[59] Stable VT can have a ventricular rate as low as 70, or if unstable, as fast as 250 bpm. The morphology can vary from monomorphic or uniform QRS complexes, to polymorphic, to bidirectional (alternating left BBB and right BBB). Bidirectional VT is suggestive of digoxin toxicity.

Ventricular fibrillation (VF) (Fig. 21.8) appears as large, rapid, and irregular oscillations at approximately 150–300 bpm. The QRS complexes have varying contour and amplitude.[59] Hemodynamic collapse is a sine qua non of VF and often evolves from VT.

Predisposing Factors

Clinical variables associated with postoperative ventricular arrhythmias include electrolyte abnormalities, acid-base disturbances, hypoxia, hypovolemia, anemia, hemodynamic instability, myocardial ischemia and infarction, acute graft closure, low cardiac output states, and antiarrhythmic use.[8] Uncomplicated PVCs and NSVT, in the absence of structural heart disease, do not significantly increase the risk of malignant arrhythmias or mortality at 3-year follow-up.[56,60] Large-scale trials in patients with moderate left ventricular dysfunction (EF 35–40%), coronary artery disease, and

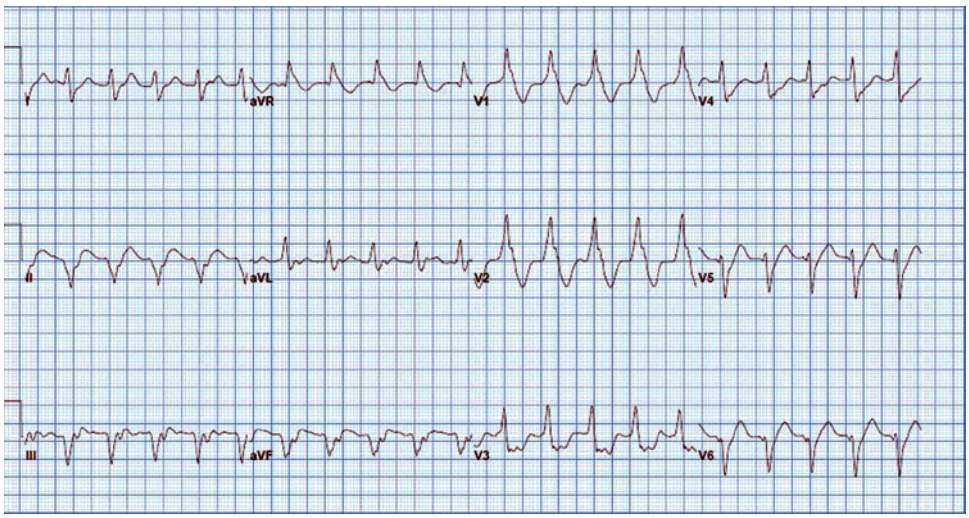

Fig. 21.7. Ventricular tachycardia (VT). The rate is approximately 140 bpm. The right bundle branch block morphology in V1 and Q waves in II, II, aVF suggest origination in the inferior wall of the left ventricle. V:A dissociation in leads III, aVL, aVF, V3–V6 and a R:S ratio <1 in V6 are both consistent with VT.

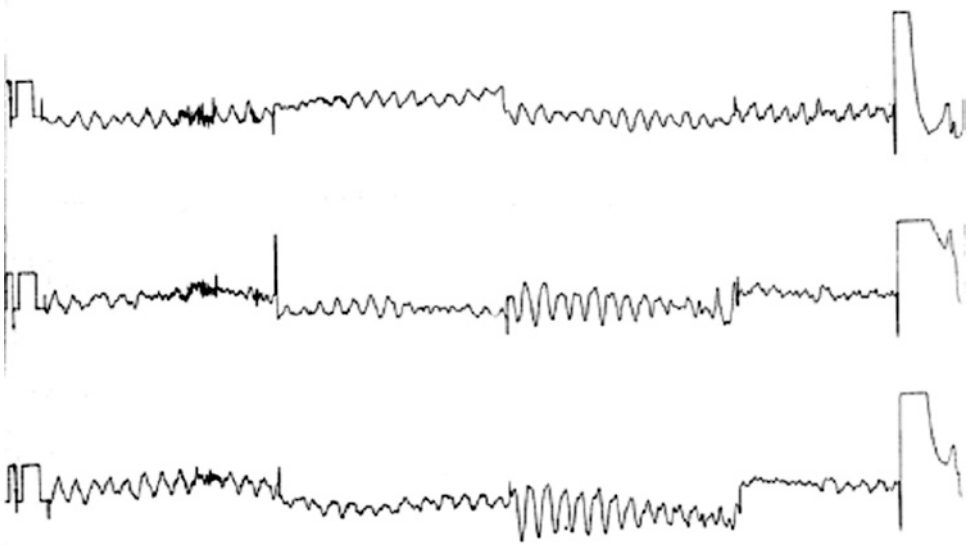

Fig. 21.8. Ventricular fibrillation (VF). This tracing was captured from a patient undergoing defibrillator function testing in the EP laboratory. Note the rapid, irregular, and "chaotic oscillations."

NSVT have shown these patients to be at higher risk of sudden cardiac death despite reasonable antiarrhythmic therapy.[61,62] Thus, left-ventricular function is one of the most important risk factors for developing postoperative VT or VF.

Prophylaxis

Empiric beta blockade should be considered in any patient with a history of coronary disease.[63] No trials to date have directly assessed beta-blockers as postoperative therapy. But perioperative atenolol was shown to decrease major adverse cardiovascular events by 15% at 6-month follow-up.[64]

Treatment

Asymptomatic and hemodynamically stable patients with non-sustained runs of PVCs or VT do not usually require immediate therapy. Reversible causes should be addressed, but it remains unclear as to whether reversing such predisposing factors is sufficient to prevent recurrence. Statin use has been shown to

have a protective effect against peri-operative cardiac events and recurrent tachyarrhythmias.[65,66] Early ICD implantation following de novo postoperative ventricular tachyarrhythmias may improve the outcome.[67] Monomorphic VT is caused by a reentry mechanism from a recent or remote myocardial infarction and/or a cardiomyopathy that resulted in fibrotic scarring of the myocardium. Polymorphic VT raises concern for acute myocardial ischemia or metabolic disorder. Polymorphic VT may be faster than monomorphic VT, but the former often terminates spontaneously.

Hemodynamically stable, sustained VT is conventionally treated with IV lidocaine followed by an infusion; alternatively, IV amiodarone followed by an infusion may be administered. Lidocaine is given in two boluses, the first 1–1.5 mg/kg IV, then 0.5–0.75 mg/kg IV, followed by an infusion of 2–4 mg/min. Amiodarone can also be used as a first-line treatment for stable VT. An IV bolus of 150 or 300 mg is followed by 1 mg/min infusion for 6 h, then 0.5 mg/min for 18 h. In patients with epicardial ventricular wires still in place, overdrive ventricular pacing by "burst" pacing at a rate faster than the VT rate may be therapeutic.

For hemodynamically unstable VT, VF, or VT refractory to antiarrhythmics, immediate defibrillation is required according to the recently updated ACLS guidelines.[68] If acute coronary syndrome is the cause of polymorphic VT or VF, appropriate revascularization should be employed. If no identifiable cause for VT of VF is determined, the patient may warrant an electrophysiology study and possible implantable cardioverter-defibrillator (ICD) once the acute arrhythmia episode has resolved.

Those patients with NSVT, prior myocardial infarction, and left ventricular ejection fractions less than 40% are at increased risk for sudden cardiac death.[61,62] A sub-study of the MUSTT trial showed that in post-myocardial infarction patients there is a high risk of sudden cardiac death, independent of the results of programmed electrical stimulation. Another large-scale study of post-myocardial infarction patients demonstrated that a low ejection fraction, without additional risk stratification, identifies a high risk population that would benefit from prophylactic ICDs.[69] A large study of patients with ejection fractions less than 35% undergoing CABG with a positive signal averaged ECG, did not show a mortality benefit from a prophylactic ICD implantation strategy after 48 months follow-up.[70] However, patients with sustained arrhythmias were excluded from this study, and left ventricular function (which often improved post-operatively) was assessed prior to revascularization. Hence, the peri-operative mortality from a fatal arrhythmia in patients without significant arrhythmia risk is indeed low, and risk stratification by left ventricular function should be reassessed after revascularization.

An algorithm outlining the general diagnostic approach to tachyarrhythmias is shown in Fig. 21.9.

Classification of Bradyarrhythmias and Conduction Disturbances

Bradyarrhythmias are primarily classified by their anatomic location of origin: from the sinus node, the AV node, or the His–Purkinje system below the level of the AV node. Bradyarrhythmias due to sinus node dysfunction include sinus pause

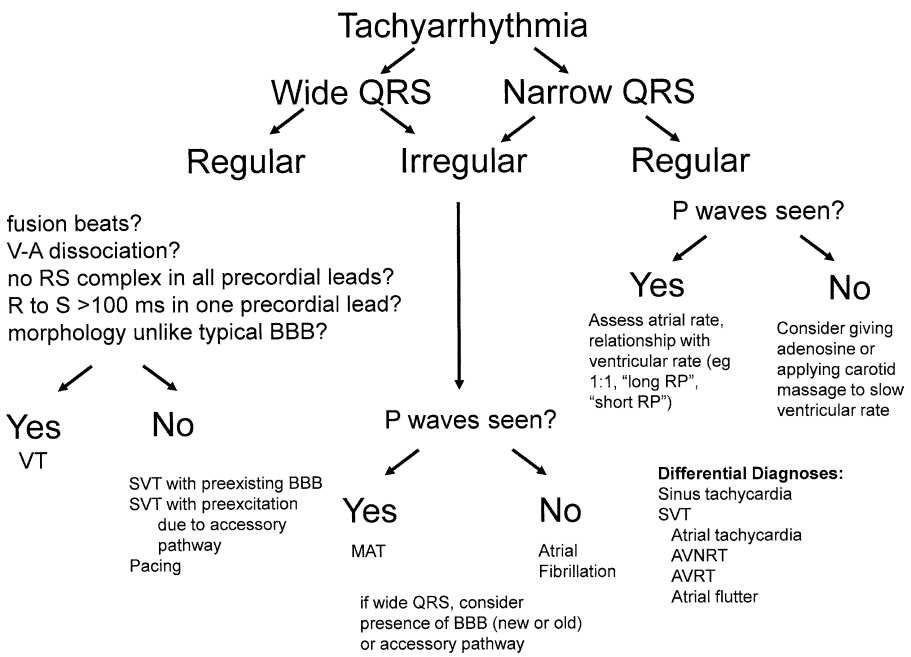

Fig. 21.9. General algorithm for diagnosis of narrow and wide complex tachycardias. *AVNRT* atrioventricular nodal reentrant tachycardia; *AVRT* atrioventricular reentrant tachycardia; *BBB* bundle branch block; *MAT* multifocal atrial tachycardia; *SVT* supraventricular tachycardia; *VT* ventricular tachycardia.

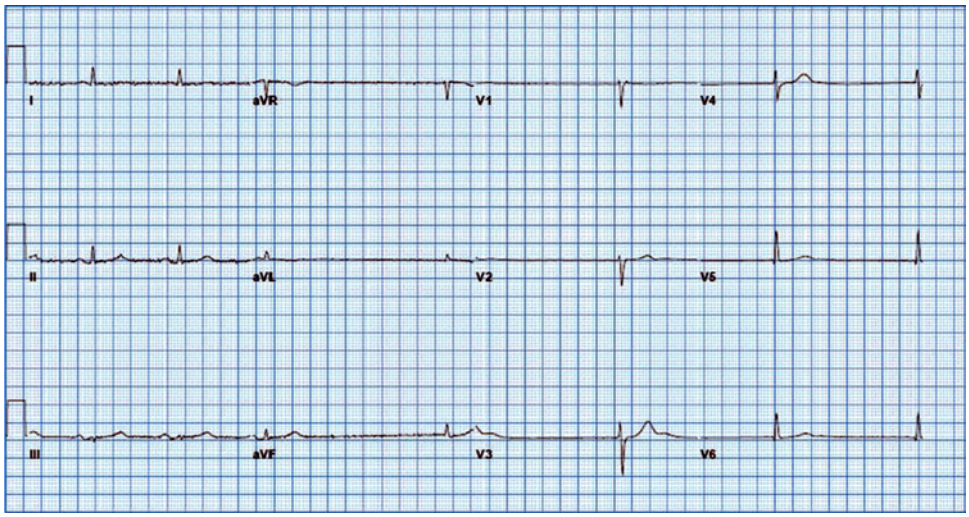

FIG. 21.10. Sinus pause. In the first half of this ECG, the patient is in sinus rhythm with low amplitude P-waves. In the second half, there are no discernable P-waves. Here, the rhythm is a narrow-complex junctional escape. This finding is likely due to intrinsic sinus node disease ("sick sinus syndrome"), although enhanced vagal tone inhibits sinus node conduction.

or arrest, sinoatrial block, and sinus bradycardia. Heart block at the AV node is classified by the degree and level of the block. Bundle branch blocks and fascicular blocks may also be seen post-operatively.

Epidemiology

Disturbances of the conduction system seem to be particularly associated with valve surgery and the type of cardioplegia solution used (less often with crystalloid than blood).[6] New conduction abnormalities, of which right bundle branch block is most common, can occur in over half of all patients undergoing coronary bypass surgery; they usually do not increase the mortality, and are most often transient.[71,72] Bradyarrhythmias may reflect rejection in orthotopic heart transplant patients. Following CABG, permanent pacing for either sinus node dysfunction or AV block is required in 0.8–3.4% of patients.[8] Valve surgeries are associated with a higher incidence of non-transient AV conduction abnormalities than that occurring after coronary surgery; and permanent pacing is required after repeat valve surgery approximately four times as often as after initial valve surgery.[73,74]

Diagnosis

Sinus bradycardia is defined as a sinus node rate of less than 50 bpm. In the post-operative patient receiving no rate-slowing drugs, a rate of less than 60 bpm would be considered abnormal and, although this requires no therapy, it often represents prima facie evidence of sinus node disease.

Sinus node pauses (Fig. 21.10) result from failure of electrical discharge from the sinus node. In prolonged periods of sinus pause, P-waves are absent, and junctional or ventricular foci must assume the role of cardiac pacemaker. The P–P interval does not equal a multiple of the baseline P–P interval.[59]

In *sinoatrial block*, pauses are a multiple of the basic P–P interval and reflect extensive atrial fibrosis, which blocks conduction from the sinus node to atrial tissue. Distinguishing between the different degrees of sinoatrial block may require intracardiac recordings.[59]

In *first degree AV block* (Fig. 21.11), the PR interval is greater than 0.2 s, but 1:1 atrioventricular conduction is preserved so that true block is not present.

In *Mobitz Type I second degree AV block* (also known as Wenckebach block; Fig. 21.12) there is progressive prolongation of the PR interval until the atrial impulse fails to reach the ventricle, resulting in a dropped beat.

In *Mobitz Type II second degree AV block* (Fig. 21.13), the atrial impulses intermittently fail to reach the ventricle, although the PR interval remains fixed (and often prolonged). It is very important to distinguish this condition from blocked atrial premature beats by examining the P-wave timing since the former is potentially malignant but the latter is always benign (Fig. 21.14a, b).

Third degree AV block (Fig. 21.15) occurs when conduction from atrium to ventricle is completely blocked either in, or below, the AV node. A twelve-lead EKG will show AV dissociation and more P-waves than QRS complexes, which reflect an escape rhythm either from the His–Purkinje system or ventricular muscle.

When 2:1 AV block is present, one cannot easily distinguish between Type I and Type II second degree AV block. Determination of the site of block requires evaluation of the PR interval, QRS duration, effects of various maneuvers, and presence of retrograde conduction (during an electrophysiology study). In short, maneuvers that increase the vagal tone

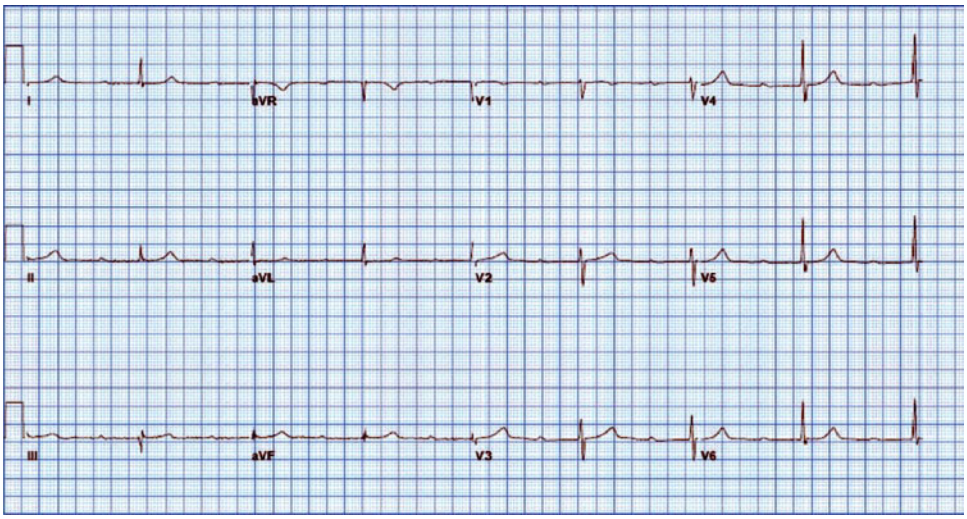

FIG. 21.11. First degree AV Block. This ECG shows sinus bradycardia at 50 bpm. The PR interval is constant and markedly prolonged (420 ms).

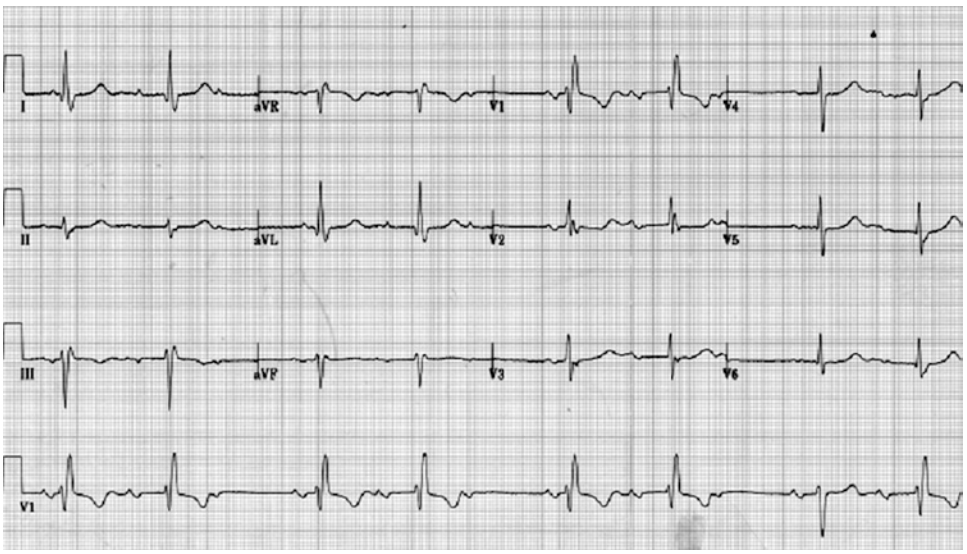

FIG. 21.12. Mobitz Type I Second Degree AV Block (Wenckebach). The rhythm is sinus with 3:2 Wenckebach block. The PR interval prolongs for the first two complexes followed by a nonconducted P-wave. The "group beating" pattern present in the rhythm strip is classic for Wenckebach block. The QRS is not wide, but has a right bundle branch block pattern. A premature atrial contraction occurs in the next-to-last beat of the rhythm strip.

will slow the sinus rate and the conduction down the AV node: If block is at the AV node, such block will worsen and consecutively non-conducted P-waves will be observed. However, if the block is infra-nodal, the block will usually improve because there is more time for recovery of excitability at the site of block after blocked impulses. Sympathomimetic or vagolytic interventions will have the reverse effects, relieving block at the nodal level and increasing block that is caused by infra-nodal disease.

Conduction Disturbances

Right or left bundle branch block (BBB) and left anterior or posterior fascicular block (FB) (Fig. 21.16a, b) reflect conduction delay or block at various points within the intraventricular conduction system. Right BBB is due to delay in the main right bundle branch, or distal right ventricular conduction system. Right BBB has increasing incidence with age and is as high as 12% by the eighth decade.[75]

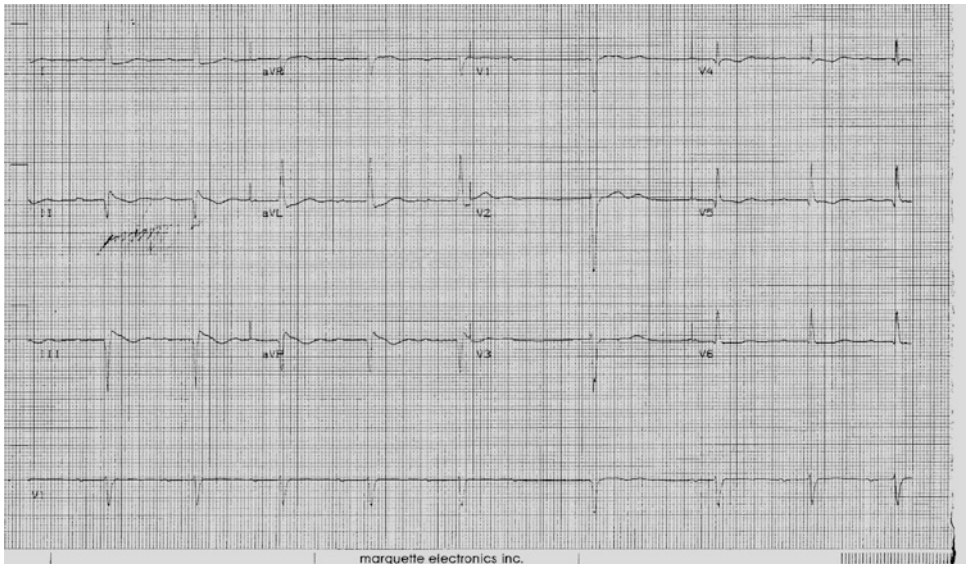

FIG. 21.13. Mobitz Type II Second Degree AV Block. The rhythm is sinus and the PR interval is prolonged yet constant. The sixth P-wave in the rhythm strip is not conducted to the ventricle. This event is followed by a junctional escape beat, a nonconducted atrial premature beat, then a resumption of sinus rhythm. Prominent Q waves in leads II, III, and aVF are suggestive of an old inferior myocardial infarction.

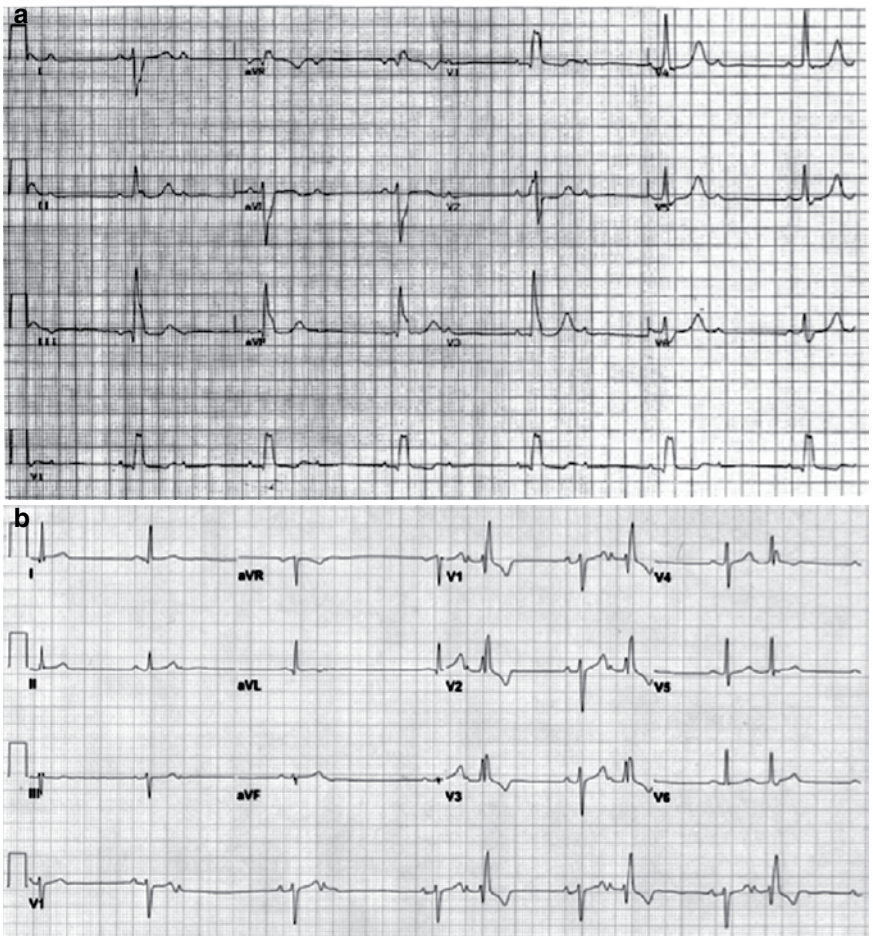

FIG. 21.14. (**a**) There is 2:1 AV block with short PR interval and LBBB for conducted beats, which strongly suggests infra-nodal level of block and a high risk of progression to complete heart block. This should be contrasted with (**b**), which shows blocked atrial premature beats – some conducted with RBBB. The major difference between the two ECGs lies in P–P timing: in (**a**) there is no change in P–P interval, whereas in (**b**) there is a clear prematurity of the blocked P-waves.

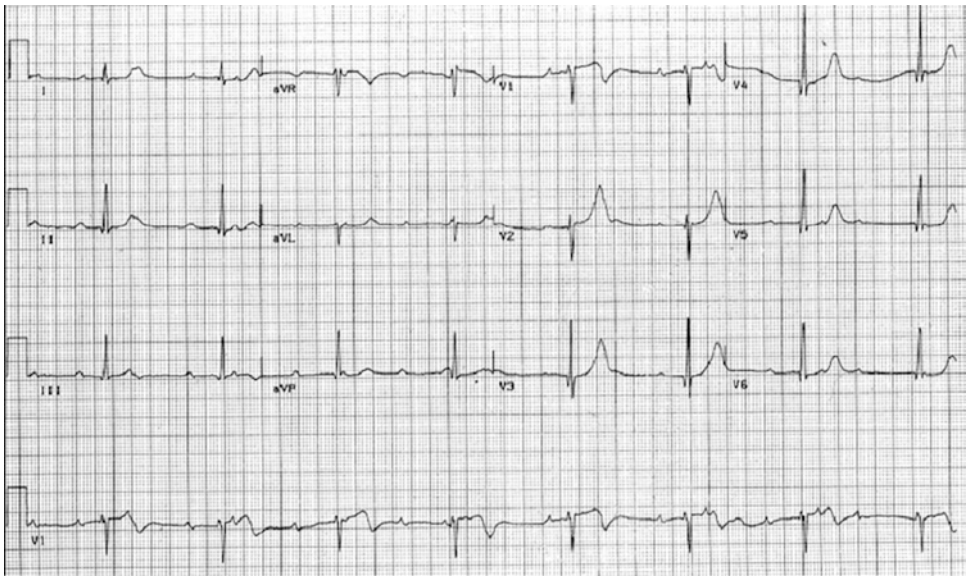

FIG. 21.15. Third degree AV block. The ventricular rate is approximately 50 bpm with a normal QRS duration, reflecting an escape mechanism from the AV junction. The atrial rate is variable between 100 and 125 bpm. There is no relationship between the P-waves and QRS complexes.

On ECG, the QRS duration exceeds 120 ms, the right precordial leads (V1, V2) show notched R-waves, and the left precordial leads (V5, V6) show wide and deep S-waves. Left BBB results from conduction block in the bundle of His, main left bundle branch, or either the anterior or posterior fascicle. Left BBB on ECG demonstrates a QRS greater than 120 ms, deep S-waves in the right pre-cordial leads, and wide notched R-waves in the lateral precordial leads. Left anterior FB is caused by block in the anterior fascicle in the left ventricle and results in marked left axis deviation (greater than −45) on ECG. While commonly associated with myocardial infarction, left ventricular hypertrophy, and numerous cardiomyopathies, left anterior FB alone has little prognostic significance.[59,76] Left posterior FB is relatively uncommon in the absence of underlying cardiac disease. Conduction delay in the left posterior fascicle causes marked right axis deviation on ECG.

Predisposing Factors and Prophylaxis

The most common cause of acquired conduction system disease is fibrosis. Sinus node dysfunction is often exacerbated by increased vagal tone from anesthesia or the surgery itself. Acute myocardial infarction, especially involving the right coronary artery, is a common cause of transient AV block and can persist up to 48 h. Risk factors for permanent pacing in the perioperative period include advanced age, left bundle branch block, peri-valvular calcification, left main coronary artery disease, left ventricular aneurysm, number of coronary bypasses, and cardiopulmonary bypass time.[8]

Treatment

Although often transient and asymptomatic, bradycardia that is sustained may require atropine or ephedrine. Drugs that suppress the AV node – such as beta-blockers, calcium channel blockers, and digoxin – should be discontinued, although they are rarely responsible in isolation for the emergence of the arrhythmia. Rarely, temporary transcutaneous or transvenous pacing is required.

Postoperative patients with complete heart block, symptomatic second degree AV block, and/or symptomatic sinus node dysfunction should receive temporary pacing.[77] Cardiac surgery patients may have local edema impinging on the sinus node or conduction system that usually resolves within 4–7 days. If the bradyarrhythmia persists for 7 days, whether the surgery was cardiac or noncardiac, and if all AV nodal agents have been withdrawn, then the patient should be considered for a permanent pacemaker. It may be reasonable to not wait 7 days in the patients with no reversible cardiac injury to explain the bradyarrhythmia.[78]

BBB and FB have been described in up to 60% of patients following coronary artery bypass grafting, but the majority of these patients had resolution of the defects prior to discharge.[72,76,79,80] One small study found that preoperative left BBB portended a higher incidence of postoperative bradyarrhythmia

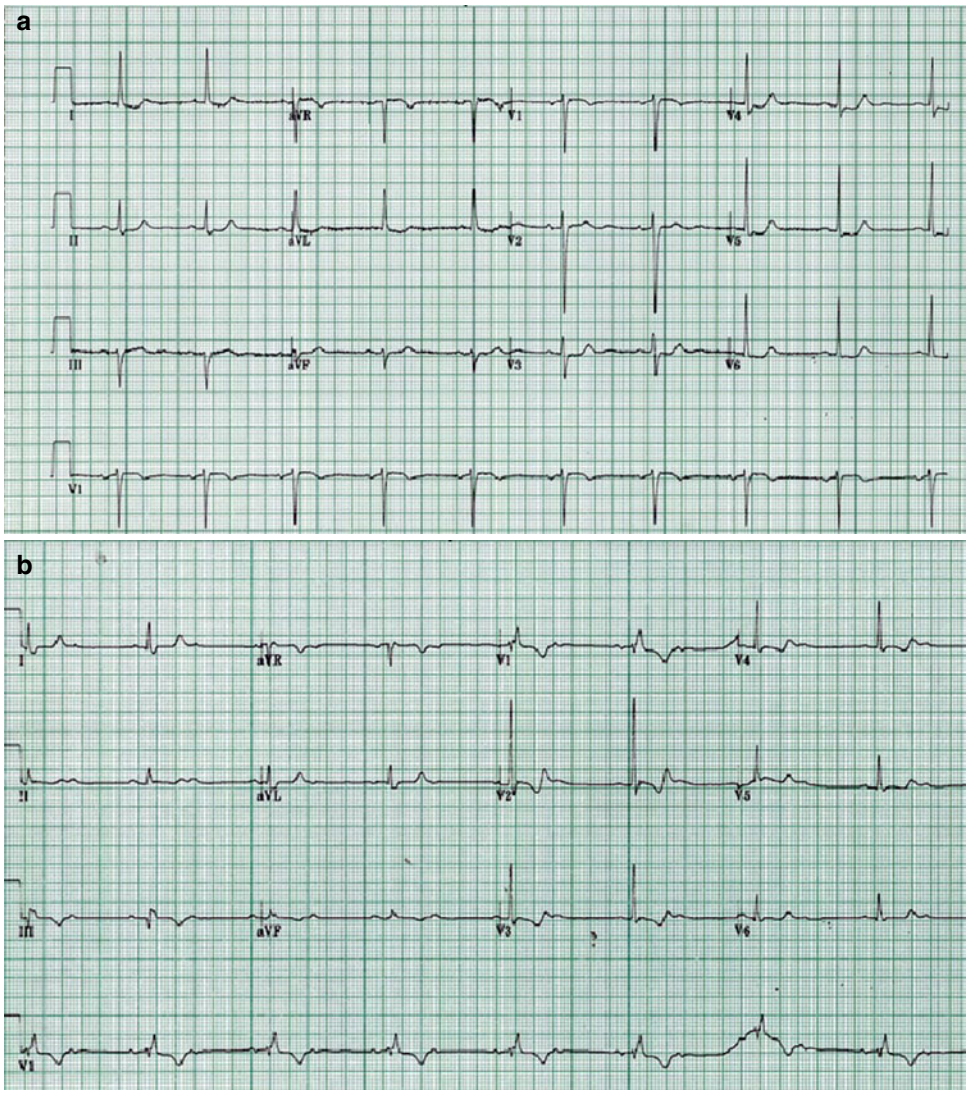

FIG. 21.16. (**a**) A preoperative tracing from a 70-year-old female about to undergo an aortic valve replacement. (**b**) Post-procedure, she developed new right bundle branch block and 2:1 AV block. These changes persisted, and the patient received a dual-chamber pacemaker prior to discharge from the hospital.

requiring permanent pacing.[80] In another study of patients undergoing aortic valve replacement, new and persistent postoperative BBB (either right or left) was an independent predictor of adverse events (complete AV block, syncope, or sudden cardiac death).[81] More than 50% of the events occurred in the first 6 months of follow-up.

Of those patients who receive a pacemaker perioperatively, approximately 30–40% with sinus node dysfunction remain pacemaker-dependent. In contrast, 65–100% of such patients with complete heart block are pacemaker-dependent at follow-up.[8] In fact, postoperative complete AV block has been shown to be the most important predictor of pacemaker dependency.[82] In patients who have undergone aortic valve or mitral valve replacement, complete AV block that persists more than 48 h is unlikely to resolve and warrants permanent pacing prior to discharge.[83]

Perioperative Care of Patients with Pacemakers and Implantable Cardioverter Defibrillators

Increasingly, patients referred for surgery already have a pacemaker and/or defibrillator due to an existing arrhythmia (e.g., complete heart block) or an increased risk for developing one

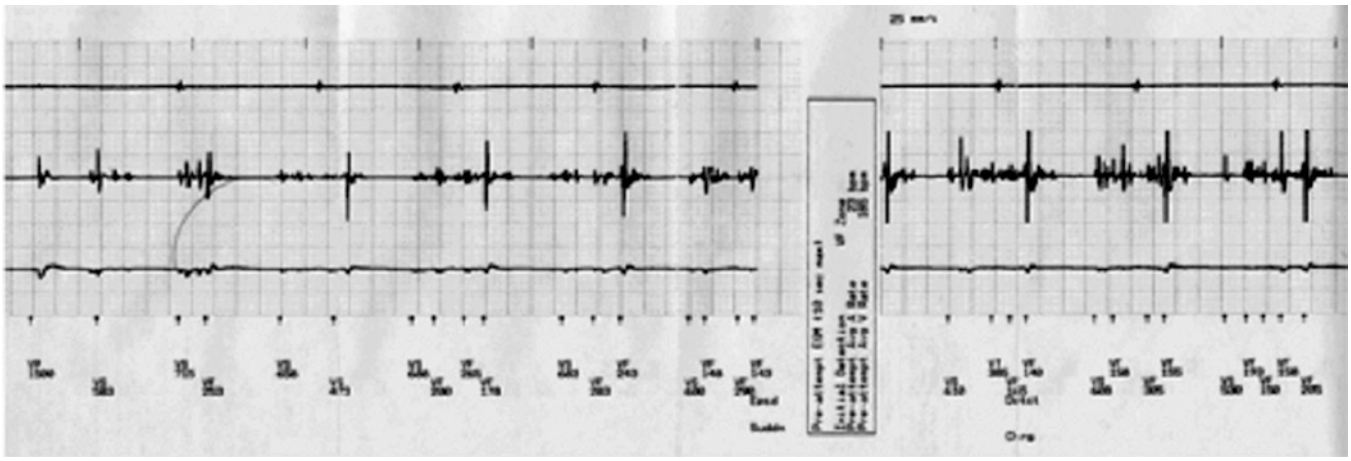

FIG. 21.17. Ventricular oversensing by ICD during placement of a dialysis catheter. This conscious patient was undergoing central venous catheter placement by an interventional radiologist who was unaware of the defibrillator's presence. The metal guidewire made contact with the sensing electrodes in the right ventricle, causing the multiple low amplitude potentials seen on the electrogram recording. Ultimately, this triggered an inappropriate shock from the device.

(e.g., VT in a patient with ischemic cardiomyopathy). Such implanted devices are potentially vulnerable during surgery and it is crucially important that the operative team be aware of not only the existence of such a device, but also of its anatomic path and functional status to be confirmed prior to the patient entering the operating room. Generally, pacemakers are less vulnerable to the depredations of the surgical environment than implanted defibrillators; however, electrocautery can interfere with the function of both types of device. Pacemaker activity may be inhibited in the presence of electromagnetic interference such as would be exemplified by cautery use. Therefore, the use of cautery is expected to inhibit pacing in a device that has intact sensing function. In a pacemaker-dependent patient, it is therefore important to inhibit sensing once cautery is applied, and this is typically done by application of a magnet over the device.

Implanted defibrillators are robust devices that have protective Zener diodes, which prevent damage to the electronics during voltage surges; however, they are designed to detect intracardiac signals of millivolt amplitude and, therefore, such devices may be activated by electrocautery, which penetrates the system during surgery. Cautery signals may be interpreted as ventricular fibrillation and therefore trigger shock delivery, which may have no effect upon the anesthetized patient although the surgical team may certainly become alarmed. Intravascular procedures that may mechanically interact with the implanted defibrillator lead system can also cause low voltage potentials, which have the potential to cause troublesome interference (Fig. 21.17).

Electrocautery, especially in the thorax, is associated with particularly increased risk of damage to implanted devices. Such electromagnetic energy always takes the path of least resistance and, therefore, may be transmitted down the leads, potentially damaging the electrode-myocardial interface; this local effect may permanently impair sensing and increase the pacing threshold.[84]

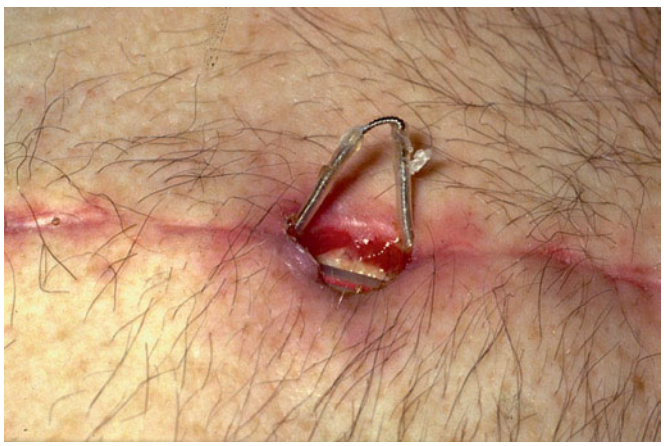

FIG. 21.18. An abdominal incision in close proximity to a previously placed pacemaker in the abdomen resulted in exposure of a lead through the wound.

A comprehensive evaluation should be performed preoperatively to ascertain the type of device, the indication for implantation, dependency for pacemaker function, and the patient's intrinsic rhythm.[85] Consultation with the patient's cardiologist should be sought if needed. If the site of surgery is remote from the device, and the device was evaluated within the 3 months prior to surgery, the risk of malfunction is very low.

If the site of surgery is in close proximity to the device, additional surgical planning is needed to ensure that neither the leads nor the generator are disrupted (Fig. 21.18).

To reduce the risk of complications, ICD sensing and therapies can be temporarily disabled for the surgical procedure with

a magnet placed on the skin over the device at the beginning of the procedure and removed at the conclusion of the procedure. This inhibits sensing of any potential ventricular arrhythmias, and thereby inhibits inappropriate shocks from noise detection. Bradyarrhythmia therapies are not inhibited. If the patient were to develop VT or VF, the patient should be externally defibrillated. Removal of the magnet to allow the ICD to revert to its programmed state and to deliver appropriate therapy may not permit delivery of automatic shocks quickly enough. Following the procedure, program settings should be confirmed with the ICD programmer.

For patients who are pacemaker-dependent, placement of a magnet over the device site should ensure asynchronous, continuous pacing. Following review of the location, the type, duration of the procedure, and the patient's dependency on pacing, such a strategy should be considered in consultation with the cardiac team.

Antiarrhythmic Agents

Commonly used antiarrhythmic drugs for postoperative arrhythmias are presented in Table 21.2. It should be emphasized that with the notable and consistent exception of beta-blockers, there is no evidence from multiple trials that these drugs improve outcomes such as survival. They are useful primarily for acute management of arrhythmia symptoms.

However, both statins and fish oil have been shown to help prevent perioperative arrhythmias and cardiac complications.[65,86,87] We would suggest continuing statins and/or fish oil in the perioperative period in those patients already taking them, but further studies are needed before widespread use can be recommended.

Conclusion

Perioperative cardiac arrhythmias are common. The approach to treatment should focus foremost on the clinical status of the patient, followed by diagnosing the arrhythmia, controlling the ventricular rate, and addressing hemodynamic instability. Many arrhythmias are associated with reversible conditions such as volume overload, electrolyte or acid/base imbalance, pain, and stress. Preexisting conditions such as depressed ventricular function or conduction abnormalities increase the likelihood of developing arrhythmias in the postoperative period. Patients with persistent arrhythmias and/or a high risk of recurrence may warrant permanent pacing and/or ICD placement.

Table 21.2. Commonly used antiarrhythmic agents in management of postoperative arrhythmias.

Medication	Dose	Indication	Adverse reaction
Adenosine	6 mg; then 12 mg IV, repeat once	Rapid SVT	Flushing, chest discomfort, heart block (transient)
Amiodarone	150–300 mg bolus IV over 10 min, then 1 mg/min × 6 h, then 0.5 mg/min × 18 h	AF; refractory VT or VF	Heart block, mild hypotension; long-term pulmonary, hepatic, thyroid toxicity
Atropine	0.5–1 mg IV	Bradycardia	Myocardial ischemia, tachycardia
Digoxin	0.25–0.5 mg IV bolus, then 0.25 mg IV every 6 h × 4 doses	AF	Delayed onset; nausea, transient heart block, ventricular arrhythmias, renal cleared
Diltiazem	5–20 mg bolus IV, then 5–15 mg/h infusion	Rate control for SVT	Mild hypotension
Esmolol	0.5 mg/kg bolus IV, then 0.05 mg/kg/h infusion, increase by 0.05 mg/kg/h every 4 min up to 200 mcg/kg/min infusion	Rate control for SVT	Short acting; bronchospasm, pulmonary edema
Flecainide	50 mg PO every 12 h, increase by 100 mg total/day every 4 days up to 150 mg every 12 h	AF	Avoid if structural heart disease or coronary artery disease
Ibutilide	1 mg IV over 10 min, repeat once if needed	AF, cardioversion	Torsade de pointes, QT prolongation
Metoprolol	5 mg IV every 5 min × 3; or 25–100 mg orally 2–3 times/day	Rate control	Bronchospasm, mild hypotension
Procainamide	15–17 mg/kg IV over 30 min; or 100 mg IV every 5–10 min; or 1–1.25 mg oral	Rate control, bypass tract	Renally excreted
Propafenone	150 mg oral every 8 h; every 3 days may increase to 225 mg every 8 h, then 300 mg every 8 h	AF	Avoid if structural heart disease or coronary heart disease
Sotalol	80 mg oral every 12 h, increase dose by 80 mg every 3 day up to 640 mg total/day	AF	Torsade de pointes, QT prolongation, bradycardia; exclusively renally excreted; must be loaded as inpatient

AF atrial fibrillation; *SVT* supraventricular tachycardia; *VF* ventricular fibrillation; *VT* ventricular tachycardia.

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Part IV
Pulmonary Medicine

22
Acute Respiratory Failure

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Respiratory failure is defined as the inability of the respiratory system to maintain normal oxygen and carbon dioxide tensions (PaO_2 and $PaCO_2$, respectively), when breathing room air. Normal $PaCO_2$ ranges from 35 to 45 mmHg, while normal PaO_2 ranges from 80 to 100 mmHg and declines with age according to the following formula[1]:

$$PaO_2 = 102 - 0.3 \cdot Age$$

Respiratory failure may be defined as acute when it presents as a sudden, often life-threatening impairment in either oxygenation or ventilation. Oxygenation failure is characterized by low PaO_2 (hypoxemia) and normal or low $PaCO_2$ (normo- or hypocapnia). Ventilatory failure is characterized by high $PaCO_2$ (hypercapnia), which is usually, also, associated with hypoxemia. Oxygenation failure and ventilatory failure have different pathophysiologies and benefit from different therapies. Since both forms may occur in patients undergoing surgery, an understanding of their pathophysiologies is, therefore, essential.

Pathophysiology

Oxygenation Failure

Hypoxemia results from two basic mechanisms: (1) alveolar hypoxia, i.e., a reduced fraction of oxygen on the alveolar side of the pulmonary units (FaO_2); and (2) the presence of shunt, i.e., a condition in which blood perfusing the lung parenchyma does not enter into contact with the alveolar gases (Table 22.1).

Alveolar Hypoxia

A low alveolar concentration of oxygen may be caused by reduced barometric pressure (e.g., high altitude) or by inhalation of gas mixtures with abnormal composition (i.e., inspired oxygen fraction, $FiO_2 < 21\%$). The most common cause of alveolar hypoxia, however, is an abnormally low ventilation/perfusion ratio (Va/Q). The consequences of this condition may be quantitatively described by a rather intricate series of equations.[2] The underlying concept, however, is rather simple. Perfusion removes from pulmonary units a given amount of oxygen, per unit time. A normal alveolar oxygen concentration is, therefore, maintained only if ventilation provides, per unit time, the same amount of oxygen as that carried away by perfusion. This condition corresponds to a Va/Q ratio close to the unit. The amount of oxygen provided by ventilation (Va) is:

$$VO_2 = (FiO_2 - FeO_2) \cdot VQ$$

where FeO_2 is the expired oxygen concentration and VO_2 is oxygen consumption/requirement. The amount of oxygen subtracted by perfusion is:

$$VO_2 = \Delta c(a\text{–}v)O_2 \cdot CO$$

where $\Delta c(a\text{–}v)O_2$ is arterial–venous blood oxygen content difference and CO is cardiac output. It can be seen that if alveolar ventilation decreases (e.g., by 50%), with oxygen consumption remaining the same, an inverse increase in the difference between inspired and expired oxygen fractions must be observed (i.e., it must double, in our example). If the inspired oxygen fraction is not varied, this would imply a proportional decrease in the expired oxygen concentration, which would cause, in turn, alveolar oxygen tension to decrease. It can also be seen that if cardiac output remains constant, arterial oxygen concentration (and venous oxygen concentration, as well) will decrease. Arterial oxygen content, however, usually decreases more than venous oxygen content, since cardiac output actually increases, as a compensatory response to hypoxemia. Since

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Table 22.1. Hypoxemia and hypercapnia – causes and treatments.

Condition	Primary cause	Mechanism	Correction
Arterial hypoxemia	Alveolar hypoxia	Decreased barometric pressure ($PO_2 = FiO_2 \times Pb$) Decreased inhaled oxygen fraction ($PO_2 = FiO_2 \times Pb$) Decreased ventilation/perfusion ratio	Increase inspired oxygen fraction (to correct hypoxia) Increase ventilation (to correct hypercapnia)
	Shunt	Ventilation/perfusion ratio equal to zero	(1) Increase inhaled oxygen fraction (to correct hypoxia) (2) Recruitment (3) Pulmonary blood flow diversion
Hypercapnia		Decreased ventilation (increased alveolar carbon dioxide concentration and arterial tension)	Increase ventilation, treat underlying disease

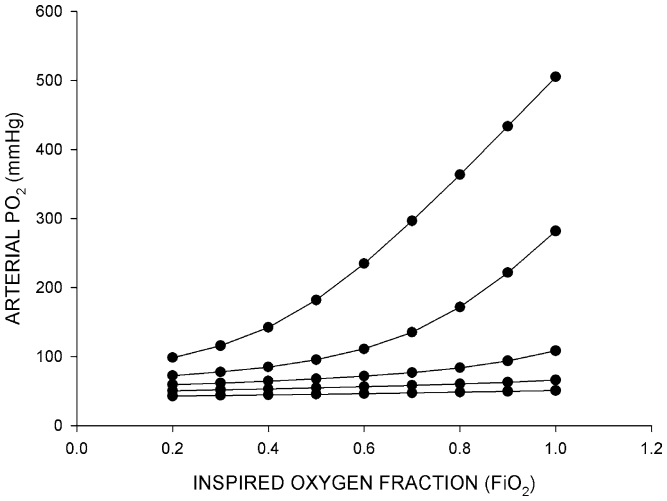

Fig. 22.2. Arterial oxygen tension (PaO_2) values predicted for different inspired oxygen concentrations (FiO_2). Each line is representative of the condition observed with a different shunt fraction, as indicated on the right.

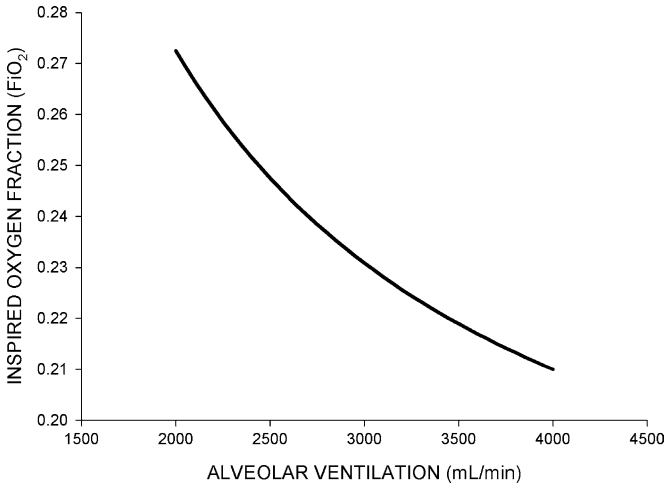

Fig. 22.1. Theoretical predicted inspired oxygen fraction (FiO_2) required to maintain a normal arterial oxygen tension (PaO_2) for each level of alveolar ventilation (Va).

alveolar hypoxemia is only due to a lower-than-normal FaO_2, it can simply be corrected by raising the inspired oxygen fraction. In Fig. 22.1, we represent the FiO_2 necessary to maintain a normal FaO_2, when alveolar ventilation is progressively decreased, while cardiac output remains constant. As shown, the correction of alveolar hypoxemia is an easy task.

Hypoxemia Due to Shunt

Intrapulmonar shunt is the fraction of cardiac output that perfuses unventilated regions of the lung.[3] The pulmonary end-capillary blood perfusing shunt regions has the same gas tensions as those of mixed-venous blood. Shunt is the worst-case alteration of the ventilation/perfusion ratio, being $Va/Q = 0$. This implies that no gas exchange occurs in the shunt compartment, due to the absence of gas within alveolar units (e.g., micro-atelectasis, other material filling the alveoli). Hypoxemia due to shunt can only be partially corrected by increasing FiO_2, since a greater inspired oxygen concentration will increase alveolar oxygen tension (PaO_2) within ventilated compartments only, but will not affect the gasless shunt regions. With shunts of 30–35%, PaO_2 can only be increased up to roughly 100 mmHg, even if breathing 100% FiO_2. The approach for correcting hypoxemia due to intrapulmonary shunt varies considerably from those employed for correcting alveolar hypoxia. The latter is an easy task, as shown in Fig. 22.1; the former, especially with consistent shunt fractions, is far more difficult (Fig. 22.2), since it requires either a modification of pulmonary blood flow distribution or a modification of the anatomical status of the unventilated pulmonary units.[4]

Ventilatory Failure

Ventilatory failure, by transiently limiting the excretion of the normal metabolic CO_2 load (i.e., 150–200 mL/min, variable according to the metabolized substrates), results in the inability of the respiratory system to maintain normal levels of $PaCO_2$. The latter are determined by the alveolar carbon dioxide tension ($PaCO_2$), which is in equilibrium with its partial pressure in blood. Since the alveolar fraction of CO_2

($FaCO_2$) is equal to $PaCO_2/(Pb - PH_2O)$, where Pb is barometric pressure and PH_2O is saturated water vapor pressure (47 mmHg, at body temperature), it follows that, for a given alveolar ventilation:

$$VCO_2 = FaCO_2 \cdot Va$$

where VCO_2 is carbon dioxide production. This simple formula clearly indicates that, in order to maintain an adequate metabolic CO_2 elimination, if alveolar ventilation decreases, the alveolar fraction of CO_2 must increase proportionally in order to maintain VCO_2 constant. As an example, if Va halves and VCO_2 remains constant, a new equilibrium will be reached when $FaCO_2$ is doubled, i.e., $VCO_2 = ½Va \cdot (2FaCO_2)$. As can be seen, the hallmark of ventilatory failure is increased $FaCO_2$. This is usually associated with decreased alveolar oxygen concentration. While the oxygenation impairment due to ventilatory failure is easily corrected by raising FiO_2, hypercapnia due to ventilatory failure may only be corrected by increasing alveolar ventilation and/or by decreasing the CO_2 load produced as a consequence of body metabolism.

Approach to the Patient with Respiratory Failure

Clinical Symptoms

It is evident, from the previous discussion, that blood gas determinations are required for diagnosing respiratory failure. However, several clinical signs are also associated with this condition, and we will briefly describe here the ones, which are most relevant in a surgical scenario.

The patient history is of great importance, usually providing precise information on the chronic or acute nature of the respiratory failure. In patients affected by chronic respiratory failure, the assessment of cardio-circulatory status is of paramount importance, since hemodynamic impairment may be the determinant of a sudden deterioration in respiratory function. Respiratory rate must be carefully monitored. Tachypnea, with or without dyspnea, is present in most cases of shunt-related hypoxemia, while decreased respiratory rate and/or shallow breathing may indicate residual sedation or muscle relaxation. The observation of thoracic asymmetry may suggest the presence of pneumothorax or atelectasis. However, it is important to remember that severe respiratory failure may occur in the presence of only subtle clinical signs.

Instrumentation

Gas Analysis

PaO_2 and $PaCO_2$ values give immediate information on the "nature" of respiratory failure, i.e., whether it is caused by oxygenation or ventilatory failure. A test challenge, performed by measuring blood gases after breathing gas mixtures with two different FiO_2 (see Fig. 22.1), may help diagnose the primary mechanism causing hypoxemia.

If hypoxemia is corrected by enriching inspired air with oxygen, the origin of failure is alveolar hypoxia. If oxygenation is only partially corrected, instead, shunt is the most likely mechanism involved. It must be stressed that ventilatory failure, however, is only indicated by increased $PaCO_2$ (higher than 45 mmHg). A summary of the different diagnoses suggested by different $PaO_2/PaCO_2$ combinations is presented in Table 22.2.

In most clinical contexts, pulse oximetry is an adequate surrogate for arterial PaO_2,[5,6] while end-tidal CO_2 may reasonably well reflect arterial $PaCO_2$.[7] Moreover, in the steady state, arterial $PaCO_2$ also strongly correlates with central venous carbon dioxide tension ($PvCO_2$), the latter being 4–5 mmHg higher than the former.[8] Consequently, a central venous $PvCO_2$ greater than 50 mmHg is suggestive of ventilatory failure.[9] In contrast, venous blood oxygen tension (PvO_2) cannot surrogate arterial PaO_2, since the two are poorly correlated.[8] This derives from the fact that central venous PvO_2, and central venous oxygen saturation (SvO_2), do not depend only on arterial oxygenation (SaO_2, arterial oxygen saturation), but are also determined by oxygen consumption (VO_2), hemodynamics (as reflected by cardiac output, CO), and hemoglobin concentration ([Hb]), as shown by the formula below:

$$SvO_2 = SaO_2 - \frac{VO_2\,(mL/min)}{CO\,(L/min)} \frac{1}{[Hb] \cdot 1.36}$$

While the diagnosis of hypoxemia cannot be made from central venous PvO_2, or central venous saturation, these two quantities, particularly SvO_2, provide nonspecific but extremely sensitive

Table 22.2. Diagnoses suggested by different $PaO_2/PaCO_2$ combinations.

	Normal $PaCO_2$	Low $PaCO_2$	High $PaCO_2$
Normal PaO_2	Normal	Hyperventilation (anxiety, stress, metabolic acidosis)	Ventilatory failure while breathing with $FiO_2 > 0.21$
Low PaO_2	Oxygenation failure due to shunt, high altitude, $FiO_2 < 0.21$	Oxygenation failure due to shunt, high altitude, $FiO_2 < 0.21$	Ventilatory failure if $FiO_2 < 0.21$; ventilatory failure + shunt if $FiO_2 > 0.21$
High PaO_2	$FiO_2 > 0.21$ and normal ventilation	Hyperventilation and $FiO_2 > 0.21$	Ventilatory failure with $FiO_2 > 0.21$ or mismeasurements

information on metabolism, hemodynamics, and oxygen-carrying capacity, as indicated by the following rearranged formula:

$$SvO_2 = Lung - \frac{Metabolism}{Hemodynamics} \frac{1}{Anemia}$$

Chest X-Rays

The imaging technique traditionally used in the diagnostics of respiratory failure is the bedside portable chest X-ray. While it may be still useful to detect pulmonary infiltrates, pneumothorax, and pleural effusions, its sensitivity is relatively poor. In fact, anterior pneumothorax or posterior consolidation/atelectasis and effusions may only be uncovered using CT-scanning.[10] According to several authors,[11,12] routine daily chest X-rays are no longer recommended for managing critical care patients. In the case of clinically suspected respiratory failure, chest X-rays are still a valid preliminary examination to perform. However, further investigation with CT-scanning (see next section) is warranted in cases of overt respiratory failure, particularly if large discrepancy exists between the severity of symptoms (e.g., severe hypoxemia) and the chest X-rays' presentation.

CT-Scanning

With CT-scanning, a complete examination of the lung parenchyma, including those lung regions not explorable with traditional antero-posterior chest X-rays, is possible. Although a detailed discussion of the indications and uses of whole-lung CT-scanning is out of the scope of this chapter and may be found elsewhere,[10,13] it is important to stress that quantitative CT-scan analysis makes it possible to determine the degree of aeration of each lung region (i.e., over-, normal-, poor- or non-inflation[14]). The most information from CT-scanning, in the context of respiratory failure – in particular oxygenation failure – can be obtained by quantitatively analyzing whole-lung CT-scan images of the lung taken at two different airway pressures: one at a low airway pressure (end-inspiration) and one at total lung capacity. With this information it is then possible to quantify with great accuracy the potential for lung recruitment,[15] i.e., the amount of lung parenchyma that is collapsed but can still be opened (i.e., recruited) with increasing airway pressure. This strategy is particularly indicated in patients suffering from acute respiratory distress syndrome (ARDS), but has also been found useful in some post-surgical patients presenting with profound hypoxemia and near-normal chest X-rays.[16,17] In these instances, precise determination of the lung parenchymal abnormalities is possible with CT-scanning, which also provides a quantification of the amount of recruitable lung and helps titrate the most appropriate positive end-expiratory pressure (PEEP).

Hemodynamics

In order to fully understand the pathophysiology of respiratory failure and, particularly, the alterations in gas exchange, the hemodynamic status also has to be carefully assessed. In fact, we must always bear in mind that arterial blood gases are determined by a process involving both ventilation and perfusion. From a clinical perspective, two main issues have to be taken into account:

1. For a given ventilation/parenchymal inflation, if perfusion increases, oxygenation decreases and $PaCO_2$ tends to be constant or to increase. In contrast, if perfusion decreases, arterial PaO_2 decreases and $PaCO_2$ decreases, at least initially after cardiac output reduction.
2. "Shunt" increases and decreases with decreasing and increasing cardiac output, respectively. Several mechanisms, possibly, determine this phenomenon, which has been known since the early 1970s,[18,19] the most important factor probably being the extent and degree of pulmonary vasoconstriction.[20]

These effects of cardiac output on gas exchange have to be kept in mind in clinical practice. As an example, a patient may well increase his arterial PaO_2 after an increase in airway pressure, but this can either be due to effective recruitment of previously collapsed (non-aerated) lung regions, or to a sudden decrease in cardiac output brought about by the increase in intra-thoracic pressures, which is not accompanied by any degree of lung recruitment. Indeed, we believe that assessing hemodynamics is crucial to understanding a patient's altered gas exchange condition, and that it is mandatory, in particular, when judging a patient's response to positive pressure ventilation and PEEP.[21]

Etiology and Diagnosis of Hypoxemia

Hypoxemia is diagnosed with certainty only with blood gas analysis or, with lesser accuracy, with pulse oximetry. Cyanosis is not a reliable marker of hypoxemia, due to the confounding effects that anemia, light conditions, methemoglobinemia, and vasoconstriction may exert. Surgical patients, in the early postoperative period, frequently show some degree of hypoxemia. The primary cause of hypoxemia, in normo-ventilating patients (see later), is the reduction of aerated lung volumes (functional residual capacity, FRC) due to lung collapse (atelectasis). Several CT-scanning studies have shown that anesthesia/deep sedation (even without muscle paralysis) induce compression atelectasis in gravity-dependent lung regions.[22,23] These collapse phenomena are exaggerated in patients with increased abdominal pressure.[24] In morbidly obese patients, for example, the interaction between the effects of anesthesia and those of increased abdominal weight may cause their functional residual capacities to be reduced to as low as 350–500 mL,[25] i.e., lung volumes comparable to those

observed only in severe ARDS. The level of hypoxemia is, however, moderate (with PaO_2 being only 10–15 mmHg lower than normal) due to the activation of compensatory mechanisms, such as hypoxic pulmonary vasoconstriction.[26] Shunt, after anesthesia, is usually 8–10%.[27] Such moderate hypoxemic conditions are generally ignored, since their clinical consequences are minimal (i.e., minor increases in cardiac output and respiratory rate). Compression atelectasis, even without intervention, usually resolves in 24–48 h. Administration of relatively high airway pressures, however, can correct this type of atelectasis in a few minutes.[16]

Pulmonary Edema

Pulmonary edema does not frequently occur in the postoperative period. Lung edema – i.e., increased extravascular water in the interstitium and alveoli – may either be caused by increased capillary hydrostatic pressure, by altered capillary wall permeability, or by a combination of these two mechanisms.

High Hydrostatic Pressure Edema

Capillary hydrostatic pressure increases either because of water overload or because of left ventricular failure associated with increased left atrial pressure that transmits back to the lung capillaries. Clinical history, electrocardiography, echocardiography, and fluid balance assessment can point to the correct diagnosis. A typical "butterfly" pattern can be identified on the chest X-rays. Variable distributions of densities, however, may be observed. The diagnosis may be substantiated with the assessment of cardiac output, pulmonary artery pressure, wedge pressure >18 mmHg and mixed venous oxygen saturation. We believe that the currently unpopular[28] Swan-Ganz catheter is still useful to help discriminate between cardiogenic and inflammatory edema. When edema is caused by high capillary hydrostatic pressure, PaO_2 is low and $PaCO_2$ is nearly normal. Hypocapnia is rare in these patients, due their limited ability to hyperventilate (reduced muscular reserves, due to heart failure or advanced age). Hypoxemia is primarily due to true shunt, with the exception of patients with preexisting chronic respiratory failure, in whom the presence of low-Va/Q regions may play a more relevant role.

Inflammatory Lung Edema

Lung edema caused by increased capillary wall permeability, secondary to a widespread inflammatory process in the lung, is referred to as Acute Respiratory Distress Syndrome (ARDS).[29] A number of pulmonary and extra-pulmonary factors may trigger this syndrome.[30] In surgical patients, ARDS is most commonly secondary to extra-pulmonary causes such as pancreatitis, abdominal infarction, massive transfusion, septic shock, inhalation injury, and multiple trauma. Such extra-pulmonary triggers are thought to release a number of cytokines. When these inflammatory products reach the lung vessels, their endothelium is activated, which, in turn, boosts the activation of the coagulation and inflammatory cascades.[31] Capillary wall permeability is finally increased, leading to extra-vascular accumulation of a protein-rich fluid. Such lung edema increases the weight of the lung, so that gravity-dependent lung regions are compressed (i.e., atelectasis develops) by the weight of the heavier than normal "superimposed" nondependent ones.[32] The lung regions open to ventilation are poorly represented; i.e., functionally, the lung behaves as a "baby lung."[33] This anatomical setting causes "true shunt" due to the fraction of pulmonary blood flow that perfuses the dependent gasless lung regions. The hypoxemia ensues and the use of high oxygen fraction is mandatory and is part of the treatment. Such severe hypoxemia is often associated, in the early phase, with hypocapnia and dyspnea. When, 2 to 3 weeks later, structural modifications of the lung parenchyma (e.g.,fibrosis) begin to occur within the context of lung edema,[34] $PaCO_2$ then starts to increase. Increased alveolar dead space, which is associated with this form of hypercapnia, is a marker of the structural alterations developing within the lung parenchyma.[35] There is no typical chest X-ray pattern, with variable distribution of the densities. With CT-scanning, a gravitational distribution of the densities can be observed.[36] In ARDS, as previously found,[37,38] lung edema is quite homogeneously distributed throughout the lung parenchyma. The fact that lung densities are more common in dependent lung regions is not because edema is preferentially distributed toward these areas, but rather because alveolar gas is "squeezed" out from these regions, which are compressed by the "superimposed" regions above. This interpretation is confirmed by CT-scanning studies of patients with ARDS placed in the prone position. When the position was changed from supine to prone, opacities moved from the dorsal to the anterior lung regions.[39]

Myocardial Infarction

Perioperative myocardial infarction is not a rare occurrence, especially in patients with underlying coronary artery disease.[40] Depending on the site and extent of the myocardial lesions, lung edema and respiratory failure may develop.

Thromboembolism

Thromboembolism is another life-threatening complication observed in the perioperative period. Mechanisms of thromboembolism-related hypoxemia are not clear.[41,42] Hypercapnia is often present. Typically, thromboembolism is an acute and sudden phenomenon. However, it is circulatory rather than respiratory failure that carries the most morbidity.

Aspiration Pneumonia

Aspiration pneumonia may occur in the context of urgent or emergent surgery or with pregnant or obese patients undergoing

general anesthesia. It is associated with severe shunt-related hypoxemia and hypocapnia.

Hypoventilation

As previously described, hypoventilation may cause hypoxemia. Hypoxemia is due to alveolar hypoxia and may easily be corrected by increasing the oxygen fraction in the inspired mixture.

Etiology and Diagnosis of Hypercapnia (Hypoventilation)

The clinical signs and symptoms associated with hypercapnia are variable, depending on the extent and rate of $PaCO_2$ increase. High $PaCO_2$ levels bring about an increase in sympathetic tone (increased heart rate, arterial pressure, cardiac output) and determine venoconstriction in central venous vessels.[43–45] This can be observed despite the fact that CO_2 causes direct smooth muscle relaxation.[46] Hiccups, thrills, hallucinations, and coma are also associated with increased $PaCO_2$. Sometimes, increased $PaCO_2$ directly causes increased pulmonary artery pressure.[47,48]

During anesthesia, patients are usually mechanically ventilated. $PaCO_2$ control, therefore, is not a major problem. When, after extubation, spontaneous breathing is resumed, hypercapnia can occur, with several different mechanisms potentially causing it.

Comorbid States

In the surgical setting, hypercapnia may occur because of preexisting comorbid states. Neuromuscular diseases, chest wall alterations, and several intrinsic pulmonary illnesses may all be associated with hypercapnia. Surgical interventions may worsen those preexisting conditions and render the patient prone to develop hypercapnia.

Central Depression and Residual Curarization

In the perioperative period, several administered drugs (e.g., narcotics, analgesics, muscle relaxants) may cause respiratory depression and lead to hypoventilation. Patients may become hypercapnic, with no apparent dyspnea or tachypnea. If the patient is breathing room air, hypoxemia would also be present, while oxygenation might be normal if the inspired mixture is enriched with oxygen. Residual curarization may also cause hypercapnia. However, in this case, the hypercapnic drive to the respiratory center is intact, and tachypnea would ensue.

Increased Work of Breathing and Muscle Fatigue

Hypercapnia may occur in patients suffering from muscle fatigue. This frequently happens when the function of breathing is increased, such as in patients with high airway resistance (e.g., morbidly obese patients, patients with tracheo-bronchial obstructions and bronchospasm). In the setting of persistently elevated function of breathing, patients may develop muscle exhaustion. Decreased ventilation with hypercapnia will follow. Increased function of breathing may also be observed in the setting of increased VCO_2 (e.g., hypercaloric parenteral nutrition) or in patients with severe metabolic acidosis (e.g., diabetic ketoacidosis) striving, with their compensatory ventilatory response, to raise their low blood pH.

Oxygen Administration to Patients with Chronic Respiratory Failure

The administration of an oxygen-enriched mixture to hypercapnic patients *may* cause decreased ventilation. In some patients with chronic respiratory failure, *hypoxemia* (and not hypercapnia) is the most important drive to the respiratory center. Correction of hypoxemia, in such cases, may cause further depression of ventilation. Consequently, in patients suffering from chronic pulmonary diseases, it is always important to assess both arterial $PaCO_2$ and PaO_2 levels.

Treatment of Respiratory Failure

The treatment of respiratory failure should be directed toward three different targets:

1. "Symptomatic" therapies, which aim at correcting the consequences (e.g., hypoxemia) of the disease causing the respiratory failure, when they are severe enough to put the patient at risk of death.
2. "Pathogenetic" therapies, which aim at interrupting the link relating the primary pathologic insult to its clinical consequences. An example would be corticosteroids administration to blunt the widespread inflammatory reaction in ARDS.[49]
3. "Etiologic" therapies, which aim at correcting the underlying disease triggering the respiratory failure. Antimicrobials to treat bacterial pneumonia or surgery in the case of abdominal insults would be appropriate examples.

Symptomatic, pathogenetic, and etiologic therapies should be delivered in concert so as to obtain the maximum possible result. Symptomatic therapies, however, have an outstanding importance, in that they allow us to buy time while pathogenetic and etiologic therapies can exert their effects.

Treatment of Hypoxemia

Although several treatment options are available, we believe that the correct therapeutic approach should be chosen after answering a few basic questions. Firstly, the mechanism causing hypoxemia should be determined. If hypoxemia is due to alveolar hypoxia, then symptomatic treatment

(i.e., moderate increase in inspired oxygen intrapulmonary fraction) is extremely simple and effective. In contrast, if hypoxemia is primarily due to intrapulmonary shunt, a few other considerations should guide treatment: (a) the presence of recruitable lung regions and their extent should be evaluated; (b) the level of positive end-expiratory pressure adequate for each particular patient should be determined with formal testing[15]; and (c) finally, the best way to deliver positive pressure ventilation (i.e., spontaneous breathing, assisted mechanical ventilation, controlled mechanical ventilation) should be determined.

Lung Recruitability

Lung recruitability may be defined as the amount of non-aerated lung tissue that regains aeration when appropriately high airway pressures are applied.[15] The concept of recruitability implies the presence of recruitable lung units that, despite being "closed," are "empty," i.e., they are simply collapsed. In contrast, non-recruitable lung units are "consolidated," i.e., filled with material other than gas, such as edema fluid, cell debris, blood, and pus. Hypoxemia in surgical patients, most commonly, originates from anesthesia-related atelectasis.[50] In this condition, lung volume is reduced due to gas loss, and the weight of the lung is normal (i.e., there is no fluid accumulation). Atelectasis may involve 5–10% of the lung parenchyma and can be fully resolved with the administration of airway pressures of 35–45 cmH_2O. The latter would correspond to transpulmonary pressures (i.e., the difference between airway pressure and pleural pressure) of 18–25 cmH_2O, which are in the range of pressures observed at total lung capacity when the lung parenchyma is fully distended.

Lung collapse is also observed, to some extent, in the presence of lung edema. ARDS is the most studied lung edema model. Indeed, while the total volume of an ARDS lung is nearly normal, its weight is abnormally increased. In this disease, the lung can be thought of as being composed of: (1) nearly normal regions; (2) consolidated (and not recruitable) regions; and (3) collapsed (and recruitable) regions, the latter collapsing under the excessive weight of the "superimposed" lung regions. Lung recruitability in ARDS is actually extremely variable, ranging from nearly 0 to 40–50% of the whole lung parenchyma (median 9–10%).[15]

The presence and extent of atelectatic tissue can be best determined with CT-scanning. In order to differentiate between collapsed and consolidated lung regions, however, lung CT images must be acquired at two different airway pressures (usually, 5 and 45 cmH_2O, the latter being reasonably able to open all recruitable lung parenchyma).

Opening anesthesia-related atelectasis is not a difficult task. Airway patency has to be ensured and sufficient opening pressure must be provided to the atelectatic regions. Sometimes deep breathing (i.e., generating high transpulmonary pressures) associated with optimal body positioning (i.e., atelectatic side up) is sufficient for reopening those regions. If atelectasis persists, positioning should be associated with positive pressure ventilation. A few hours of continuous positive airway pressure (CPAP) at 10 cmH_2O is usually sufficient to restore normal lung aeration.

The issue is more complicated when atelectasis develops within lung edema, such as in ARDS. In this case, deep inspiratory maneuvers are *not* sufficient to restore aeration to the collapsed pulmonary units, since they tend to collapse again during the expiratory phase. An adequate end-expiratory pressure is, therefore, also warranted. Different kinds of recruitment maneuvers have been reported in the literature.[51,52] We believe that recruitment maneuvers, in order to be effective, must satisfy two requirements: (1) they must provide sufficient transpulmonary pressure (45 cmH_2O airway pressure is usually sufficient, unless severe obesity or deformation of the chest wall are present, in which case higher pressure would have to be used); and (2) they should not cause major hemodynamic impairment, which is an inevitable consequence of the elevated intra-thoracic pressures. Accordingly, full lung inflation should last only a few seconds and may possibly be repeated, if required. In ARDS, however, we suggest that lung recruitability be quantified with CT-scanning. If low lung recruitability is demonstrated, recruitment maneuvers are useless. Selection of an adequate positive end-expiratory pressure is another important issue. The effects of lower or higher PEEP levels, in ARDS, have been tested in several studies.[53–55] These data do not support the concept that high PEEP (>15 cmH_2O) is better than low PEEP (<10 cmH_2O). We believe that the reason why these studies failed to prove the superiority of one PEEP level over another was that higher and lower PEEP were applied *randomly*, i.e., the individual patient's lung recruitability was not taken into account. It is well possible that the harmful consequences of administering high PEEP to patients with low lung recruitability may have cancelled out the beneficial effects observed when high PEEP was administered to higher recruitability patients. Likewise, the advantages of administering low PEEP to lower recruitability patients balanced out the disadvantages caused in a higher recruitability group. Indeed, at present, no universally accepted method for PEEP selection can be suggested. In our clinical practice, higher PEEP is administered to patients with higher lung recruitability, while lower PEEP is administered to patients with lower lung recruitability.

Positive Pressure Ventilation

According to the severity of respiratory failure, positive pressure ventilation may be delivered while the patient is breathing spontaneously, while he is being assisted with noninvasive strategies of mechanical ventilation, or while undergoing conventional invasive (i.e., with intubation) mechanical ventilation. A detailed description of all the various ventilation techniques is out of the scope of this chapter and is also, probably, useless. We believe that only a few basic principles have to be kept in mind. First, there is no doubt that avoiding

tracheal intubation carries several advantages: sedation is not usually required and, more importantly, the physiological ciliary movements and bacterial clearing processes within the trachea and airways remain intact. Unfortunately, in surgical patients these advantages, however, have to be weighed against the advantages of conventional mechanical ventilation, which include the easy access to the airways, the ability to titrate pain medication, the possibility to deliver known tidal volumes or airway pressures and gas mixtures of known composition (i.e., inspiratory oxygen fraction), and the capability to control the function of breathing. Noninvasive ventilation, either as continuous positive airway pressure (CPAP) in a spontaneously breathing patients or as an assist strategy of mechanical ventilation, should be reserved for those patients in whom one anticipates respiratory failure to resolve within a few hours. Otherwise, conventional mechanical ventilation should be initiated in order to avoid the life-threatening risk of endotracheal intubation in a severely hypoxic, hypercapnic, and muscle-fatifued patient.

Ventilatory Treatment

Until 20 years ago, mechanical ventilation was performed with low PEEP and high tidal volume.[56] The only concerns were the putative harm of high FiO_2 and hemodynamic impairment. During the last two decades, however, it has been progressively realized that mechanical ventilation, per se, may induce severe lung damage.[57–59] The paradigm of this phenomenon is exemplified by mechanical ventilation of the ARDS lung. Although "gentle lung treatment" and "lung rest" have been suggested since the middle 1970s,[60–62] these concepts gained widespread acceptance only after Hickling suggested a role for "permissive hypercapnia,"[63] and after this found its definite place in the ventilatory management of critical care patients following the publication of the ARDS net study dealing with lower vs. higher tidal volume ventilation.[64] Basically, the validity of "gentle lung treatment" has evolved from the concept of lung strain. When airway pressure is varied, lung volume changes. Lung strain may be quantified as the observed change in lung volume relative to the patient's resting lung volume (i.e., functional residual capacity, FRC). During normal breathing, lung strain is about 0.2–0.3, being normal tidal volume approximately 500 mL and FRC roughly 2,500 mL. In severe ARDS, aerated portions of the lung (i.e., the functional residual capacity) may add up to volume as low as 300–500 mL. It is then evident that ventilation with even normal tidal volumes may induce strains up to five- to tenfold the normal ones. Distortion of the structures of the lung brought about by these excessive strains is one of the main causes of ventilator-induced lung injury.[31] Excessive strain, in fact, activates endothelial and epithelial lung cells, stimulating cytokine production and neutrophil recruitment, with consequent full-blown inflammation.

Indeed, the cornerstone of "safe" mechanical ventilation in ARDS is *low tidal volume ventilation*, despite the fact that with this strategy some degree of hypercapnia has to be tolerated. The same concept, however, also applies to mechanical ventilation of the non-ARDS lung. It is not well recognized, for example, that during anesthesia with muscle paralysis, lung volume is decreased even in normal subjects. In certain cases, such as with morbidly obese patients, lung volume may be reduced to as low as that recorded in the most severe forms of ARDS (~350 mL). Indeed, the concept of low-tidal volume ventilation and "gentle lung treatment" could also be appropriately advocated during anesthesia. There is, in fact, growing evidence that even short-term mechanical ventilation, such as that administered during surgery, can damage lung tissue.[65–67] Indeed, at present, hypoventilation is not thought to represent a major problem but is believed to be an acceptable consequence of a rational way to perform "safe" mechanical ventilation. We do believe that severe hypoventilation, instead, should be monitored and possibly corrected. In order to do so, its causes (sedative drugs, complete reversal of curarization, airway clearance, bronchospasm correction) should be fully addressed.

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Mechanical Ventilation

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Positive pressure mechanical ventilation was first introduced during the polio epidemic about 50 years ago and represents the most common form of life support in a modern intensive care unit (ICU).[1] Management of the ventilated patient requires an understanding of how ventilators and the human respiratory system interact and what types of ventilators are available. In this chapter, we discuss the basics of mechanical ventilation, the most common modes of ventilation, the choice of ventilatory modalities in specific disease states, and the complications of mechanical ventilation.

Components of a Mechanical Breath

A mechanical ventilator is an automatic machine designed to provide all or part of the tidal ventilation. The complete ventilatory cycle controlled by a mechanical ventilator consists of four phases: (1) starting inspiration, occurring when the exhalation valve closes and fresh gas starts entering the lungs under pressure; (2) inspiration itself; (3) ending inspiration or cycling, that is the mechanism by which the ventilator determines when to terminate a positive pressure breath and allow exhalation to occur; and (4) exhalation, when fresh gas flow is stopped or interrupted and the exhalation valve is open.

Triggering

Triggering is how the ventilator determines when to start or initiate a positive pressure breath and is the point at which expiration changes to inspiration. Triggering can occur in response to time, pressure, and flow. Time triggering means that inspiratory flow starts because a preset expiratory time interval has elapsed. Pressure triggering occurs when the patient initiates a breath that reduces airway pressure to a set level or threshold in the respiratory circuit. The amount of pressure drop in the airway necessary to trigger the ventilator is called the sensitivity. The greater the pressure drop, necessary to trigger the ventilator, the less the sensitivity. Once the machine triggers a breath, the exhalation valve is closed, and the circuit is pressurized, which delivers a breath. Flow triggering occurs when inspiratory flow decreases in the respiratory circuit. The ventilator detects the patient's attempt to initiate a breath through changes in inspiratory flow created by the patient. Flow triggering has been shown to be more comfortable for the patient as it reduces the function of breathing.[2,3]

Cycling Mechanisms

Cycling is the changeover from inspiration to expiration, or the mechanism by which the ventilator determines when to terminate a positive pressure breath and allow exhalation to occur, the point at which inspiration changes to expiration. Cycling can occur in response to elapsed time, delivered volume, or a decrease in flow rate. Pressure-cycled mechanical ventilation was used in the past and will not be covered in this chapter.

Volume-Cycled Breaths

A set volume, determined by the clinician, is delivered by the machine. The pressure rise in the ventilator circuit is dependent on the airway resistance, the flow rate of gas, the volume delivered, and the compliance of lungs and chest wall. Volume-cycled ventilators can, in theory, deliver the entire set tidal volume no matter how high a pressure develops in the circuit, but this can be deleterious to the lungs. Therefore, volume cycling

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uses a "pop-off" valve to protect the lungs from pressure injury. This "pop-off" pressure is linked to the pressure limit alarm. If the pressure limit is reached, inspiration is terminated and the expiration valve is opened. The full tidal volume is not delivered as set. The length of inspiration with this mode of ventilation is determined by the inspiratory flow rate, the set tidal volume, and the I:E ratio.

Time-Cycled Breaths

In time-cycled breaths the inspiratory time is preset. Inspiration continues for the preset time. Exhalation begins at the end of inspiration when the inspiratory time has elapsed. Time cycling is typically used in conjunction with pressure preset ventilation where the airway pressure is maintained constant during inspiration. Inspiratory flow is high at the beginning but tapers off as the airway pressure quickly rises to the preset level. The delivered tidal volume varies depending on inspiratory time, lung compliance, and airway resistance.

As the inspiratory time is set, it is possible to adjust the inhalation:exhalation (I:E) ratio. This can be adjusted to 2:1 or 3:1 (inverse-ratio I:E), for example, depending on the needs of the patient. The advantage of this mode of ventilation is that it limits inspiratory pressure in patients with acute respiratory distress syndrome (ARDS).[4] As airflow is higher during the initial part of inspiration, the majority of the inspired volume is delivered early in the inspiratory cycle. This allows for more uniform distribution of tidal volume throughout the lung during the latter part of inspiration and theoretically should result in improved ventilation–perfusion matching and improved oxygenation.[5] Another advantage is that it provides enough flow in case of an air leak, aiming to maintain the airway pressure during inspiratory time.

Flow-Cycled Breaths

Paradoxically, the mode of ventilation called pressure support involves breaths that are flow-cycled. Flow-cycling takes place when the ventilator detects a decrease in the inspiratory flow rate. Typically, the decrease in the flow rate necessary to terminate inspiration is 25% of the initial flow rate. In pressure support ventilation, a breath is initiated by a very high level of inspiratory flow. Almost immediately, airway pressure increases to the preset level of pressure (hence the name "pressure-support"). If airflow continued at its initial high level, airway pressure would rise because of the lungs filling (compliance, elastic recoil) and airflow resistance throughout the airways. Therefore, the ventilator adjusts flow downward to maintain the preset pressure level and continues until the flow rate has fallen to the level that results in cessation of inspiration and the start of exhalation.

Flow-cycled breaths are also pressure preset, meaning there will be no increase in pressure above this preset level as a result of changes in the airways or ventilator circuit (e.g., coughing, endotracheal tube kinking, or narrowing by secretions) or as a result of changes in respiratory system compliance (e.g., pulmonary edema), and inspiration will be terminated when flow rate decreases as described previously. Flow-cycled breaths are therefore not uniform in size but change in response to patient conditions. As a result, pressure support or flow-cycling may not be advisable when delivery of an exact sized breath is desired. With pressure support or flow-cycled breaths, inspiration is initiated by the patient. The tidal volume also depends on the inspiratory effort: the greater the effort, the longer the inspiratory flow is maintained.

Modes of Ventilation

Common modes of ventilation include assist-control (AC), synchronized intermittent mechanical ventilation (SIMV), pressure support ventilation (PSV), airway pressure-release ventilation (APRV), and high frequency oscillatory ventilation (HFOV).

Assist-Control Ventilation

With AC ventilation, the ventilator delivers a breath either when triggered by a patient's inspiratory effort (assisted) or independently, if such an effort does not occur within a preselected period (controlled). The patient receives the preset rate in conjunction with tidal volume (AC volume ventilation) or pressure (pressure control ventilation or PCV) even in the absence of any respiratory effort. However, additional breaths can be triggered by the patient. When there is a respiratory effort and the trigger is sensed, the preset tidal volume or preset pressure is delivered. If no patient effort occurs within the preselected time period, the ventilator will deliver the breath at a preset rate (backup rate). If the patient's spontaneous respiratory rate exceeds the preset rate, all the additional breaths are also fully supported. The work of breathing in AC mode is minimal and near complete rest is given to the patient. Volume AC ventilation guarantees the delivery of a set tidal volume, but can produce excessive inspiratory pressures. The PCV reduces lung injury, limiting the peak inspiratory pressure, but can result in low tidal volumes causing hypercapnia and a respiratory acidosis (Fig. 23.1a, b).

Synchronized Intermittent Mandatory Ventilation

SIMV is an improvement on the original, intermittent mandatory ventilation (IMV) that involves delivering a set number of volume-cycled breaths. The patient can breathe spontaneously between machine breaths. However, IMV suffers from patient-ventilator dyssynchrony; the machine breaths are not coordinated in any way with the patient's attempts to breath. This can result in the machine attempting to deliver a breath as the patient exhales. In SIMV mode, the operator sets the minimum mandatory respiratory rate and typically sets tidal volume as a volume-cycled mode or, less commonly, pressure. The patient will get only this set rate as assisted breaths. The patient can breathe spontaneously between machine-initiated

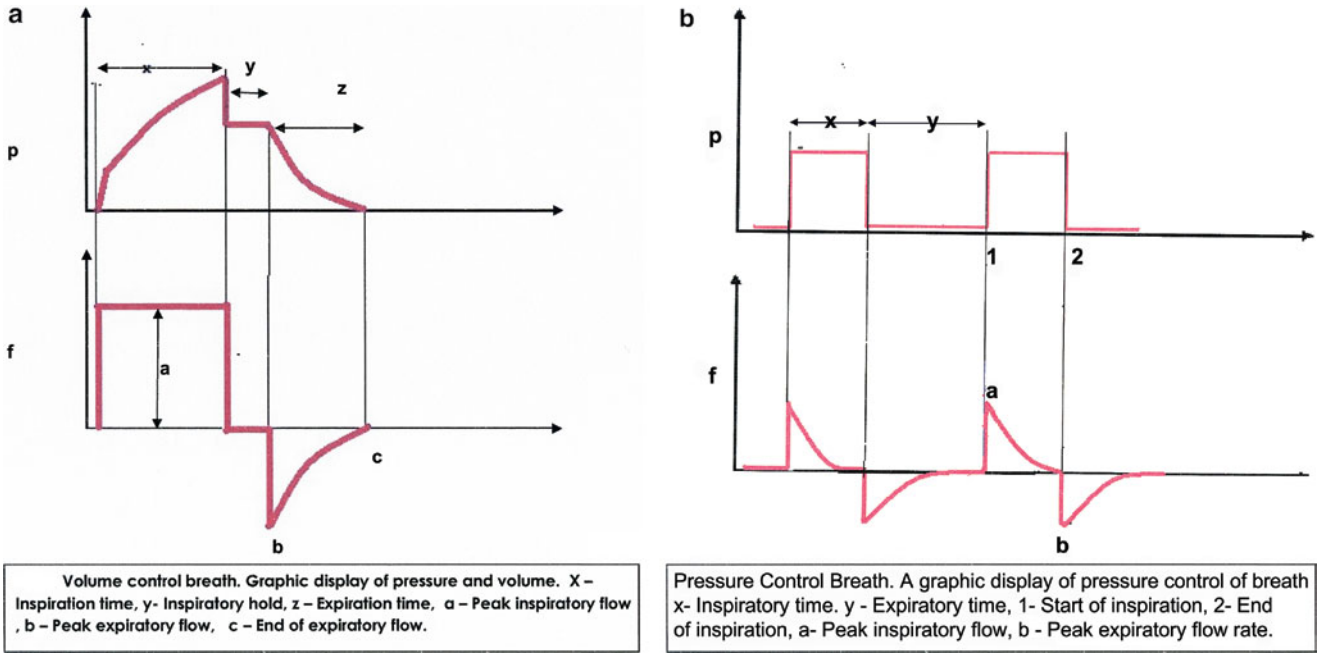

FIG. 23.1. AC mode: (**a**) a preset tidal volume (AC volume ventilation) or (**b**) a preset applied pressure (pressure controlled ventilation) is delivered at a preset minimum rate.

breaths. The other significant aspect of this mode of ventilation is that the ventilator becomes "sensitized" to detect any respiratory effort around the time that the next mechanical breath is due, in which case the mechanical breath is synchronized with the patient's attempt to inspire. Any breaths above the set rate are not assisted and the work of breathing can be very significant in this setting. Therefore, SIMV is often combined with pressure-support ventilation to support spontaneous breaths above the mandatory rate in order to offset the increased work of breathing of the spontaneous breaths.[6] Although SIMV was commonly utilized in weaning in the past, it is no longer the standard of care and its use should be discouraged because it may lengthen the period of weaning (Fig. 23.2).

Pressure Support Ventilation

This mode of ventilation is patient-triggered, pressure preset, and flow-cycled ventilation. The respiratory rate is determined by the patient. The tidal volume is dependent on the patient's effort, the degree of airway obstruction, and the compliance of the lungs. Because the patient controls the major components of the ventilation and because the patient receives breaths only when he/she initiates them, pressure support is well tolerated or at least better tolerated than in other modes of ventilation. The patient must have an intact respiratory drive and reasonable respiratory muscle strength for pressure support ventilation to be successful. Although the implementation of PSV in modern ventilators entails a back-up rate for safety, PSV should not be used if the patient's spontaneous respiratory rate is very low or if the respiratory drive is suppressed. Pressure support weaning is used in daily spontaneous breathing trials and has been shown to be effective in reducing the number of ventilator-dependent days[7] (Fig. 23.3).

Airway Pressure-Release Ventilation

This mode of ventilation was described by Downs et al. in 1987.[8] It is also referred to as BiVent or BiLevel ventilation and is a modified form of continuous positive airway pressure (CPAP) ventilation, whereby the patient is allowed to breathe spontaneously between two levels of CPAP. Periodically, the higher level of CPAP is released (decreased) to a lower level for a moment to allow a larger breath (exhalation) for carbon dioxide elimination. In essence, this is a pressure mode of ventilation designed to optimize lung recruitment. The brief exhalation is followed immediately by reinstitution of CPAP to its higher level to prevent alveolar de-recruitment. Functionally, this is a form of inverse ratio ventilation.

More specifically, APRV involves setting two pressure levels, P_{hi} and P_{lo}, and two time settings, T_{hi} and T_{lo}. P_{hi} and P_{lo} are two levels of CPAP, one high and one low. P_{lo} is also the level of positive end-expiratory pressure (PEEP). T_{hi} and T_{lo} are the times that P_{hi} and P_{lo} are maintained, respectively. T_{lo} is also known as the release time. The sum of T_{hi} and T_{lo} determine the number of cycles per minute. For example, if T_{hi} is 5 s and T_{lo} 1 s, each cycle is 6 s long and there are 10 such cycles per minute. The patient continues to breathe at his/her spontaneous rate as airway pressures cycle between the higher and lower levels of CPAP.

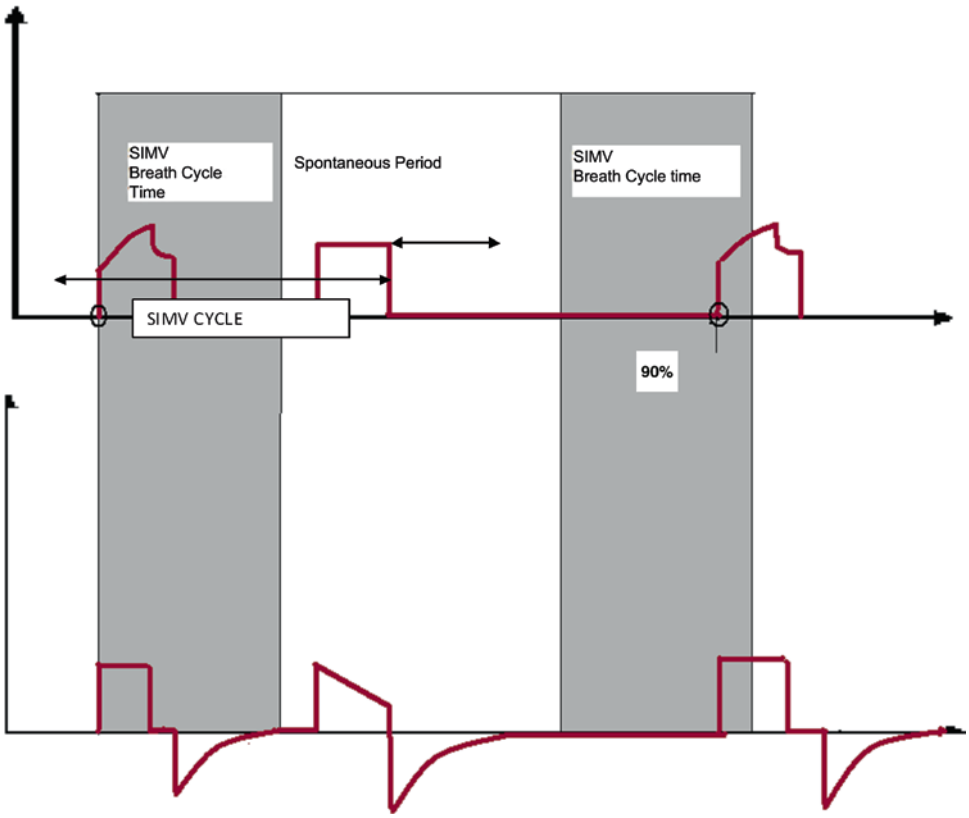

FIG. 23.2. SIMV mode. Graphic display of SIMV breaths and pressure support breath during spontaneous period. If SIMV rate is set at 10/min, the SIMV cycle is 6 s. If the breath cycle is set at 3 s, the spontaneous period would be 3 s. If the patient has not triggered a breath during the 90% of breath cycle, a mandatory breath will be delivered.

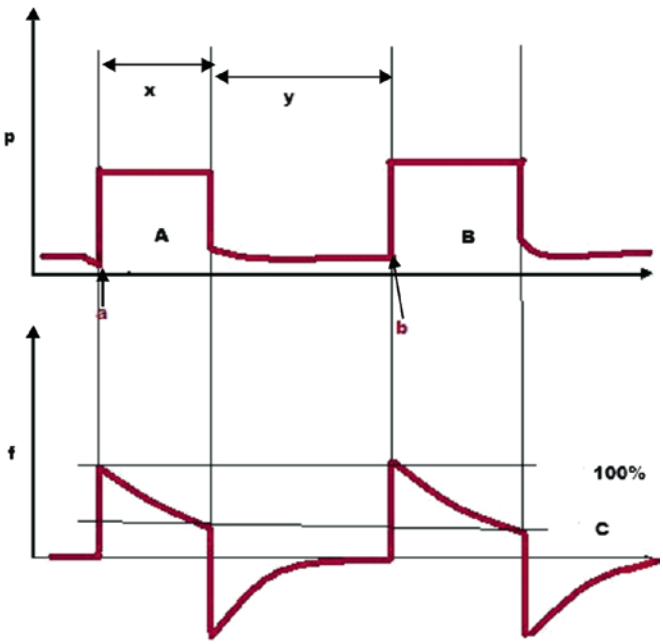

FIG. 23.3. PSV mode. Each pressure support breath is initiated by a spontaneous effort. As the level of pressure support remains the same in each breath, the peak airway pressures are similar.

APRV limits plateau airway pressures at the expense of increased mean airway pressure, and carbon dioxide elimination is achieved with lower minute ventilation. The fraction of inspired oxygen (FiO_2) requirement is lower for achieved arterial oxygen tension (PaO_2) compared to that for conventional ventilation. Patients seem to tolerate APRV well with levels of sedation that are lower than with conventional ventilator modes. As a result, patients contribute more to the minute ventilation with spontaneous breathing. Spontaneous breaths ventilate the areas of the lungs (posterior basal) that are not normally adequately ventilated by conventional mechanical ventilation.[9,10] This results in better ventilation and perfusion (V/Q) matching and improved oxygenation.[11,12] Although APRV is appealing because it improves oxygenation, it has not been shown to improve outcome in a variety of randomized trials.

As the respiratory muscles are used in active respiration, there is a distinct possibility for the muscles not to atrophy. There are even some reports of shorter ventilator days in trauma victims compared to historical controls on conventional ventilation. However, the exact role of APRV needs to be defined with more controlled clinical trials.[13] APRV can also be used as a weaning mode of ventilation (Fig. 23.4).

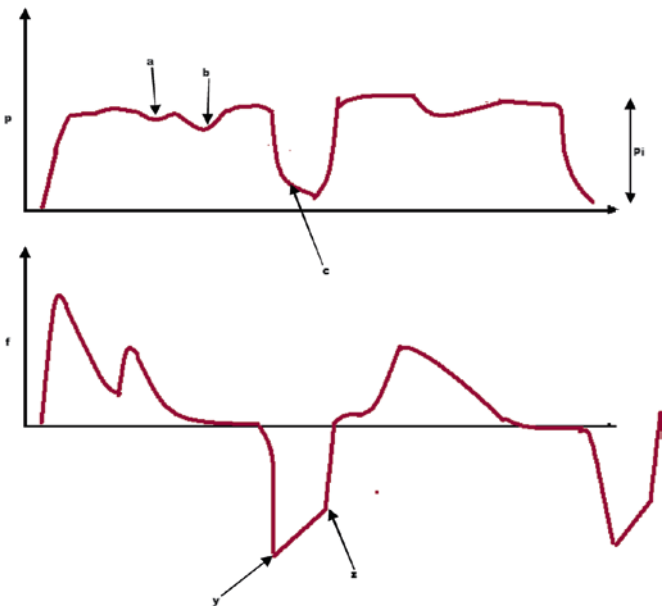

FIG. 23.4. Airway Pressure-Release Ventilation. Airway pressure is maintained at a specific level, and from time to time the airway pressure is reduced for a short duration in return to the baseline. This is in effect a bimodal level of airway pressure. Each decrease in airway pressure represents an exhalation phase.

High Frequency Oscillatory Ventilation

HFOV was developed to ventilate neonates. By maintaining higher than normal mean airway pressure and rapid oscillation of pressure delivering small tidal volumes (1–4 ml/KG), HFOV meets the criteria for open lung and lung protective ventilation. Animal studies support the premise that HFOV is lung protective and reduces the incidence of ventilator induced lung injury (VILI).[14,15]

In humans, HFOV has been used as a rescue therapy for patients that fail maximal conventional therapy for refractory ARDS. Clinical trials, so far, fail to support HFOV as a superior form of ventilatory support in the ARDS patient population and further studies are necessary to define the role of this mode of ventilation in patients with acute lung injury.[16]

Continuous Positive Airway Pressure and Positive End-Expiratory Pressure

CPAP involves positive airway pressure throughout the respiratory cycle, regardless of whether the patient is breathing spontaneously or receiving positive pressure ventilation. In contrast, PEEP describes positive pressure at the end of expiration, regardless of the airway pressure throughout the rest of respiratory cycle. If the airway pressure never falls below ambient pressure, which typically occurs with positive pressure ventilation with pressure support, then CPAP and PEEP are synonymous. On the other hand, if the airway pressure falls below ambient pressure at any point in the cycle, then the positive pressure is no longer continuous and PEEP is present. This occurs with spontaneous breathing and no pressure support (Fig. 23.5). Because CPAP and PEEP have similar characteristics, they will be used interchangeably.

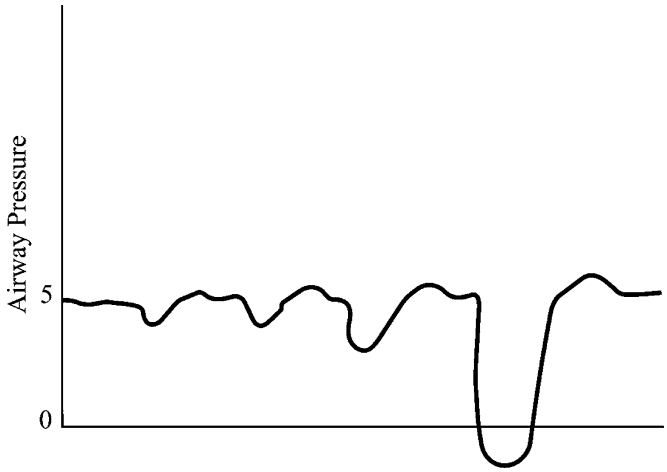

FIG. 23.5. Illustration of CPAP and PEEP during spontaneous ventilation. During the first three breaths, airway pressure remains above atmospheric pressure for the entire respiratory cycle (CPAP). During the fourth breath, the airway pressure falls below zero at end inspiration (PEEP).

PEEP opens the collapsed alveoli (lung recruitment) and increases the functional residual capacity (FRC) that is reduced in disease states such as ARDS, interstitial lung disease, hypersensitivity pneumonitis, and pulmonary edema. By recruiting collapsed alveoli there is a better matching of ventilation and perfusion and less perfusion to unventilated alveoli, resulting in improved oxygenation. The restoration of the lung volume improves compliance, which reduces the work of breathing.[17–24] As oxygenation improves, the FiO_2 and plateau pressure can be lowered to safer levels. On the other hand, PEEP applied to a mechanically ventilated patient prevents repeated collapse and distention of alveoli reducing cytokine release, the systemic inflammatory response, and lung injury.

The reported complications of PEEP include pulmonary barotrauma, increased intracranial pressure, and decreased venous return and cardiac output. High PEEP levels may cause an increase in the size of the right ventricle and a leftward shift of the interventricular septum resulting in a decrease in left ventricular size, compliance, and contractility.[21,24]

Noninvasive Positive Pressure Ventilation

Typically all patients who require positive pressure mechanical ventilation need endotracheal intubation in order to deliver breaths under pressure, maintain positive end-expiratory pressure, and protect the airway from aspiration of gastric contents or oropharyngeal secretions. However, during the last 15 years, interest has been shifting toward administering positive pressure ventilatory support by a face mask covering both the

mouth and nose in order to avoid endotracheal intubation and its associated complications. The most attractive part of noninvasive positive pressure ventilation (NPPV) is the ease of application and the demonstrated benefit and survival advantage in certain disease states.[25–35]

NPPV is most often delivered by bilevel positive airway pressure (BiPAP), which provides positive pressure to assist inspiration. With BiPAP, the ventilator cycles between high positive pressure inspiration and low positive pressure exhalation. When inspiration is detected by a fall in inspiratory pressure, a breath is instituted. Inspiration is terminated when the inspiratory flow falls below a preset threshold level, usually 25% of the initial flow rate. The inspiratory pressure is referred to as IPAP and the expiratory pressure as EPAP. This is essentially pressure support ventilation with PEEP in a more conventional sense.[36] The IPAP is equivalent to the sum of PEEP and the PSV level whereas the EPAP is equivalent to the PEEP level. Thus, a bilevel setting of 12 cm of H_2O for inspiratory pressure and 5 cm of H_2O for expiratory pressure is equivalent to a standard ventilator setting of 7 cm of H_2O for pressure support and 5 cm of H_2O for PEEP.

NPPV has been tried in many disease states and there is evidence to support its use in chronic obstructive airway disease (COPD), acute cardiogenic pulmonary edema, and in immunecompromised patients, conditions characterized by ventilatory rather than oxygenation failure. A trial of NPPV may be justified in postoperative respiratory failure, but because supporting evidence is not as compelling, patients should be carefully selected and intubation and mechanical ventilation should be instituted early if NPPV is not successful.

NPPV should be the first choice for treating respiratory failure in patients with COPD exacerbations.[37] NPPV rapidly improves vital signs and gas exchange and reduces the need for endotracheal intubation, decreasing mortality and length of hospital stay.[38] NPPV can also be used as a "bridge" to early extubation in patients with exacerbation of COPD. Candidates are those who require endotracheal intubation and show improvement but fail weaning trials and can tolerate NPPV. Nava observed that patients who displayed persistent weaning failure and who were subsequently managed with early extubation to NPPV had a shorter duration of intubation, fewer ICU days, shorter hospital stay, and improved ICU and hospital survival.[39]

There is also evidence to support the use of NPPV in acute cardiogenic pulmonary edema where it lowers intubation and mortality rates.[40] The use of NIV is also well described in immunocompromised patients – such as those with hematologic malignancies, acquired immunodeficiency syndrome (AIDS), and following solid-organ or bone marrow transplants – who are at high risk for infectious complications from endotracheal intubation. Although there is evidence to support the use of NIV in several pathologic conditions, clinicians should strongly consider intubation without delay if patients do not have an early favorable response to NIV.

Initial settings are *usually* IPAP of 10–15 cmH_2O and EPAP of 5 cmH_2O with a FiO_2 of 1.0 in a spontaneous mode. Vital signs, pulse oximetry, mental status, and respiratory rate should be followed closely. NPPV is best utilized in the alert, cooperative patient whose respiratory condition is expected to improve in 48–72 h. Patients should be hemodynamically stable, able to control airway secretions, and able to coordinate with the ventilator. The successful initiation of noninvasive ventilation is highly dependent on patient cooperation. For this reason, an experienced clinician conveying an air of confidence and assuredness to patients is crucial for success. Contraindications to NPPV include hemodynamic instability, myocardial ischemia or severe arrhythmias, altered mental status, inability to protect the airway, active upper gastrointestinal hemorrhage, and facial trauma. The complications associated with the NPPV mask include discomfort, local damage to facial tissue, eye irritation, and mild gastric distension.

Mechanical Ventilation for Specific Diseases

Acute Respiratory Distress Syndrome

Management of the patient with ARDS primarily consists of supportive care. The immediate goals include the treatment of the underlying process, the establishment of effective mechanical ventilation, and the anticipation and prevention of medical complications. Over the past years, numerous ventilator strategies have been suggested with variable results and the management of ARDS remains a challenge for the critical-care community.

It is well recognized that high inflationary pressures used with traditional tidal volumes of 10–12 ml/kg lead to overdistention of the alveoli resulting in VILI.[41–48] In addition, cyclic alveolar expansion during inspiration and collapse during expiration create shear forces that distend adjacent alveoli and extend the area of lung injury. Open lung ventilation is a ventilatory strategy that combines small tidal volumes (to lessen alveolar overdistension) and an applied PEEP above the low inflection point on the pressure volume curve (to lessen cyclic atelectasis) (Fig. 23.6). It was hypothesized that using a tidal volume of 6 ml/kg of predicted body weight, a plateau pressure less than 30 cmH_2O, and PEEP would improve survival in patients with ARDS. A multicenter clinical trial by the ARDS Network tested this hypothesis in acute lung injury and ARDS and demonstrated reduced mortality compared to the traditional tidal volume group.[47]

In the ARDS Network's multicenter ALVEOLI trial,[48] patients who were undergoing low tidal volume ventilation for ARDS were randomly assigned to a high PEEP strategy or low PEEP strategy. The mean applied PEEP was 13 cmH_2O in the high PEEP group and 8 cmH_2O in the low PEEP group. Although the high PEEP strategy improved gas exchange and compliance, the plateau pressure was higher and the mortality was unchanged. More recently, two additional trials[49,50] studying high PEEP versus low PEEP were completed. They also

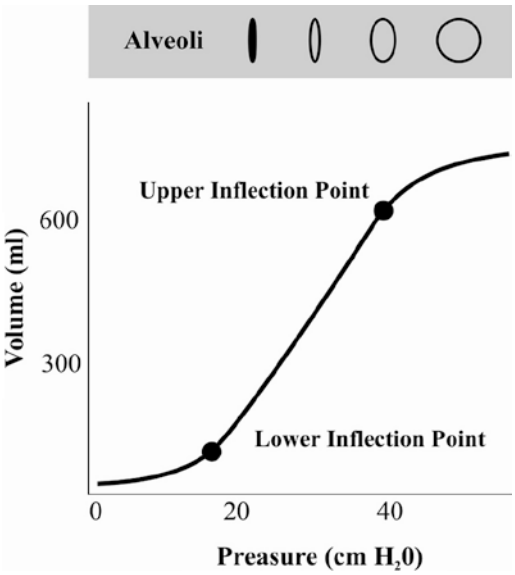

FIG. 23.6. Static compliance curve of the respiratory system. PEEP above the lower inflection point optimizes compliance and is thought to minimize shear injury. A plateau pressure below the upper inflection point avoids overdistension.

showed that a higher PEEP strategy improved oxygenation, reduced FiO_2 exposure, and improved compliance over a lower PEEP strategy, but did not show a mortality benefit. In conclusion, in the management of patients with ARDS, low tidal volume ventilation (i.e., 6 ml/Kg predicted body weight), with the maintenance of plateau pressures of <30 cmH_2O, remains the standard of care as it is the only method of mechanical ventilation that has been proven to reduce the mortality rate. Although the use of PEEP is advocated in patients with ARDS, the use of high PEEP may be helpful only in selected situations of severe hypoxemia and its use is not widely recommended.

The lung-protective ventilation with the use of low tidal volumes may result in hypercapnia and a respiratory acidosis, which is well tolerated by most patients, except by those patients with elevated intracranial pressure. Although there is no consensus about whether the acidemia should be corrected, some authors suggest administering sodium bicarbonate, carbicarb, or tris-hydroxymethyl aminomethane (THAM) as needed to maintain an arterial pH in the range of 7.15–7.20.

Chronic Obstructive Airway Disease

Patients with exacerbation of COPD may require ventilatory support. This can be either NPPV or invasive mechanical ventilation. NPPV has been efficacious as a mode of first-line ventilatory support for acute respiratory failure, reducing the need for endotracheal ventilation, shortening hospital length of stay, and decreasing hospital mortality.[51,52]

Initial settings for BiPAP might include pressure support between 5 and 8 cm H_2O above the EPAP, which can be increased slowly to achieve a reduction in partial pressure of carbon dioxide in arterial blood ($PaCO_2$) of 5–10 mmHg. The EPAP is often set at 5 cm H_2O to offset effects of intrinsic positive end-expiratory pressure (PEEPi) and to prevent atelectasis. Those patients who respond will show a reduction in respiratory rate, heart rate, and $PaCO_2$.

In the absence of improvement using NPPV, intubation and positive pressure ventilation should be initiated without delay. The mode of mechanical ventilation for an intubated patient can include assist control (volume AC or pressure AC) or pressure support. PSV is better tolerated by most patients as it allows the patient to regulate the depth and rate of breathing. As with NPPV, initial ventilatory pressure support can be set between 5 and 8 cm H_2O above EPAP and increased slowly to achieve a reduction of $PaCO_2$ of 5–10 mmHg. As with NPPV, PEEP is often set at 5 cm H_2O to offset effects of PEEPi and to prevent atelectasis. As the patient improves, one can see a significant reduction in respiratory rate, which can be observed at the bedside. By monitoring the respiratory rate and utilizing pulse oximetry, the need for frequent blood gases may be lessened.

Invasive ventilatory support for COPD should be aimed at reducing the work of breathing. The initial treatment of COPD exacerbations requiring mechanical ventilation includes stabilization of the patient, correction of any underlying conditions contributing to respiratory failure, and resting of the patient's respiratory muscles. Once these have been achieved, consideration of ventilator weaning is appropriate. If inspiration is initiated prior to complete exhalation, air trapping in the alveoli ensues. The pressure difference between the alveolar pressure at the end of expiration and the level of PEEP that is set is known as PEEPi, which is not recorded on the ventilator gauge. An expiratory hold gives adequate time for airway pressures to equilibrate and gives an indication of the presence of PEEPi. PEEPi has significant and similar effects on the respiratory system and hemodynamic parameters as PEEP. Venous return is impaired with a reduction in cardiac output and blood pressure. Patients may have difficulty triggering the ventilator because it takes additional effort to lower airway pressures and PEEPi also increases airway pressures leading to barotrauma and volutrauma. In fact, a sudden onset of hypotension in a ventilated patient with COPD is often due to PEEPi. PEEPi can be quickly identified as the cause of the problem by giving 100% oxygen and disconnecting the ventilator for 30–45 s or reducing the respiratory rate to 2–3 breaths/minute for a similar time. Blood pressure will rapidly return to baseline if hyperinflation is relieved. PEEPi is treated by decreasing inspiratory time effectively and increasing the time for exhalation. The decrease in the inspiratory time is obtained by increasing the inspiratory flow rate, or by decreasing the respiratory rate or tidal volume. If the increase in the flow rate is excessive, the patient might fight the ventilator; and if the flow is inadequate, the patient would attempt to over breathe the ventilator. Both conditions lead to patient-ventilator asynchrony.

Airway Obstruction: Bronchial Asthma

Endotracheal intubation should be instituted on patients who display signs of imminent cardiopulmonary collapse such as central cyanosis, hypotension, profound tachycardia, pulsus paradoxus, altered mental status, or frank depression of consciousness. The decision to intubate should be primarily on the basis of clinical deterioration, but worsening hypercapnia despite therapy and hypoxemia is worrisome and generally indicates a need for urgent intubation and institution of mechanical ventilation.

The goal of ventilation in asthmatic patients is to oxygenate while minimizing the risk of barotrauma. The significant elevation of CO_2 might suggest that hyperventilation would be appropriate. However, hyperventilation in the setting of airway obstruction can lead to excessive airway pressures and air trapping, both of which can result in barotraumas such as a pneumothorax or pneumomediastinum. Therefore, normocapnia is not the immediate aim when initiating mechanical ventilation in an asthmatic patient. Hypercapnia is a result of increase in dead space due to bronchospasm. Normoxic hypercapnia is an acceptable goal of ventilatory support in status asthmaticus.[53,54] Initial ventilatory settings are a tidal volume of 7–9 ml/Kg (or less, as dictated by airway pressures) and a respiratory rate of 12–16 breaths/minute (or less, again as indicated by airway pressures and oxygenation) with an inspiratory flow 80–100 l/min. High levels of inspiratory flow associated with low tidal volumes could significantly raise airway resistance, compromising the ventilation. The only significant contraindication to this approach is in a patient with significant raised intracranial pressure. In this instance the relative risks and benefits of hypercarbia versus normocapnia will need to be weighed.

Development of auto PEEP is a constant threat in asthmatic patients and should be suspected when hypotension with an increase in airway pressures is noted. Treatment includes the reduction in the respiratory rate and tidal volume to increase the time for exhalation as well as sedation to reduce the respiratory drive.

Complications of Mechanical Ventilation

Barotrauma

Pneumothorax or pneumomediastinum can occur as a result of mechanical ventilation.[55–62] Studies have suggested means of avoiding barotrauma.[63] In general, appropriate setting of mechanical ventilation parameters and vigilance is required to avoid and prevent this complication. The most feared complication is a tension pneumothorax. Use of low tidal volumes, limiting peak and plateau pressures, and avoiding high levels of PEEPi may be helpful in preventing a pneumothorax or a tension pneumothorax. Periodic chest roentgenograms may be helpful in detecting hyperinflation or a pneumomediastinum that could presage the development of a pneumothorax. However, the sudden development of hypoxemia, high airway pressures, hypotension or cardiovascular collapse, unilateral absence of breath sounds, and tracheal shift away from the side of absent breath sounds in the setting of mechanical ventilation are all very suggestive of a tension pneumothorax. It should be treated as an emergency with immediate needle decompression followed by chest tube thoracostomy.

Ventilator-Associated Lung Injury

It is well accepted that mechanical ventilation can produce as well as exacerbate lung injury and contribute to patient morbidity and mortality. The mechanisms involved include volutrauma and atelectrauma. Volutrauma occurs when the lung is overinflated and alveoli are overstretched, whereas atelectrauma is caused by the repetitive opening and closing of recruitable alveoli. Whether caused by overstretching or repetitive opening and closing of alveoli, ventilator-induced lung injury (VILI) is associated with the production and release of inflammatory mediators that not only contribute to the exacerbation of local pulmonary injury but may also lead to a systemic inflammatory response that can result in multiple organ dysfunction syndrome. Ventilation strategies aimed at minimizing lung injury consist of the use of low tidal volumes and limitation of the plateau pressure to minimize alveolar overdistension in conjunction with PEEP to reduce repetitive recruitment and de-recruitment of lung units.[64–77]

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is a constant threat to all mechanically ventilated patients and refers to pneumonia that arises more than 48 h after endotracheal intubation.[78] It occurs in ~9–27% of mechanically ventilated patients and the incidence increases with duration of ventilation.[79] The risk is the highest during the early days with ~3% incidence during the first 5 days, ~2% during the next 5 days, and drops to ~1% thereafter.[80] Early onset VAP (first 4 days) has a better prognosis as it is more likely caused by sensitive organisms.

The diagnosis is suspected in patients with a new infiltrate and evidence that the infiltrate is of infectious origin. There also should be at least two clinical features including fever greater than 38°C, leukocytosis or leukopenia, and change in secretion pattern such as purulence or change in color. There is much debate in clinical and research communities regarding how best to culture the causative organisms. Whether bronchoalveolar lavage (BAL), mini-BAL, protected specimen brush, or tracheal cultures should be employed as a diagnostic tool is being debated in the research community.

Early diagnosis and appropriate treatment will improve patient outcome with VAP and intensive care unit practice should be aimed at minimizing its risks. Semi-recumbent position, early enteric feeding (preferably post-pyloric tube

placement), prevention of aspiration, protocol-driven weaning and early extubation, and avoidance of reintubation have been shown to reduce the incidence of VAP (see Chap. 29).

Weaning from Mechanical Ventilation

Weaning from mechanical ventilation can be defined as the process of abruptly or gradually withdrawing ventilatory support and includes the interruption of mechanical ventilation and extubation. Although major advances have been made in the area of weaning from mechanical ventilation, no weaning technique has proven universally successful, probably because of the diversity of etiologies for respiratory failure. Some patients are weaned prematurely, necessitating reintubation, and yet others are maintained on mechanical ventilation for far too long, resulting in an increased patient morbidity and unnecessary costs.

Two large multicenter studies[81,82] have demonstrated that mechanical ventilation can be discontinued abruptly in approximately 75% of patients whose underlying cause of respiratory failure has either improved or been resolved. The remaining patients will need progressive withdrawal from mechanical ventilation that may comprise up to 40% of the total time that they require mechanical ventilation.[83]

All patients should be evaluated on a daily basis in order to determine whether or not they are candidates for discontinuation of mechanical ventilation. A patient should be considered a candidate for withdrawal of ventilatory support if (a) the underlying disease process that necessitated mechanical ventilation has significantly improved or is resolved, (b) the gas exchange is adequate (most studies define this condition as an arterial oxygen tension/fractional inspired oxygen ratio higher than 200), (c) hemodynamic variables are stable, and (d) there is the capability to initiate spontaneous breaths.[84]

Once a patient has been considered ready to be weaned, a spontaneous breathing trial (SBT) will determine the suitability for discontinuation of mechanical ventilation. The most common methods to perform the SBT are a T-piece, minimum pressure support ranging from 5 to 7 cmH_2O (for example 7 cmH_2O PS/5 cmH_2O PEEP) or a continuous positive airway pressure for 30 min. Failure of SBT is defined by objective indices such as tachypnea, tachycardia, hypertension, hypotension, hypoxemia, acidosis, and arrhythmias and by subjective indices, such as agitation, distress, depressed mental status, diaphoresis, and evidence of increasing effort. Failure of an SBT is often related to cardiovascular dysfunction or the inability of the respiratory pump to support the work of breathing.[7,85,86]

A patient who successfully completes an SBT has been shown to have a high likelihood of tolerating ventilator discontinuation permanently. The next step is removing the artificial airway. The decision as to whether the artificial airway can be removed is made on the basis of the patient's alertness, the ability to follow commands, a good strong cough, and a minimal need for suctioning (Fig. 23.7) The risk for post-extubation upper airway obstruction needs to be considered. Some have advocated the routine use of the "cuff leak test" (assessing the presence of air movement around a deflated endotracheal tube cuff) before extubation, but conflicting data exist on the utility of this practice. If there is clinical concern about post-extubation upper airway edema and/or inflammation, corticosteroids can be administered 24 h before the planned extubation[85,86]

The patients who do not tolerate SBT (weaning failure) require a return to partial or full ventilatory support to allow adequate rest before the next trial. Patients who fail SBT have to be evaluated to correct reversible causes of respiratory failure. Common causes of SBT failure include poor respiratory mechanics that may be improved by tight control of the fluid balance and fluid restriction, appropriate titration of bronchodilators in patients with COPD, mobilization of the patient, physiotherapy, and nutrition.[7] The SBT should be repeated frequently in order to determine the earliest time at which the patient can be successfully extubated. Pressure support or assist-control ventilation modes should be favored in patients failing an initial trial.

Indices to Predict Outcome

Numerous studies have evaluated a wide variety of physiologic indices to predict the ability of the patient to sustain spontaneous ventilation without mechanical ventilation. Yang and Tobin[88] studied the predictive power of several weaning indices and showed that the rapid, shallow breathing index (*f*/*V*t), (where "*f*" is the respiratory rate and "*V*t" is the tidal volume) measured during the first minute of a T-piece trial had the best predictive value. In their study, 95% of patients with *f*/*V*t ratio greater than 105 failed a test of spontaneous breathing.

Respiratory Failure After Extubation

Failure to oxygenate or ventilate after extubation usually occurs within 48–72 h following removal of the endotracheal tube and often requires non-invasive (NIV) or invasive ventilatory support. It is a complication associated with an increased risk of nosocomial pneumonia, longer length of ICU and hospital stay, and higher mortality. In a more recent study, the use of NIV in the management of respiratory failure after extubation did not show clinical benefits, although the clinical trial included a small proportion of patients with chronic respiratory failure. In contrast, NIV is effective in avoiding respiratory failure immediately after extubation in patients at risk for this complication, particularly those with chronic respiratory disorders and hypercapnic respiratory failure.[89] It is strongly recommended to not delay reintubation if NIV does not improve oxygenation and ventilation soon after its initiation.

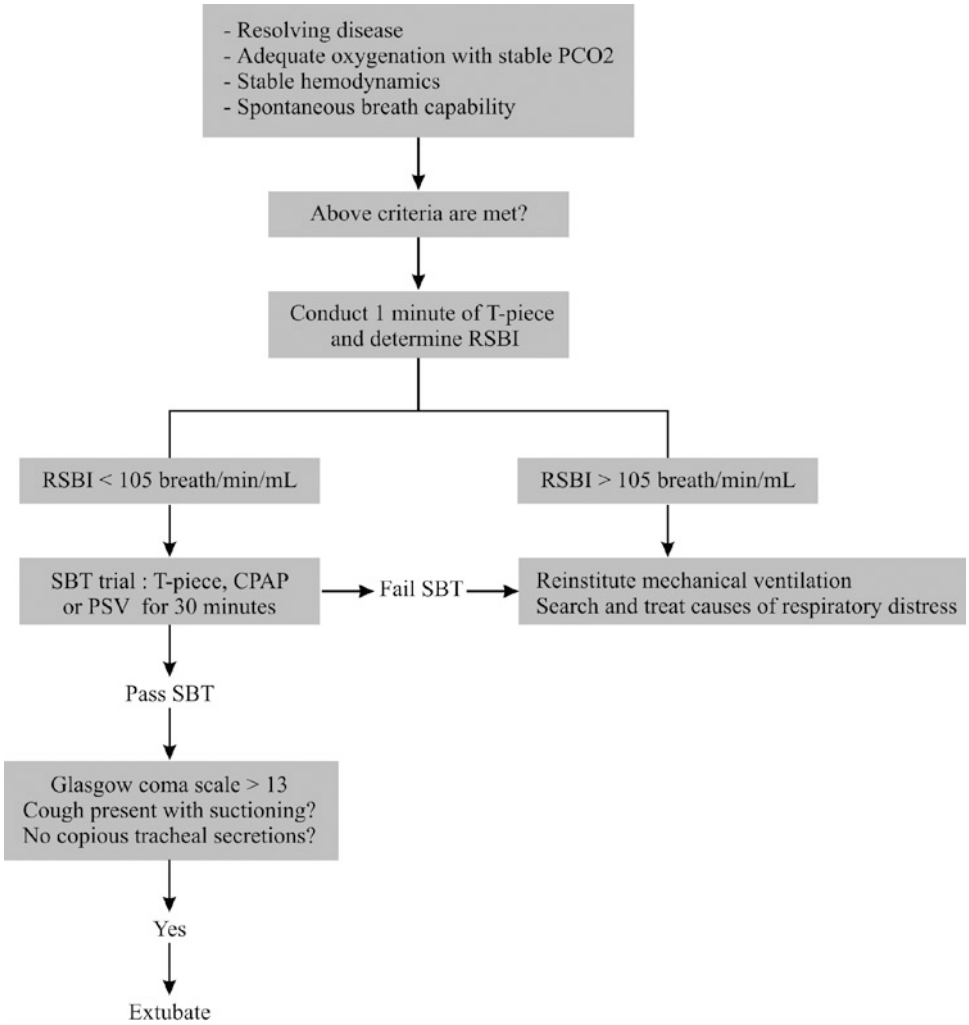

FIG. 23.7. Suggested approach to weaning a patient from mechanical ventilation. RSBI = rapid shalow breathing index.

Weaning by Protocols

A number of studies revealed that the weaning by protocols resulted in a reduction in the duration of mechanical ventilation, length of ICU stay, and hospital costs.[90,91] Although the use of protocols may be beneficial in most ICUs, they may be less necessary in a closed ICU with generous physician staffing and structured rounds.[92]

Tracheostomy

Tracheostomy has become an increasingly common intervention in surgical ICU (SICU) with the introduction of percutaneous techniques performed by the intensivist at the bedside. Proposed advantages for tracheostomy include easier airway management, improved patient comfort and communication, reduction in sedative use, earlier weaning from respiratory support, improved respiratory mechanics, earlier transition to oral feeding, reduced oropharyngeal trauma, and prevention of ventilator-acquired pneumonia.[7,85,93] Adverse effects include misplacement or displacement of the tracheostomy tube, hemorrhage, obstruction, impairment of swallowing reflexes, and late tracheal stenosis. Many studies have been aimed at finding the optimal time for performing a tracheostomy in the SICU patient. American guidelines from 2001 advocate the use of tracheostomy if the expected time on mechanical ventilation is judged to exceed 21 days.[7,85,93] More recently, the use of earlier tracheostomy has been recommended by several authors in different categories of patients. Two large-scale prospective clinical trials are presently running to answer the controversy about the timing of tracheostomy.

Conclusion

Mechanical ventilation represents an essential component in the management of the critically ill surgical patient. Years of research and experience have propelled our understanding of

pulmonary pathophysiology and respiratory mechanics, resulting in the proliferation of new modes of mechanical ventilatory support. The goals include providing adequate oxygenation and ventilation, minimizing ventilator-associated lung injury, rehabilitating fatigued and deconditioned respiratory muscles, and promoting successful weaning. Mechanical ventilation is not therapeutic but rather supportive and hence, a search for the underlying disease process should always be initiated and appropriate therapy instituted. Because mechanical ventilation is associated with serious complications, its indications should be reassessed on a daily basis and weaning and extubation employed as soon as possible. Care must be individualized to include an understanding of the patient's health status before hospital admission, an appreciation for acute comorbidities, social and religious factors, and patient and family preferences regarding the relief of pain and suffering, and the prolongation of life when further medical support is futile.

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24
Venous Thromboembolism

Andrew G. Villanueva and Nicholas P. Tsapatsaris

The term *venous thromboembolism* (VTE) describes a spectrum of disease that includes both deep venous thrombosis (DVT) and pulmonary embolism (PE), and more precisely reflects a sequential disease process.[1] Despite a better understanding of the pathophysiology of VTE, improvements in diagnostic approaches and techniques, extensive clinical research of treatment options, and widespread recognition of the importance of DVT prevention, VTE continues to be a common and life-threatening problem. It has been estimated that acute PE accounts for 5–10% of deaths among hospitalized patients and that up to three million persons die of PE annually in the United States[2,3]; up to 70% of deaths are not recognized antemortem.[4] The prevalence of proximal DVT in patients admitted to an intensive care unit (ICU) has been reported as approximately 10%, and the incidence of proximal DVT during critical illness as being 9–40% in older studies.[5–7] More recent studies seem to show a decrease in the prevalence and incidence of VTE in ICUs[8]; in a large multicenter observational study, Cook et al. reported that among 12,338 ICU patients in Canada, 1–2% developed VTE and that most of these cases resulted from prophylaxis failure rather than failure to provide prophylaxis.[9] Nevertheless, VTE prevention, diagnosis, and treatment remain challenging problems in the ICU.

This chapter focuses on the aspects of VTE most relevant to those clinicians caring for patients in the ICU. It describes some fundamental concepts regarding the pathophysiology, risk factors, diagnostic approaches, treatment, and prevention for VTE. A plethora of articles have been written about VTE over the years; this review emphasizes the new developments in diagnostic and treatment approaches that have recently become clinically applicable.

Fundamental Concepts

The vast majority of thrombi that embolize the pulmonary artery circulation arise from the lower extremity veins; the clots usually form in the deep veins in the calf and then propagate into the proximal veins, including and above the popliteal veins, from which they are more likely to embolize.[10] It has been estimated that 10–50% of patients with a lower extremity DVT develop a PE.[11,12] In older studies, more than 90% of PEs reportedly came from DVT of the lower extremities.[13] Thrombi within the calf posed little risk for embolization, whereas thrombi within or proximal to the popliteal veins posed a significant risk.[14] Even though this concept generally remains true, more recent studies have shown that the upper extremities, cardiac chambers, and central catheters are becoming increasingly recognized as sources for thromboemboli.[15,16] This may be especially important in the ICU, where central venous catheters are frequently used.

There are no reliable prospective data on the natural history of VTE, but retrospective studies have suggested that 75–90% of deaths from PE occur within the first few hours after the embolic event.[17] When death occurs after the first few hours, it is the result of recurrent emboli.[1] Even though VTE has significant detrimental effects on pulmonary gas exchange, the mortality from PE is almost always the result of profound hemodynamic consequences such as right ventricular failure, which can be demonstrated echocardiographically,[18–20] or refractory hypotension, rather than severe hypoxemia.[21] In their classic paper, Dalen and Alpert estimated that the mortality resulting from an untreated PE was about 30% compared to 8% in patients treated with heparin,[17] and thereby highlighted the importance of making the often-missed diagnosis of VTE.[22]

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Risk Factors for VTE

Risk factors for VTE can be acquired, inherited, or mixed (Table 24.1). An underlying cause for thrombosis can currently be identified in up to 80% of cases.[23]

Acquired Causes of Venous Thrombosis

Age is a major determinant of thrombotic risk. The risk increases from 1 per 10,000 per year before 40 years of age to 1 in 100 per year over 75 years of age.[24,25] Malignancy increases the risk of thrombosis five- to tenfold.[26] The estimates of the prevalence of cancer among patients with a VTE vary from 3 to 18%.[27,28] Oral contraceptives have been reported to confer a four- to sixfold increased risk,[29,30] and hormone replacement therapy a two- to fourfold increased risk.[31] Pregnancy and the puerperium reportedly increase the risk five- to tenfold.[32] Among patients with venous thrombosis, a lupus anticoagulant or antiphospholipid antibodies have been reported in 5–15%, and this abnormality has been estimated to lead to a ninefold increased risk of thrombosis.[33,34] Heparin-induced thrombocytopenia (HIT), estimated to occur in approximately 2.6% of patients exposed to heparin for more than 4 days,[35] has been increasingly recognized as a risk factor for venous thromboembolism,[36] including upper-extremity DVT.[37] The uncommon disease, polycythemia vera, can cause both bleeding and thrombotic complications.[38]

Common risk factors for venous thrombosis in patients in the ICU include surgery, trauma, and immobilization. Surgery is a major risk factor for VTE, with a 30–50% risk reported in orthopedic, neurologic, abdominal, gynecologic, and urologic surgeries.[39–43] Trauma is also an important risk factor for VTE, with the highest risk of about 50–60% in patients with head trauma, spinal injury, and fractures of the pelvis, femur, and tibia.[44,45] A recent population-based case-control study showed that minor leg injuries within the previous 4 weeks resulted in a fivefold increase in VTE.[46] Immobilization is a well-known cause of VTE and explains the occurrence of thrombosis from paralysis, bed rest, plaster casts, and prolonged travel.[47] It has been estimated that even with the widespread use of anticoagulant prophylaxis, surgery and immobilization each still accounted for 15% of all thrombotic events.[48] Other reported ICU-acquired VTE risk factors include mechanical ventilation, femoral venous catheter, and use of medications for sedation and neuromuscular blockade.[8]

The major risk factor for upper-extremity DVT (DVTUE) is the presence of indwelling central venous catheters, commonly used in the ICU.[49] While the prevalence of DVTUE in critically ill patients with central venous catheters is unknown, a recent prospective study showed that 12% of cancer patients with a central venous catheter developed DVTUE – most of whom were asymptomatic. [50] The significance of upper-extremity DVT has been minimized compared with iliofemoral thrombosis, probably because of the erroneous belief that subsequent pulmonary thromboembolism is rare. Although the risk for PE from an upper-extremity DVT is not precisely known, it is felt to be higher than previously appreciated,[49] particularly if the venous thrombosis is related to placement of a catheter, such as a central venous catheter [15] or a peripherally inserted central catheter (PICC).[51]

Table 24.1. Risk factors for VTE.

Acquired	Inherited	Mixed
Age >40	Associated with deficiencies of coagulation factor inhibitors [52]	Hyperhomocysteinemia
Previous thrombosis	Antithrombin deficiency	High levels of factor VIII
Immobilization	Protein C deficiency	
Major surgery	Protein S deficiency	
Orthopedic surgery	Associated with increases in the levels or function of the coagulation factors [52]	
Trauma	Factor V Leiden	
Spinal cord injury	Prothrombin G20210A mutation	
Malignancy	Other disorders	
Oral contraceptives	Dysfibrinogenemia	
Hormonal replacement therapy	Plasminogen deficiency	
Pregnancy and postpartum		
Congestive heart failure		
Myeloproliferative disorders		
Anti-phospholipid antibody syndrome		
Polycythemia vera		
Heparin-induced thrombocytopenia		

Inherited Causes of Venous Thrombosis

Congenital thrombophilic states associated with venous thrombosis can be classified into two groups: those associated with reduced levels of the inhibitors of the coagulation cascade and those associated with increased levels or function of the coagulation factors (see Table 24.1).[52] Before the early 1990s, a hereditary cause of thrombophilia was rarely found in patients with a VTE because protein C,[53,54] protein S,[55,56] and antithrombin III [57] deficiencies were the only identifiable causes. Deficiencies in these natural anticoagulants are very rare, affecting less than 1% of the population, and account for only 1–2% of venous thrombotic events in the population.[58,59] In the 1990s, two prothrombotic mutations were discovered and found to be prevalent in white populations – the factor V Arg506Gln mutation (more commonly known as factor V Leiden), which results in resistance to activated protein C,[60] and the prothrombin mutation (G20210A), which increases prothrombin activity.[61] Heterozygous carriers of factor V Leiden are present in 3–15% of this population and are three to eight times more likely to have venous thrombosis compared to the general population,[62,63] 35 times more likely if using oral contraceptives,[64] and 50 times more likely if having sustained a minor leg injury within the previous 4 weeks.[46] Patients who are homozygous for factor V Leiden are 80 times more likely to develop venous thrombosis.[65] Heterozygous carriers for prothrombin mutation are present in 2–6%

TABLE 24.2. Risks for and incidence of a first episode of venous thrombosis.[59]

Variable	Relative risk	Annual incidence (%)
Normal	1	0.008
Hyperhomocysteinemia	2.5	0.02
Prothrombin G20210A mutation	2.8	0.02
Oral contraceptive use	4	0.03
Factor V Leiden heterozygote	7	0.06
Oral contraceptive use and factor V Leiden mutation	35	0.3
Minor leg injury and factor V Leiden mutation [46]	50	
Factor V Leiden homozygotes	80	0.5–1

and are at a slightly higher risk of having venous thrombosis compared to the general population.[51] Among unselected white patients presenting with an initial symptomatic episode of DVT, 12–20% will be heterozygous for the factor V Leiden mutation, compared to 6% of asymptomatic control populations, and 6% will be heterozygous for the prothrombin G20210A mutation, compared to 2% of asymptomatic control populations.[59] There are some forms of thrombophilia that are thought to be of mixed genetic and acquired origin and may increase the risk for VTE, including hyperhomocysteinemia [66] and elevated levels of factor VIII.[67,68]

While routine screening for thrombophilia in all patients presenting with VTE is unnecessary,[69] thrombophilia testing may be warranted in patients with recurrent thromboembolism, in young patients, or in patients without obvious acquired risk factors for VTE.[10] A thrombophilia evaluation for hereditary and mixed risk factors should include genetic testing for factor V Leiden and prothrombin G20210A mutation, functional assays for antithrombin, protein C, and protein S, as well as testing for lupus anticoagulant and antiphospholipid antibodies, and blood homocysteine levels.[59] Identifying abnormalities of one or more of these factors may not necessarily affect the immediate treatment plan, but may influence decisions about duration of treatment and future prevention strategies (Table 24.2).

Diagnosis of Acute VTE

Imaging Studies for the Diagnosis of DVT

A patient's symptoms and physical examination cannot be used to confirm or exclude the diagnosis of DVT.[70] The presence of erythema, warmth, pain, swelling, tenderness, or Homan's sign may suggest the presence of DVT, but the sensitivity is reported to range from 56 to 82% and the specificity 26–74%.[71] Conversely, the lack of these findings does not exclude the diagnosis. Thus, diagnostic imaging studies are always required.

Contrast Venography

Contrast venography (CV) is considered the gold standard test in that it has a sensitivity and specificity that approaches 100%,[72] and indeed remains the gold standard for assessing the incidence of DVT in clinical trials.[73] CV, however, is invasive, painful, and contraindicated in patients with renal insufficiency and severe intravenous contrast allergy. Noninvasive tests, which have also proven to be highly sensitive and specific in most clinical situations, are more appropriate for first-line imaging.

Impedance Plethysmography

Impedance plethysmography (IPG) relies on the principle that the volume of blood in the leg affects its ability to conduct an applied electrical current, which is inversely proportional to the impedance between two electrodes placed along the calf. To conduct the test, a small electrical current is passed between one set of electrodes, while the second measures changes in voltage. A cuff is inflated around the thigh to obstruct venous outflow but not arterial inflow. As blood accumulates in the leg below the cuff, impedance between the calf electrodes falls. When venous pressure builds to the point that it equals that of the cuff, venous outflow is reestablished and the tracing plateaus. The sudden release of cuff pressure results in a sudden surge of blood flow proximally (the blood volume of the leg decreases), resulting in a rapid increase in impedance. If DVT is present in any major vein that drains the lower extremity (from the popliteal to the iliac veins), the rate of venous emptying will be significantly slower and the tracing will have a slower return toward baseline.[74] This technique is insensitive to the thrombi that do not decrease the rate of venous outflow, such as most calf thrombi and small, unobstructing thrombi in the proximal veins.

Numerous studies have documented excellent sensitivity and specificity for IPG. Hull et al. reported a sensitivity of 93% and a specificity of 96%.[74] IPG is noninvasive, safe, inexpensive, and portable, but its accuracy is operator-dependent, it does not detect unobstructing thrombi, and it cannot be used to diagnose upper-extremity DVT. IPG is no longer in widespread clinical use and has been supplanted by compression ultrasound as preferred screening for DVT.

Compression Ultrasound with Venous Imaging (Duplex Ultrasound)

Compression ultrasound with venous imaging is noninvasive, widely available, and has been proved accurate for diagnosing acute, symptomatic lower extremity proximal DVT. In contrast to Doppler venous flow detection, which only offers information about blood flow, real-time sonography permits two-dimensional cross-sectional representation of the lower extremity veins. The combination of the two techniques is termed "duplex ultrasound" and has evolved as the preferred initial diagnostic modality to assess for DVT of the lower and

upper extremities. To examine for lower extremity DVT, the patient is positioned supine and the deep femoral vein is evaluated at the bifurcation of the common femoral vein. Compression is applied with the transducer at short intervals over the entire length of the vessels, including the calf veins. The diagnosis of DVT is made if there is noncompressibility of the vein (the most reliable sign) or if an echogenic thrombus, venous distention, complete absence of spectral or color Doppler signal from the vein lumen, or loss of flow phasicity during the Valsalva maneuver is detected.

Several prospective trials have shown a high degree of reliability, particularly for proximal lower extremity DVT, with a sensitivity of 89–100%, specificity of 86–100%, positive predictive value of 96–100%, and negative predictive value of 75–100%.[75–80] A recent systematic review found that the odds of positive ultrasound in proximal veins were 379 times higher and in distal veins 32 times higher among patients with DVT than among those without DVT.[81] Another systematic review and meta-analysis of 100 cohort studies confirmed that venous ultrasound has a high sensitivity (94.2%) and specificity (93.8%) for detecting proximal venous thrombosis, but is less sensitive (63.5%) for the detection of calf vein DVT.[82] Ultrasonography yields fewer false-positive results than impedance plethysmography.[83] Duplex ultrasonography using compression ultrasound and color-flow Doppler has a higher sensitivity for detecting distal DVT but slightly lower specificity than ultrasonography using compression ultrasound alone.[82]

Compression ultrasonography is clinically useful because it is noninvasive, safe, available, relatively inexpensive, portable, and good for detecting proximal lower-extremity DVT and upper-extremity DVT.[84,85] The limitations include operator dependency and decreased accuracy in chronic DVT, pelvic DVT, and patients who are massively obese, as well as in those with severe edema and casts or other immobilization devices.[72]

Computed Tomography Venography

Duplex ultrasonography has become the most used noninvasive imaging modality to diagnose DVT of the upper and lower extremities because of its ease of use and documented reliability. Computed tomography venography (CTV), however, especially when combined with computed tomography angiography (CTA) may have practical advantages over duplex ultrasonography – CTV is a better modality for detecting inferior vena cava or pelvic vein thrombosis, can be done as a single study with CTA for evaluating VTE,[86] and may be more readily available during evenings and night time in many institutions.[87]

Studies comparing CTV with ultrasonography have shown similar test sensitivity and specificity with a prospective case series of 650 consecutive patients, which showed that CTV had a sensitivity of 97% and a specificity of 100% for diagnosing femoropopliteal DVT compared to duplex ultrasonography.[88] Cham et al. found that 35% of patients undergoing combined CTA and CTV as an evaluation for PE had DVT but no PE, thus increasing the diagnosis of VTE by 18%.[89] Most recently, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II trial reported that combined CTA and CTV increased the sensitivity for diagnosing VTE from 83 to 90%, compared to CTA alone.[90]

Compared to ultrasonography, there are relative disadvantages of CTV, including the need for higher volumes of intravenous iodinated contrast when combined with CTA, thus increasing the risk for nephrotoxicity, higher cost, and a significant increase in radiation exposure.[87] The risks, benefits, and value for combined CTA and CTV are still being debated and there is as yet no consensus as to whether CTV should be routinely added to CTA as part of the imaging evaluation for VTE.

Magnetic Resonance Imaging

Reports comparing magnetic resonance imaging (MRI) to CV in diagnosing DVT have found a high degree of sensitivity and specificity. A recent systematic review and meta-analysis reported a sensitivity of 91.5% and a specificity of 94.8% for magnetic resonance venography (MRV).[91] There are some potential advantages of MRV over IPG, ultrasonography, and CV in that the sensitivity and specificity are excellent for both thigh DVT and pelvic vein thrombosis[92]; it can also be potentially useful for upper-extremity DVT.[93] Other advantages include lack of operator dependency and the ability to scan patients without intravenous access or contrast.[87] The disadvantages include the fact that the patient cannot have any metallic devices, which makes the procedure less useful in patients who have had surgery or sustained trauma. Other contraindications include claustrophobia, the inability to cooperate, and massive obesity. It is also an expensive test and requires transporting the patient to the MRI scanner, in contrast to ultrasonography, which can be done at the patient's bedside. MRV, therefore, remains a second-line diagnostic tool because of higher cost, technical limitations, limited availability, and logistical constraints,[87] particularly in critically ill patients.

Imaging Studies for the Diagnosis of Acute PE

Like DVT, the clinical diagnosis of PE cannot be made with any degree of confidence without objective testing. Studies continue to show the frequent failure to make the antemortem diagnosis of PE; autopsy studies have shown that the diagnosis is missed 55–70% of the time.[4,94] PE should be considered when a patient presents with unexplained dyspnea, tachypnea, tachycardia, hypotension, or worsening gas exchange. The most sensitive test should be the clinician's degree of clinical suspicion for VTE, which will be discussed in more detail in the section on Diagnosis of Acute VTE: Diagnostic Approach. If the clinical suspicion is sufficiently high, one can proceed with imaging studies.

Chest Radiography

While the chest radiograph is often normal, most patients with an acute PE have an abnormal chest radiograph, particularly patients in an ICU. Common findings include cardiac enlargement, atelectasis, pleural effusion, pulmonary infiltrates, and elevation of a hemidiaphragm.[95,96] Classic findings suggestive of PE such as Hampton's hump or decreased vascularity (Westermark's sign) are suggestive, but occur infrequently. In general, the chest radiograph cannot be used to prove or exclude PE. It can, however, be helpful in diagnosing other processes that can cause symptoms similar to those associated with PE, such as pneumonia, pneumothorax, or rib fractures.

Contrast-Enhanced Computed Tomography Arteriography

Since the previous edition of this textbook,[97] contrast-enhanced computed tomography (CT) arteriography, also known as helical CT, spiral CT, or CT angiography (CTA), has supplanted the ventilation–perfusion scan as the most commonly used initial imaging study for the diagnosis of PE. [87,98] CTA is done by having a patient continuously move through the CT scanner to allow for concurrent scanning by a constantly-rotating gantry and detector system; it results in rapid scanning with continuous volume acquisitions obtained during a single breath. A contrast bolus is required for imaging of the pulmonary vasculature; after contrast administration, CTA provides visualization of the pulmonary arterial system, which current-generation CT scanners scan as multiplanar images and three-dimensional reconstructions.[87] Radiographic findings diagnostic of an acute PE include an intravascular filling defect in a pulmonary artery that partially or completely occludes the vessel and is often associated with increased diameter of the affected vessel.[87] The technique has the greatest sensitivity for emboli in the main, lobar, or segmental pulmonary arteries; the sensitivity is generally poor for subsegmental emboli on using single-detector CT scanners, but multidetector-row CT scanners are increasing the sensitivity for detecting subsegmental emboli.[99,100] While the ability to detect subsegmental thromboemboli may seem advantageous, there is debate and uncertainty about the clinical importance of these radiographic findings and the need for treatment based on these findings.[101,102]

Several studies in the 1990s, reviewed by Rathbun et al.[103] and Mullins et al.[104] in 2000, reported a wide range of sensitivity (53–100%) and specificity (81–100%) for CTA. In their systematic reviews, both Rathbun et al.[103] and Mullins et al.[104] noted that none of the studies reviewed met all of their methodological criteria for adequately evaluating the sensitivity and specificity of a diagnostic test, and that additional research was required to establish the role of CTA for the diagnosis of PE in clinical practice. A more recent systematic literature review by Eng et al.[105] also sounded caution about the quality of published studies, citing potential selection bias and heterogeneity in the studies they reviewed. Despite the lack of scientific rigor of earlier studies, there has been widespread acceptance of CTA as the first-line imaging study for the diagnosis of PE by clinicians because of its wide availability, speed, ability to diagnose nonthrombotic pathology, and the ability to combine CTA with CTV, as mentioned earlier, to look for both PE and DVT.[87] Moreover, the rapid technological advancement of CT scanners has outpaced the ability of clinical investigators to perform large, multicenter randomized controlled trials for each new generation of scanners. Recent studies have reported high sensitivity and specificity of CTA when combined with a diagnostic algorithm that includes preliminary laboratory testing, determination of a pretest probability, and, if necessary, other imaging studies [90,100,106,107]; these studies will be discussed in detail later in this chapter.

The major limitations of CTA include the need for experience and expertise of the interpreting radiologist, expense, lack of portability, and the risk associated with intravenous contrast bolus, including allergy and nephrotoxicity.[87] ICU patients, therefore, with iodinated contrast allergy or renal insufficiency, or who exceed weight limits of the x-ray table, are not good candidates for CTA.

Ventilation–Perfusion Scan

The ventilation–perfusion (V/Q) scan, once the pivotal diagnostic test in evaluating patients for the presence of an acute PE, is now reserved for patients who cannot undergo CTA or who are at healthcare facilities in which either CTA is not available or the radiologists are inexperienced in interpreting the study.

V/Q scanning is most likely to be diagnostic in the absence of cardiopulmonary disease, but the test is non-diagnostic in most cases. The original PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study was a multicenter trial designed to determine the sensitivity and specificity of the V/Q scan in patients with suspected acute PE, using pulmonary angiography as the gold standard.[107] The usefulness of the test increased when it was combined with the clinical suspicion for an acute PE (Table 24.3). For example, a high probability V/Q scan with a high clinical suspicion was reliably predictive (96%) of an acute PE, whereas a normal V/Q scan made an acute PE unlikely regardless of the clinical suspicion (4%). The results also showed that a PE is often present in patients with non-diagnostic lung scans (not high probability or not normal) when associated with a high clinical suspicion of a PE (59%). The PIOPED data therefore showed that high-probability V/Q scans and normal V/Q scans were clinically helpful, particularly when combined with clinical probability, but that patients with intermediate or low probability V/Q scan results (73% of the scans) needed further imaging to diagnose or exclude VTE.

Studies have addressed the use of V/Q scans in patients in an ICU. Worsley et al.[108] analyzed the PIOPED data and concluded that very low and low probability scans in patients who had either prolonged immobilization, lower-limb trauma, recent surgery,

Table 24.3. Using clinical assessment and V/Q scan to diagnose acute PE. Percent of patients in each category with an acute PE documented by pulmonary angiogram. Data are summarized from the PIOPED study.[108]

V/Q scan probability	High clinical probability (%)	Intermediate clinical probability (%)	Low clinical probability (%)
High	96	88	56
Intermediate	66	28	16
Low	40	16	4
Normal	0	6	2

or central venous instrumentation were associated with a fourfold increased incidence of PE compared with that in patients without these risk factors. Therefore, in patients at high risk for DVT, a low-probability V/Q scan cannot exclude the diagnosis, and further testing may be necessary. The value of the perfusion scan without a ventilation scan has been examined. The available data suggest that if a ventilation scan cannot be performed (for example, on a patient requiring mechanical ventilation), an isolated perfusion scan is useful if the scan is high probability or normal.[109] Henry et al. evaluated the PIOPED data and found that scintigraphic lung scans and clinical assessment retain their diagnostic value even in critically ill patients.[110]

Magnetic Resonance Imaging

MRI may be a useful tool for diagnosing acute PE. Potential advantages over CTA include lack of radiation, lower risk for nephrotoxicity with gadolinium contrast agents compared to iodinated contrast material, and the ability to assess perfusion to the smaller pulmonary vessels.[111] Three prospective studies [112–114] comparing magnetic resonance angiography (MRA) to pulmonary angiography, still considered the gold-standard test for PE, reported that the sensitivity of gadolinium-enhanced MRA ranged from 77 to 100%, and the specificity ranged from 95 to 98%. In a detailed review of these studies, Stein[112] noted that there were insufficient data to recommend where gadolinium-enhanced MRA might fit in a diagnostic pathway for VTE, but suggested that it may be useful in patients with a strong suspicion of PE, in whom the results of other tests are equivocal and radiographic contrast materials or ionizing radiations are relatively contraindicated.

Disadvantages of MRA include longer imaging times (compared to CTA), limited availability, need for special expertise in interpreting studies, poor inter-observer agreement,[115] and lower sensitivity for the detection of emboli in smaller vessels, compared to CTA.[115] For reasons mentioned in the previous section on diagnosing DVT, the use of MRI with patients in the surgical ICU may be limited.

Echocardiography

Right ventricular failure is usually the mechanism for death caused by acute PE. Dysfunction of the right ventricle frequently accompanies massive PE caused by large emboli or recurrent emboli. Studies of patients with documented PE have revealed that more than 80% of patients have imaging or Doppler abnormalities of right ventricular size or function that may suggest acute PE,[116] but this finding is nonspecific. Visualization of large emboli within the main pulmonary artery has been reported with surface echocardiography, but this appears to be unusual.[117] Transesophageal echocardiography has been used to document emboli in the main or right and left pulmonary arteries.[118–120] Even though echocardiography cannot currently be recommended as a primary test to diagnose acute PE, it may be particularly helpful with critically ill patients who are suspected of having a PE (especially as a cause for sudden hypotension) and who are too unstable to be transported from the ICU. It can also be a useful tool for prognostication and risk stratification,[121] as it has been shown that among patients with satisfactory blood pressure the finding of moderate or severe right ventricular dysfunction is a potent marker of increased short-term [122] and long-term mortality.[123] Fremont et al. reported in a retrospective study of 950 patients that an echocardiographic right ventricle/left ventricle (RV/LV) ratio greater than or equal to 0.9 was an independent predictive factor for hospital mortality.[124]

Pulmonary Angiography

Pulmonary arteriography is still considered the gold standard for diagnosing acute PE, but its use has been declining. When V/Q scanning was the sole noninvasive imaging technique for diagnosing acute PE, pulmonary angiography was often required as the majority of V/Q scans were non-diagnostic. With CTA supplanting V/Q scans as the most commonly used imaging technique, the frequency of non-diagnostic tests has diminished, resulting in a decreased need for pulmonary angiography. The major indication for its use is when a definitive diagnosis for VTE is required and when noninvasive imaging tests for PE and DVT are non-diagnostic or equivocal, especially in the setting of a high clinical suspicion (see Diagnosis of Acute VTE: Diagnostic Approach).

Pulmonary angiography is generally safe. The mortality in the PIOPED study was 0.5%.[108] Significant complications included cardiopulmonary compromise that required intubation or cardiopulmonary resuscitation (0.4%), renal failure that required dialysis (0.3%), and groin hematomas that necessitated transfusion (0.2%). Major complications were reported to occur more commonly in patients who had been transferred for the procedure from medical ICUs. Four percent of such patients developed major complications compared to 1% of patients who were not as critically ill.

Other Diagnostic Tools

Electrocardiography

Electrocardiogram (ECG) abnormalities often accompany PE but also are nonspecific. Findings include T-wave changes, ST-segment abnormalities, and left or right axis deviation. In the

Urokinase Pulmonary Embolism Trial,[125] 26% of patients with a massive or submassive PE had manifestations of acute cor pulmonale (S1 Q3 T3 pattern, right bundle branch block, P-wave pulmonale, or right axis deviation). A low prevalence of ECG findings specific to PE was also found in the PIOPED study.[108]

Arterial Blood Gas Analysis

Hypoxemia is common in acute PE, but a normal arterial oxygen tension (PaO_2) does not exclude the diagnosis, and although the alveolar-arterial difference is usually elevated, it may be normal, especially in patients without preexisting cardiopulmonary disease.[126]

D-Dimer

D-dimer is a specific degradation product released into the circulation when cross-linked fibrin undergoes endogenous fibrinolysis. As it was recognized that tests for D-dimer could be potentially helpful tools for excluding venous thromboembolism, there have been hundreds of articles published on this subject, many of which were recently systematically reviewed.[127] In their review, Stein et al. summarized data from 78 prospective studies that compared results of different D-dimer assays with findings of objective tests in patients with suspected DVT or PE and found that a negative result using the quantitative rapid enzyme-lined immunosorbent assay (ELISA) method (<500 ng/ml) was "as diagnostically useful as a normal lung scan or negative duplex ultrasonography finding," with a sensitivity of 0.97 for DVT and 0.98 for PE and a negative likelihood ratio of 0.08 for DVT and 0.05 for PE.[128] The authors also reviewed data on other assays such as latex agglutination and whole blood agglutination assays and found that the sensitivities and negative predictive values were significantly lower compared to the quantitative rapid ELISA.

D-dimer assays are most useful and cost-effective when evaluating patients who are at low risk for VTE in order to exclude DVT or PE. By definition, patients in the ICU or who have recently undergone major surgery are at high risk for VTE. They often have elevated D-dimer because of activation of their clotting and endogenous fibrinolytic system. D-dimer assay is therefore not a recommended test for the exclusion of VTE in this high-risk patient cohort.

Troponin

Cardiac troponin levels, while not diagnostic for venous thromboembolism, may be elevated because of acute right heart overload.[128] Elevated cardiac troponin levels do not help in establishing the diagnosis of VTE, but may help predict prognosis and thereby affect treatment decisions.[129,130] In a meta-analysis of 20 studies (1,985 patients) Becattini et al.[131] found that elevated troponin levels were significantly associated with short-term mortality (odds ratio [OR] 5.24), with death resulting from PE (OR 9.44); moreover, in the subgroup of hemodynamically stable patients, an elevated troponin level was still associated with a higher mortality (OR 5.90).

Brain Natriuretic Peptide

Like cardiac troponin levels, brain natriuretic peptide (BNP) levels are not useful in either diagnosing or excluding VTE but may help predict outcome.[132,133] For example, ten Wolde et al.,[133] in a study of 110 consecutive patients, found a 16.7% risk of death in patients with PE and elevated BNP levels and Kucher et al.,[134] in a study of 73 consecutive patients, found that those patients with adverse events after a PE had a higher BNP level (mean 194.2 pg/ml), compared to those patients without adverse events (mean 39.1 pg/ml).

Determination of Pretest Probability

While the clinical evaluation alone is notoriously inaccurate in diagnosing VTE, it remains important in determining the pretest likelihood of VTE. The determination of a pre-test probability has become an important part of the decision making for the diagnostic evaluation of venous thromboembolism.[134] The authors of the landmark 1990 PIOPED study[108] clarified the utility of V/Q scanning in diagnosing pulmonary embolism, but emphasized that its diagnostic accuracy was significantly increased by combining the pre-test "clinical probability" (based on experienced clinicians' gestalt) with the V/Q scan results (Table 24.3). Since the PIOPED study and the last edition of this textbook,[97] scoring systems have been developed and utilized to help determine pre-test probability, even without the "gestalt" of experienced clinicians.[70,135–137] In a review of relevant articles between 1996 and 2003, Chunilal et al. [138] found that the clinical gestalt of experienced clinicians and the clinical prediction rules used by physicians of varying experience showed similar accuracy in discriminating among patients who have a low, moderate, or high pretest probability of pulmonary embolism and advocated the use of a clinical prediction rule because it was shown to be accurate and can be used by less-experienced clinicians. It should be noted, however, that the accuracy of clinical assessment with either method varied widely (Table 24.4).

Miniati et al.[139] compared three clinical models for predicting the probability of pulmonary embolism and concluded that their own model, the Pisa Model, was superior to the Wells Model and Geneva Model for calculating the pre-test probability for PE (Table 24.5). The Wells Model,[136,140] however, has gained popularity because of its relative simplicity and because it has been validated as a predictive tool,[138] especially to exclude PE (Table 24.6). Both the Wells and Pisa Models, like the D-dimer assay, likely have limited utility in critically ill patients because of the complexity of illness and relatively high risk for VTE; one would expect that using these clinical scoring models, combined with D-dimer assays would rarely reduce the need for further imaging.

Table 24.4. Comparison of diagnostic accuracy of clinical gestalt versus clinical prediction rules in the diagnosis of pulmonary embolism.[139]

	Low pretest probability (%)	Moderate pretest probability (%)	High pretest probability (%)
Clinical gestalt	8–19	26–47	46–91
Clinical prediction rules	3–28	16–46	38–98

Table 24.5. Pisa clinical model for predicting the probability of pulmonary embolism. To estimate the probability of PE, add all of the regression coefficients that apply to a particular patient to the constant. The probability of PE then equals 1/[1 + exp(−sum)].[140]

Characteristic	Coefficient
Male sex	0.81
Age (years)	
63–72	0.59
≥73	0.92
Preexisting cardiovascular disease	−0.56
Preexisting cardiovascular disease	−0.97
History of thrombophlebitis	0.69
Dyspnea (sudden onset)	1.29
Chest pain	0.64
Hemoptysis	0.89
Fever >38°C	−1.17
ECG signs of acute right ventricular overload	1.53
Chest radiograph	
Oligemia	3.86
Amputation of the hilar artery	3.92
Consolidation (infarction)	3.55
Consolidation (no infarction)	−1.23
Pulmonary edema	−2.83
Constant	−3.26

Table 24.6. Wells Model for predicting the probability of pulmonary embolism.[141]

Characteristic	Score
Previous PE or DVT	1.5
Heart rate > 100 beats/min	1.5
Recent surgery or immobilization	1.5
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3
Hemoptysis	1
Cancer	1

Scores: <2.0: Low probability, 2–6: Moderate probability, >6: High probability (Only 2.2% of patients with a score of <4 with a negative D-dimer assay had a PE.)

Diagnostic Approach

While both PIOPED[108] and PIOPED II[90] investigators found that the minority (23–33%) of patients being evaluated for PE were actually diagnosed with PE, it is still incumbent on clinicians to have a systematic approach with these patients because of the life-threatening nature of this disorder. Over the last several years, well-validated diagnostic approaches have been developed using algorithms combining clinical probability, laboratory testing, and imaging studies.[10,106,107,141–143] These algorithms are most useful in the evaluation of ambulatory patients, particularly in emergency departments, as many patients presenting with dyspnea and chest pain can have the diagnosis of VTE excluded if there is a low pretest clinical probability and normal D-dimer assay, and/or normal V/Q scan, CTA, or duplex ultrasound.[143,144] In contradistinction to ambulatory patients, critically ill patients can be more difficult to evaluate for VTE because of cardiopulmonary instability, difficulty in eliciting symptoms, multiple concurrent medical problems, and the logistical limitations in transporting an unstable patient for imaging studies. Even with these limitations, however, it is still important for intensivists to remember that when one suspects a PE, one is trying to diagnose and treat VTE (that is, either a PE or DVT). Hull et al.[144,145] in classic studies using pulmonary angiography and CV for all patients with a suspected PE, found that 71% of patients with a PE had DVT and that 72% of patients with DVT had a PE. Importantly, 33% of patients without a PE had DVT and 35% of patients without DVT had a PE. These results were more recently supported by PIOPED II investigators [90] who found that when compared to CTA alone, CTA–CTV increased the sensitivity for diagnosing VTE from 83 to 90% because of patients who did not have a PE but had a DVT. These findings emphasize the fact that one must exclude *both* a PE and DVT when evaluating these patients. This is the approach taken by the recommended algorithms (Figs. 24.1 and 24.2). Triggers for starting these diagnostic algorithms for at-risk patients in the ICU include asymmetric limb swelling or warmth; unexplained dyspnea, respiratory distress, tachypnea, or hypoxemia; unexplained tachycardia or hypotension; evidence for acute right heart failure; and unexplained fever.[146] If the pre-test clinical probability for VTE is high, it is reasonable to begin empiric antithrombotic therapy while awaiting the outcome of diagnostic tests if there is no contraindication for anticoagulation therapy.[147]

The algorithms provide flexibility, depending on the resources at a particular institution. While determination of pre-test probabilities remains an important initial first step, the use of scoring systems, such as the Wells criteria,[136,138,141] and D-dimer assays[143,144] will not likely obviate the need for more imaging studies in critically ill patients. The pivotal imaging studies are usually duplex ultrasonography and CTA, but alternative techniques include CTA–CTV, V/Q scanning, and MRI. The gold standard tests continue to be contrast venography (now rarely used) and pulmonary angiography (less frequently used).

Echocardiography is not included in the standard diagnostic approach but may be considered in special circumstances, such as in patients suspected of having a massive PE, or as a means for risk stratification in patients diagnosed with VTE.

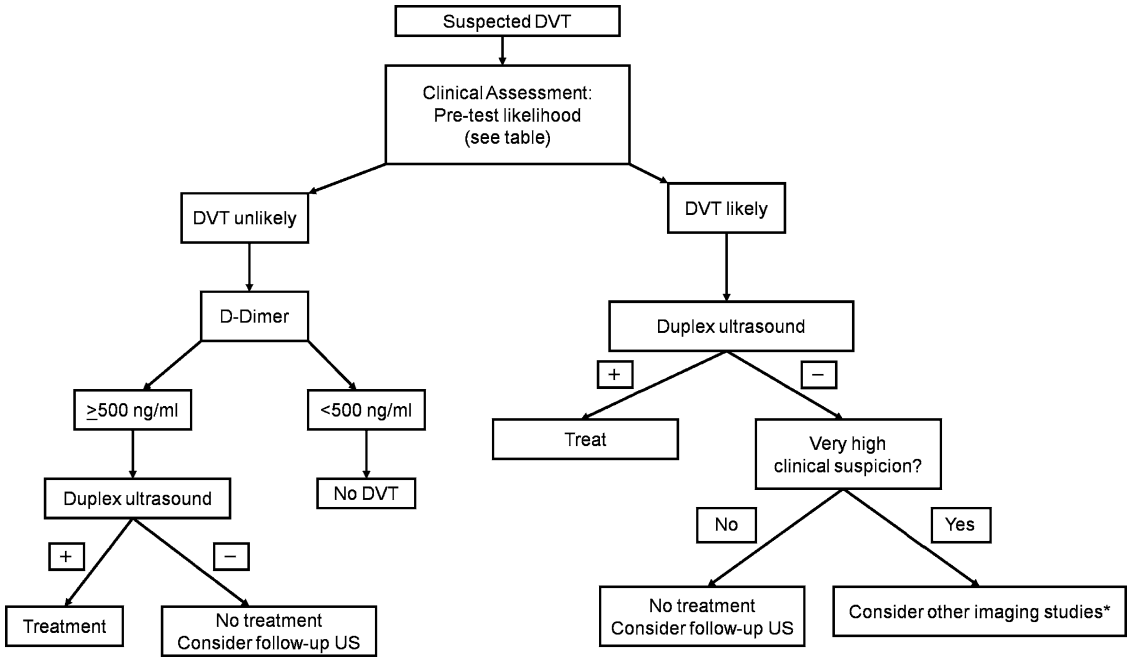

FIG. 24.1. Diagnostic approach for clinically suspected DVT.

Clinical Characteristic	Score
Active cancer	1
Paralysis, paresis, or recent immobilization of lower extremities	1
Recently bedridden	1
Localized tenderness along the distribution of deep venous system	1
Entire leg swollen	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

*A score of 2 or higher indicates the probability of DVT is "likely"; <2 indicates the probability for DVT is "unlikely"

FIG. 24.2. Diagnostic approach for clinically suspected PE.

TABLE 24.7. Example of a weight-based heparin nomogram.[154]

Situation	Action
Initial dose	80 units/kg, then 18 units/kg/h infusion
APTT < 1.2 times control	80 units/kg bolus then ↑ by 4 units/kg/h
APTT 1.2–1.5 times control	40 units/kg bolus then ↑ by 2 units/kg/h
APTT 1.5–2.3 times control	No change
APTT 2.3–3.0 times control	↓ rate by 2 units/kg/h
APTT > 3.0 times control	Hold 1 h, then ↓ by 3 units/kg/h

Treatment of VTE

Anticoagulation

The standard initial treatment of VTE in a hemodynamically stable patient is anticoagulation with either unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaprinux, unless anticoagulation is contraindicated. Anticoagulation has clearly shown survival benefit[17] by allowing the endogenous fibrinolytic system to function unopposed, thus decreasing the clot burden.[10]

Unfractionated Heparin

The use of UFH has been, until recently, considered the standard treatment for VTE and is still the most commonly used anticoagulant in the ICU. The usual anticoagulant regimen is the simultaneous use of continuous intravenous UFH and oral warfarin. Experimental studies and clinical trials have established that the efficacy of UF therapy depends on achieving a critical therapeutic level of heparin within the first 24 h of treatment.[148] The critical therapeutic level of UFH, as measured by the activated partial thromboplastin time (APTT) is 1.5–2.5 times the mean of the control value or the upper limit of the normal APTT range.[149] There is a strong correlation between subtherapeutic APTT values and recurrent thromboembolism, but the relationship between supratherapeutic APTT and bleeding is less definite.[150] The use of a prescriptive approach is preferable to using an ad hoc approach because it more often leads to adequate anticoagulation within 24 h.[151,152] The UFH dosing can be arbitrary[151] or can be weight based,[153,154] but the APTT should be checked frequently (for example, every 6 h until consistently in the therapeutic range) and the heparin dose adjusted accordingly (Table 24.7). Because of its short half life (approximately 30 min), UFH is still the anticoagulant of choice in critically ill patients who are generally

at increased risk for bleeding or who often require invasive procedures necessitating the interruption of anticoagulation.

The major acute adverse effects of UFH therapy include bleeding, heparin-induced thrombocytopenia, also known as HIT (discussed later), hypersensitivity reactions, and anaphylactoid reactions (rare). The risk of bleeding from UFH is <3%.[155] If active bleeding occurs, the UF infusion can be discontinued; in the case of severe bleeding, protamine sulfate can be given (1–1.5 mg/100 units heparin).

Low-Molecular-Weight Heparin

Low-molecular-weight heparins (LMWHs) – such as enoxaparin, dalteparin, and tinzaparin – have several potential advantages over UFH.[156] They have greater bioavailability when administered by subcutaneous injection and the duration of the anticoagulant effect is longer, permitting administration once or twice daily. The anticoagulant response (anti-Xa activity) to LMWH is highly correlated with body weight, permitting administration of a fixed dose on the basis of patient body weight. Routine laboratory monitoring is unnecessary and, in fact, discouraged,[148] as there is little correlation between anti-Xa activity and either bleeding or recurrent thrombosis. It was thought that there was a lower risk for HIT with LMWH compared to UF,[36] but a recent meta-analysis found no statistically significant difference in heparin-associated thrombocytopenia between LMWH and UH and insufficient evidence to conclude that HIT rates were different between them. Furthermore, there was no evidence from randomized comparative trials to support the contention that patients receiving treatment for VTE with UH are more prone to these complications than those receiving LMWH.[157]

In the most recent systematic review for the American College of Physicians, the authors concluded that LMWH is superior to UFH for treating DVT of the lower extremities because of its superior reduction in mortality and major bleeding during initial therapy and that it is at least as safe and effective as UF for patients with pulmonary embolism.[158,159] There is now general agreement that LMWH can be both cost-saving and cost-effective compared to UF for the treatment of VTE, should be the treatment of choice, rather than UFH, for the initial inpatient treatment of DVT, and is also appropriate for the initial inpatient treatment of PE.[148,159] It should be noted, however, that patients in these studies were not in critical care units. The use of LMWH in critically ill patients is hampered by the difficulty in reversing its prolonged anticoagulant effect quickly and a risk for over-anticoagulation in patients with renal failure, which is why UFH is more frequently used in the ICU.

For UFH, the major acute adverse effect is bleeding and HIT. LMWH is associated with less major bleeding compared with UFH in acute VTE,[156] but if active bleeding occurs, the anticoagulant effect can take several hours to reverse once the drug has been stopped; protamine sulfate is not fully effective because it does not affect the inhibition of factor Xa. While routine monitoring of anti-factor Xa blood levels is discouraged during VTE treatment,[148] it may be considered if LMWH is used in morbidly obese patients, pregnant patients, or patients with severe renal insufficiency as these are patient populations at risk for over-anticoagulation with LMWH.

Fondaparinux

Fondaparinux is an anti-Xa pentasaccharide that has been approved by the FDA to treat VTE. Like LMWH, it can be administered once daily (the usual dose is 7.5 mg daily) by subcutaneous injection and no laboratory monitoring is routinely required. It should not be used in patients with severe renal insufficiency given its renal excretion and prolonged half-life in this setting.[10] Fondaparinux has the same limitations as LMWH for use in the ICU.

Warfarin

Warfarin should be started within 3 days of initial heparin therapy, if possible. Because the first 24 h of warfarin therapy is associated with a transient hypercoagulable state due to its inhibitory effects on protein C and protein S (natural anticoagulants), heparin should not be discontinued until the international normalized ratio (INR) has been in the therapeutic range (2.0–3.0) for at least 2 days. Generally, long-term treatment with warfarin should be at least 3–6 months to prevent VTE from recurring. Warfarin can be initiated at a starting dose of 5–10 mg orally with daily dose adjustments made on the basis of the INR, preferably using an algorithm.[160] Unlike UF dosing, there has been no reliable nomogram that can predict how individual patients will respond to particular warfarin dosages as there are several factors that can alter the drug's effect, including drug–drug and drug–food interactions, advanced age, comorbidities, varying gastrointestinal absorption, and pharmacogenomics.

There are genetic phenotypes that can affect the pharmacokinetics of warfarin, such as variants of the CYP2C (enzyme of the cytochrome P450 system and the vitamin K oxide reductase (VKOR) enzyme that can make patients more sensitive to warfarin. While the FDA recently approved the updating of warfarin prescribing information to include a recommendation to screen for CYP2C9 and VKOR phenotypes, the latest recommendation from the American College of Chest Physicians (ACCP) guidelines for antithrombotic and thrombolytic therapy suggested against the use of pharmacogenetic-based initial dosing to individualize warfarin dosing in the absence of evidence from randomized trials.[160]

Bleeding is by far the most common adverse effect of warfarin and is related to the intensity of the anticoagulant effect, underlying patient characteristics, and the length of therapy.[156] There is good evidence that an INR of 2.0–3.0 is associated with a lower risk of bleeding than an INR of >3.0.[156] The anticoagulant effect can be reversed with vitamin K and, more rapidly, with intravenous infusion of fresh frozen plasma. A rare adverse effect from warfarin is skin or tissue necrosis.

Thrombolytic Therapy

Randomized clinical trials have demonstrated that administration of anticoagulant therapy can decrease the mortality rate from VTE. A mortality rate of less than 5% has been achieved with intravenous heparin and oral vitamin K antagonists, such as warfarin.[161] In patients with an acute massive PE and refractory hypotension, however, the immediate mortality rate is about 20% despite the use of anticoagulants and other supportive measures [162] and the 90-day mortality rate is >50%.[162] While randomized clinical trials have not shown a clear mortality benefit with thrombolytic therapy,[148,163] there is general consensus that thrombolytic agents, which activate the formation of plasmin from plasminogen thereby accelerating the lysis of thrombi, should be strongly considered in this group of patients with shock due to VTE.[10,148]

The precise role of thrombolytic therapy in the treatment of VTE is controversial, in large part because of the inadequate number of patients that have been studied in randomized control trials. Indeed, less than 800 patients with PE have been enrolled in randomized trials of thrombolysis plus anticoagulation versus anticoagulation alone.[148] In an early study of thrombolysis versus heparin alone to manage PE (Urokinase Pulmonary Embolism Trial), thrombolysis significantly accelerated resolution of pulmonary emboli on pulmonary angiography, lung scans, and hemodynamic measurements.[126] Although there was no significant difference in mortality rate, the greatest benefit in PE resolution was in patients with massive PE. On the basis of this and several subsequent studies, there is consensus that thrombolytic therapy, compared to anticoagulation alone, has demonstrated acceleration of thrombus lysis, reduction in elevated pulmonary artery pressures, normalization of ventricular dysfunction, and trends toward improved clinical outcomes in subgroups of patients with hemodynamic compromise.[148] The largest and most recent randomized trial of thrombolytic therapy versus UFH alone studied 118 patients with the combination of normal blood pressure and either echocardiographic or ECG evidence of right ventricular dysfunction.[164] In this study, Konstantinides et al. did not show a mortality benefit of thrombolysis with alteplase (3.4% vs. 2.2%) but did show a significantly lower incidence of treatment escalation such as emergency embolectomy, endotracheal intubation, cardiopulmonary resuscitation, catecholamine infusion, or secondary thrombolysis (10.2% vs. 24.6%). The authors concluded that thrombolytic therapy should be considered for patients with submassive PE (manifested as right ventricular pressure overload and dysfunction) who are hemodynamically stable.

The most recent recommendations of the ACCP[148] changed from discouraging the use of thrombolytic therapy for PE, unless there was hemodynamic compromise to suggesting the administration of thrombolytic therapy in selected high-risk patients without hypotension who are judged to have a low risk of bleeding. Factors predicting a poor prognosis in patients with submassive PE include (1) acutely ill appearance on clinical evaluation,[165] (2) elevated troponin,[130–132] (3) elevated BNP,[133,134] (3) right ventricular dysfunction on echocardiography,[122–125] and (4) right ventricular enlargement on CTA with a right ventricle size to left ventricle size ratio (RV/LV) of ≥0.9.[163,166]

Thrombolytic therapy appears to be associated with a 1.5- to 2-fold increase in the risk of major bleeding, compared with anticoagulant therapy alone in patients with acute VTE; there is a 1–3% risk for intracranial hemorrhage.[156,164] Absolute contraindications to thrombolytic therapy include hemorrhagic stroke, active intracranial neoplasm, recent (less than 2 months) intracranial surgery or trauma, and active or recent internal bleeding in the previous 6 months. Relative contraindications include bleeding diathesis, uncontrolled severe hypertension, recent cardiopulmonary resuscitation, non-hemorrhagic stroke within the previous 2 months, surgery within the previous 10 days, and thrombocytopenia (<1,000,000 platelets per mm^3).

When thrombolytic therapy is used for PE, the 2008 ACCP practice guidelines recommend administration via a peripheral vein rather than placing a pulmonary artery catheter to administer treatment[148] because of the higher risk for bleeding without acceleration of thrombolysis associated with the use of pulmonary artery catheters for localized thrombolytic agent infusions.[167] The practice guidelines also recommend use of regimens with short infusion times (such as tissue plasminogen activator [TPA], 50 mg in <15 min or 100 mg over 2 h) over those with prolonged infusions times (such as urokinase over 12–24 h or streptokinase 100,000 units per hour over 24 h) because of the higher risk for bleeding with the longer infusion times. Anticoagulation with UFH, LMWH, or fondaparinux should not be delayed until diagnostic testing for PE has been completed, even if thrombolytic therapy is being considered. Before thrombolytic therapy is administered, IV UFH should be administered in full therapeutic doses. During administration of thrombolytic therapy, it is acceptable to either continue or suspend the UFH infusion.[148] After administration of thrombolytic therapy, IV UFH should be restarted or continued. It is recommended that the APTT is checked immediately after completion of the TPA infusion and that, provided the APTT is not >80 s, IV UFH is restarted without a bolus at the same rate of infusion as was being used before TPA was started. If UFH has not been suspended, the infusion is continued at the same rate with ongoing adjustment according to APTT results.

Procedural and Surgical Treatments

Inferior Vena Caval Interruption

Insertion of an inferior vena caval (IVC) filter has become a commonly employed procedure for patients being treated for VTE despite a dearth of randomized controlled trials demonstrating its effectiveness for various clinical indications. Two recent exhaustive reviews[168,169] commented on the anecdotal nature of this body of literature and strongly suggested the

need for prospective randomized controlled trials. In the only randomized controlled trial, Decousus et al. reported on 400 patients with proximal DVT who were randomized to either standard anticoagulation alone or anticoagulation plus insertion of a Vena Tech®, Greenfield®, Bird's Nest®, or Cardial® IVC filter.[170] During the first 12 days after randomization, significantly fewer patients in the group that received IVC filters developed a PE (5% vs. 1%). However, after a 2-year follow-up period, there were no significant differences in survival or symptomatic PE between the two groups, and there was a significantly higher rate of recurrent DVT observed among patients who had received an IVC filter (21% vs. 12%). The development of retrievable IVC filters may allow removal of the devices after the VTE or the acute risks for VTE has resolved and thus reduce the longer-term risk for recurrent DVT.[169] The current ACCP guidelines[148] recommend that for patients with acute VTE who have an IVC filter inserted as an alternative to anticoagulation, a conventional course of anticoagulant therapy should be given if their risk of bleeding resolves.

The only clear indications for IVC filters (Table 24.8), based on the available evidence, are a contraindication to anticoagulation and complications from anticoagulation therapy.[148,169] There is a marked paucity of caval filter outcomes evidence when used within their currently approved indication and there is also a lack of retrievable filter trials.[170]

Embolectomy

Embolectomy may be performed surgically or by percutaneous catheter techniques. Data on surgical embolectomy were derived largely from retrospective reviews of historical series. The overall mortality rates from these studies were 30–42%, with a very high mortality rate (64–74%) for patients who sustained periods of cardiac arrest prior to the operations; however, if the patients did not have periods of preoperative cardiac arrest and survived the perioperative period, the longer-term outlook was good.[171,172] More recent reports have shown more encouraging data. Doerge et al.[173] examined the results of surgical embolectomy carried out in 31 patients before 1990 (prior to the advent of thrombolytic therapy for massive VTE at their institution) and in five patients after 1990 (after the introduction of thrombolytic therapy). The latter group was offered surgery only if thrombolysis was inappropriate or ineffective. No significant differences in early mortality rate (26% vs. 20%) were reported between the two cohorts. Leacche et al.[174] reported results from an institution that had liberalized the indications for surgical embolectomy for acute PE to include patients with large anatomically extensive clot and moderate-to-severe right ventricular dysfunction with or without hypotension. They reported the results of 47 consecutive patients between 1999 and 2004 who underwent emergency surgical embolectomy for massive central pulmonary embolism. The indications for surgical intervention, although not protocolized, included contraindication to thrombolysis (21 patients), failed medical treatment (five patients), and right ventricular dysfunction (43 patients, 28 of whom were hypotensive, and 15 of whom were normotensive). The perioperative mortality was 94% and the actuarial survival at 1 and 3 years' follow-up was 86 and 83%, respectively. It should be noted that the reporting institution has a multidisciplinary approach to VTE, with rapid noninvasive diagnostics, rapid risk stratification, and the availability of expert and immediate surgical treatment – resources that are not necessarily available at most institutions.

Transvenous catheter pulmonary embolectomy, which may be a substitute for surgical embolectomy, involves the use of a balloon or catheter device that is introduced and advanced from the femoral or jugular veins to extract or disrupt the embolus under radiologic control. Greenfield et al.[175] reported their experience in 46 patients with massive PEs. Embolus extraction was achieved in 76%, with a 30-day survival rate of 70% and a concurrent reduction in pulmonary artery pressures and improvement in cardiac output. In a recent review, Kucher [176] described the different percutaneous catheter devices and reported "clinical success" ranging from 67 to 100%. Data from cohort studies indicate that the clinical outcomes after surgical and catheter embolectomy may be comparable; however, there are no controlled clinical trials that compare catheter embolectomy to thrombolytic therapy or surgical embolectomy.[177]

The current ACCP guidelines recommend the use of embolectomy for selected patients[148] who are "highly compromised" and are unable to receive thrombolytic therapy because of bleeding risk or whose critical status does not allow sufficient time for systemic thrombolytic therapy. The choice of catheter versus surgical embolectomy should be determined by the expertise available at any particular institution.

Table 24.8. Indications for a vena caval filter.[169]

Clearly indicated	Contraindication anticoagulation
	Complication on anticoagulation
Possibly indicated	Failure of adequate anticoagulation
Potentially indicated but further study required	VTE prophylaxis in high-risk trauma patients-
	VTE prophylaxis in high-risk orthopedic patients
	Pre- or post-pulmonary thromboembolectomy
	Extensive free-floating iliofemoral thrombus
	Thrombolysis of ilio-caval thrombus
Not currently indicated	Treatment of VTE in cancer patients
	Treatment of VTE in patients with chronic obstructive pulmonary disease and DVT
	Treatment of VTE in patients with minimal cardiopulmonary reserve and DVT
	Treatment of VTE in pregnancy
	Treatment of VTE in organ transplant patients
	Treatment of VTE in patients with a history of gastrointestinal bleeding
	VTE prophylaxis in burn patients

Risk Stratification and Treatment Options

Once the diagnosis of VTE is made, it should be quickly determined whether the patient can undergo antithrombotic therapy and then rapid risk stratification should be done using clinical assessment, CTA findings (if available), troponin levels, BNP levels, and echocardiographic findings (if available) to determine whether a patient is at "high risk" for death (Table 24.9). A rational treatment approach for individual patients can then be implemented (see Figs. 24.3 and 24.4) for either DVT or PE. Patients who are not at "high risk" and who can undergo antithrombotic therapy should be treated with either UFH or LMWH and then warfarin. Patients who are not at "high risk" and who cannot undergo antithrombotic therapy should have an IVC filter placed. Patients with PE who are at "high risk" should be considered for thrombolytic therapy if there are no contraindications, using short term infusions of an agent such as TPA. Catheter embolectomy or surgical embolectomy can be considered if there are contraindications to thrombolytic therapy or if thrombolytic therapy has failed; the placement of an IVC filter should also be considered if there is a documented DVT in the "high risk" patients.

TABLE 24.9. Indicators of a "high risk" for mortality in patients with VTE.

Patients with DVT	Ilio-femoral disease (may be an indication for catheter-directed intervention)
Patients with PE	"Acute ill" by clinical evaluation (blood pressure, heart rate, respiratory rate, oxygenation)
	Right ventricular dysfunction by echocardiogram
	Right ventricular enlargement by CTA (RV/LV ³0.9)
	Elevated troponin
	Elevated BNP

Special Considerations in the ICU

Special considerations related to the treatment of VTE in ICU include heparin-induced thrombocytopenia, catheter-related DVT (particularly upper extremity DVT), and the treatment of pregnant patients. Detailed discussions of these problems are beyond the scope of this chapter, but are mentioned because of their importance to intensivists.

Heparin-Induced Thrombocytopenia

HIT is a life-threatening disorder that results from exposure to UFH or, perhaps less commonly, LMWH. It affects <1% of ICU patients, even though 30–50% develop thrombocytopenia, and is more common in post-surgical than in medical patients.[177] It results from the formation of antibodies against complexes of platelet factor 4 (PF4) and heparin, which can be assayed (anti-PF4/heparin antibodies). Thrombotic complications, both venous and arterial, develop in approximately 20–50% of patients.[178] A delay of 5–10 days before thrombocytopenia occurs is typical in patients who have had zero or distant exposure to UFH or LMWH, but precipitous thrombocytopenia can occur in patients who have had recent exposure to these medications. The risk of thrombosis can persist for weeks after discontinuation of heparin, even after the plate-

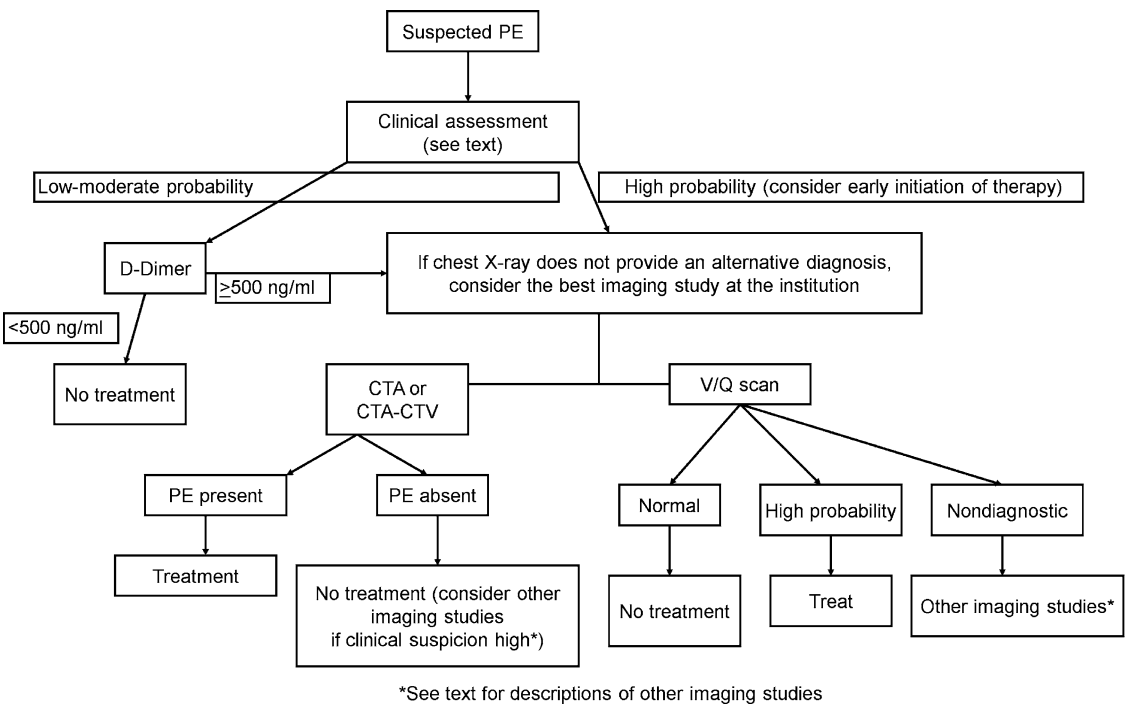

FIG. 24.3. Treatment approach for clinically suspected DVT.

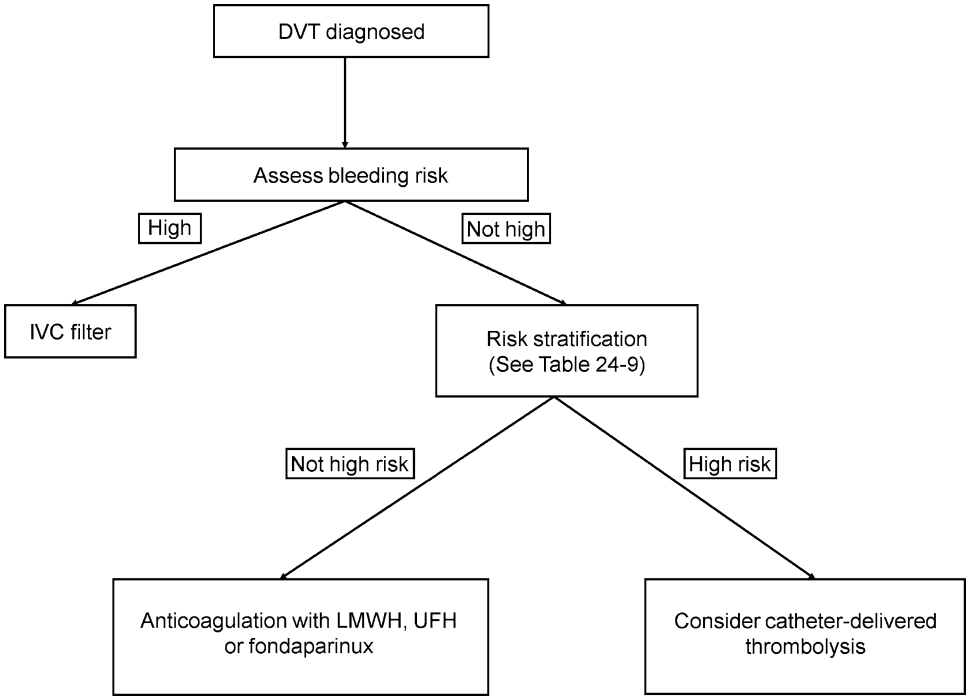

Fig. 24.4. Treatment approach for clinically suspected PE.

Table 24.10 Non-heparin anticoagulants available for patients with HIT.[178]

Direct thrombin inhibitors	Preferred for patients with renal impairment
Argatroban	Starting dose 0.5–1 μg/kg/min Monitor APTT at 4 h intervals until steady state therapeutic range (1.5- to 2.0-times control)
Lepirudin	Preferred for patients with hepatic impairment Starting dose 0.05–0.1 mg/kg/h (dose lower with renal dysfunction) Monitor APTT at 4 h intervals until steady state therapeutic range (1.5- to 2.0-times control)
Bivalirudin	Not FDA-approved for use in HIT
Heparinoids	Available in the European Union, Australia, and
Danaparoid	Canada; not available in the United States DVT prophylaxis dose: 750 units TID subcutaneously
Fondaprinux	DVT prophylaxis dose: 2.5 mg/day subcutaneously- VTE treatment: 7.5 mg/day subcutaneously Use with caution in patients with renal failure

let count normalizes.[178] The current ACCP guidelines recommend investigating for a diagnosis of HIT if the platelet count falls by ≥50% and/or a thrombotic event occurs in a patient who is receiving or who has recently received UFH or LMWH.[179] For patients with VTE and HIT who require anticoagulation, an alternative non-heparin anticoagulant should be used such as the direct thrombin inhibitors – argatroban, lepirudin, bivalirudin (not FDA-approved for HIT), the "heparinoid" danaparoid (not available in the United States), and the pentasaccharide fondaparinux (Table 24.10). For patients with renal impairment, argatroban is the preferred drug and for patients with hepatic impairment, lepirudin is preferred.[178] The ACCP guidelines also recommend the use of these non-heparin anticoagulants in patients with HIT, whether or not complicated by thrombosis, and routine ultrasonography of the lower-limb veins for investigation of DVT.[180]

Catheter-Related DVT

While it is not known with certainly what the risk for VTE is in patients with central venous catheters (CVCs), it has been repeatedly shown that CVCs are associated with a higher risk for DVT.[180–184] The risk for femoral CVC-related lower extremity DVT has ranged from 11 to 25%,[181,184] but the risk of upper extremity DVT associated with internal jugular and subclavian CVC has also been high, with a prevalence of as high as 33% in one report.[183] The risk of VTE from upper-extremity DVT (DVTUE) is not as quantifiable from the data as it is for lower-extremity DVT, but studies have indicated that the risk is not negligible – ranging from 3 to 36%.[15,49,85] It is therefore important to diagnose a DVTUE promptly, starting with a high clinical suspicion and followed by duplex ultrasonography (US). If US is inconclusive or normal in cases of strong clinical suspicion of thrombosis, contrast venography should be performed. The implementation of MRV or CTV is currently not warranted for routine clinical practice but may be considered on a case-by-case basis.[185]

The current ACCP guidelines recommend initial treatment with therapeutic doses of LMWH, UFH, or fondaparinux.[148] In patients with severe symptoms of recent onset and low

risk of bleeding, catheter-directed thrombolytic therapy can be considered.[148] The CVC associated with the acute DVT should, of course, be removed.

Pregnancy

The risk of VTE is increased in association with pregnancy, primarily during the postpartum period.[185–188] Recent U.S. epidemiologic data showed a relative risk of VTE among pregnant or postpartum women of 4.29, with an overall incidence of 199.7 cases per 100,000 woman-years.[189] Pregnant patients with suspected VTE should be viewed as having a life-threatening problem to the woman and fetus and should be subjected to the same diagnostic algorithms (Figs. 24.3 and 24.4) as non-pregnant patients; concern about exposure to radiation should not deter clinicians from using CTA or V/Q lung scanning when necessary.[10,190]

The current ACCP guidelines recommend initial treatment of VTE during pregnancy with LMWH or UFH; long-term anticoagulation therapy with either subcutaneous LMWH or UFH should be continued for at least 6 weeks postpartum, for a minimum total duration of therapy of 6 months; warfarin should be avoided as it crosses the placenta and is teratogenic to the fetus.[191] Pregnant patients require the same initial treatment approach as other patients with regard to the need for parenteral anticoagulation, placement of an IVC filter, or embolectomy. In a patient with life-threatening PE, thrombolytic therapy should not be withheld solely because of the pregnancy.[10,192]

Prevention of VTE

While most of this chapter has been devoted to the diagnosis and treatment of VTE, it is important to emphasize that DVT prevention is the most cost-effective strategy for reducing the incidence and, thus, the mortality from VTE. Recognizing and treating VTE could substantially reduce the approximately 50,000 annual deaths from PE in the United States, but preventing DVT can significantly decrease the five million annual cases of DVT and the 500,000 annual cases of PE.[17] Knowing who is at risk and how to prevent DVT is the responsibility of all clinicians. The intensivist has a particularly important role because critically ill patients are often at very high risk for VTE. For example, a patient 40 years or older who had major lower-extremity orthopedic surgery, a hip fracture, stroke, multiple trauma, or spinal cord injury has a 40–80% risk for developing calf vein thrombosis, 10–20% risk for proximal DVT, 4–10% risk for PE, and 1–5% risk for a fatal PE.[192] The ICU has been described as the "last frontier" for VTE prophylaxis [193] as there are no studies that provide a standardized approach to DVT prophylaxis in this high risk group.[194,195] Indeed, a query of Canadian ICU directors revealed a great deal of variability in prophylaxis practices in ICU patients.[196] Attia et al. systematically reviewed the medical literature on the incidence of DVT and the efficacy of thromboprophylaxis in critically ill adults, including patients admitted to ICUs and following trauma, neurosurgery, or spinal cord injury.[197] They found DVT rates of 22% to almost 80%, and found that methods of prophylaxis proven in one group do not necessarily generalize to other ICU patient groups.[198]

The current ACCP guidelines[198] state that it is essential for ICUs to develop a formal approach to thromboprophylaxis and favor pharmacologic thromboprophylaxis over mechanical thromboprophylaxis in patients who are not at high risk for bleeding. Aspirin is not recommended as thromboprophylaxis against VTE for any patient group. For critical care patients who are at moderate risk for VTE (e.g., medically ill or postoperative general surgery patients) the guidelines recommend using LMWH following the manufacturer-suggested dosing recommendations or low-dose UFH (5,000 units subcutaneously two or three times daily). For critical care patients who are at higher risk (e.g., following major trauma or orthopedic surgery) the guidelines recommend LMWH thromboprophylaxis (over low-dose UFH). For critical care patients who are at high risk for bleeding, the guidelines recommend the optimal use (i.e., with minimal interruptions) of mechanical thromboprophylaxis with graduated compression stockings and/or intermittent pneumatic compression devices. When the high bleeding risk decreases, it is recommended that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis.

A recent randomized, double-blind controlled study of 842 patients by Turpie et al.[199] compared fondaparinux (2.5 mg a day subcutaneously) combined with intermittent pneumatic compression versus intermittent pneumatic compression alone for prevention of venous thromboembolism after abdominal surgery.[199] The investigators reported that fondaprinux reduced the VTE rate by 70% (1.7% vs. 5.3%) as compared to pneumatic compression alone, with a low bleeding risk as compared to placebo. These findings would suggest that it is reasonable to use both pharmacologic and mechanical thromboprophylaxis in patients who are at high risk for VTE but at low risk for bleeding.

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25
Fat Embolism Syndrome

John M. O'Donnell

Fat embolism in humans was first recognized in 1861 by Zenker[1] who described fat droplets in the lung of a railroad worker who had suffered a fatal thoracoabdominal crush injury. Despite the patient's multiple fractures, Zenker believed that the fat originated from the contents of a lacerated stomach. Twelve years later, Von Bergmann[2] clinically diagnosed fat embolism syndrome (FES) in a patient with a fractured femur, and in 1875, Czerny[3] investigated the association of cerebral symptoms that sometimes occurred in patients with fat emboli. While most patients with FES are victims of trauma or have undergone orthopedic surgery, the entity has also been associated with a long list of medical conditions (Table 25.1).

Epidemiology

Sevitt[26] stated that "pulmonary fat embolism is a pathological but not a clinical entity," and most authorities support the contention that while fat embolism is quite common, the incidence of the clinical syndrome is relatively low. Fat emboli have been identified in more than 90% of patients with multiple trauma.[15,27] In an autopsy study of 110 soldiers who died during the Korean War, pulmonary fat emboli were present in more than 90%, yet these findings were thought to be clinically significant in only 19%.[28] Fat emboli were also found in 855 of 6,250 civilian accident victims and contributed to death in more than half.[29] Although the exact incidence of FES remains controversial, most believe that only a small percentage of patients who develop fat emboli go on to develop FES. It has been reported in less than 3.5% of patients with long bone fractures and in less than 10% of those with bilateral or multiple fractures.[15,30,31] Orthopedic surgery of the lower extremities, especially hip and knee arthroplasty and intramedullary nailing of the femoral shaft, predisposes patients to FES because the intramedullary canal pressure can reach 1,000 mmHg.[21,22] Christie[32] used intraoperative transesophageal echocardiography to study 110 orthopedic patients undergoing various procedures requiring medullary reaming and found the incidence of intracardiac fat and coagulative emboli to be 88% (97 of 110 patients). The FES is also thought to occur more frequently in cases of closed fractures than open fractures, which may be the result of the release of marrow contents and fracture hematoma pressure associated with an open wound.[21,33] The FES has a predilection to occur during the patients' second and third decades of life, probably reflecting the increased incidence of long bone fractures in this population. Gossling and Pellegrini[34] found that clinical manifestations of FES were 100 times less likely to occur in children than in adults with comparable injuries. This was thought to be partially explained by the lower fat marrow content and small amounts of liquid triolein in children's bone marrow.[17,34] There is some evidence that palmitin and stearin fats found in the marrow of children are not as likely to produce emboli as is the olein found in the marrow of older patients.[15]

Pathogenesis

The source of fat emboli has continued to elude investigators for over 80 years. Two theories have emerged. The mechanical theory seems more applicable to the orthopedic patient and proposes that long bone fractures or manipulations result in an increase in medullary pressure and disruption of medullary sinusoids. Marrow fat

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Table 25.1. Medical conditions associated with FES.

Diabetes mellitus[4]	Soft tissue infections[15]
Connective tissue diseases[5]	Sickle cell disease[16]
Burns[6]	Renal transplantation[17]
Lymphangiography[7]	Bone marrow transplantation[18]
Parenteral nutrition[8]	Liposuction[19]
High-dose corticosteroid therapy[9]	High-altitude decompression[20]
Osteomyelitis[10]	Autotransfusion[21]
Fatty liver of pregnancy[11]	Carbon tetrachloride ingestion[21]
Cardiopulmonary resuscitation[12]	Chemotherapy[22]
Cardiopulmonary bypass[13]	Alcoholic fatty liver[23]
Pancreatitis[14]	Silicone injections[24]
	Animal bites[25]

droplets gain access to the open vessels immediately by intravasation and are subsequently transported to the pulmonary vascular bed where they are deposited and trapped, occluding the small capillaries.[15,35] Thromboplastin release following orthopedic trauma induces platelet aggregation onto abnormal surfaces (i.e., fat globules) and accelerates the coagulation cascade, resulting in prolonged clotting studies and thrombocytopenia.[36]

The biochemical theory has been conveniently divided into two categories: obstructive and toxic. The obstructive mechanism is based on the theory of lipoprotein instability and the tendency for it to coalescence into macroglobules. It supports the concept that C-reactive protein, an acute phase reactant that is markedly elevated in acute illness and injury, provokes calcium-dependent agglutination of chylomicrons, very low-density lipoproteins, and liposomes of neutral fat emulsions, resulting in embolization.[37] The toxic theory maintains that catecholamine and inflammatory mediator release at the time of injury or illness results in the mobilization of free fatty acids from body fat stores in the marrow, soft tissue, and serum with consequent deposition in the lungs, brain, kidneys, and skin.[15] This mechanism seems less likely because Barie and colleagues[38] demonstrated that free fatty acids are actually bound by albumin and transported through the bloodstream and the lymphatic channels in a benign form. Whereas both mechanisms may play a role in the development of FES, it remains a mystery as to why some patients with similar injuries or illnesses develop FES while others do not.

Pathophysiology

Despite the ongoing debate regarding the genesis of pulmonary fat, most investigators feel that the major pathophysiologic mechanism is obstruction of the microvasculature. Platelets and fibrin adhere to the emboli forming obstructive plugs.[21,39,40] Lung lipase probably hydrolyzes neutral fat to toxic-free fatty acids and glycerol, resulting in endothelial damage, surfactant deactivation, and capillary leakage. Platelet sequestration and degradation result in the release of serotonin and various leukotrienes. Damaged lung parenchyma releases histamine and other mediators that combine to induce pulmonary vasospasm, bronchospasm, and worsen vascular endothelial injury. Alveolar collapse, congestive atelectasis, worsening compliance, and increasing intrapulmonary shunt result in refractory hypoxemia and increased work of breathing. If compensatory vasodilatation fails to occur, pulmonary hypertension develops and sets the stage for target organ embolization. While many investigators attribute systemic embolization to development of pulmonary hypertension with subsequent fenestration of dormant right to left communications (i.e., probe patent foramen ovale), Byrick et al.[41] found that the fluidity and deformability of intravascular fat enable it to traverse the pulmonary vasculature and embolize, even in the absence of anatomic shunts.

Controversy continues regarding the pathophysiology of the cerebral dysfunction. The once-held belief that neurologic findings were secondary solely to arterial hypoxemia or diffuse cerebral edema is no longer valid. Autopsy histologic studies of patients with clinical cerebral fat embolism describe multiple small infarcts with perivascular hemorrhage in the basal ganglia, thalamus, brainstem, and the deep white matter of the cerebral hemispheres and cerebellum, clearly implicating focal ischemic injury.[13,42,43] Despite the lack of clinical evidence of renal dysfunction, no organ seems more diffusely affected than the kidney. This is most likely the result of the filtering glomeruli, which concentrate fat globules into small, dense volumes resulting in microinfarctions.[44] The petechial skin lesions are also thought to be the result of microinfarction with associated capillary distension and endothelial fragility.[45] Their predilection for the upper torso probably reflects the buoyancy of fat in the serum.[21] Thus, the organ dysfunction from fat embolization is the result of the embolized corpuscular fat with aggregated cellular blood components impairing flow, releasing mediators, and resulting in the collapse of the capillary circulation with subsequent ischemic dissolution of the surrounding tissue.[46]

Clinical Presentation

The onset of symptoms is best described as being bimodal. Acute fulminating FES, while unusual, has certainly been described in multiple trauma patients and is characterized by the abrupt onset of respiratory insufficiency, cor pulmonale, coma, cardiopulmonary collapse, and death.[47] More often than not, however, the presentation is more insidious and is most notable for its evolving pulmonary, cerebral, and cutaneous manifestations. Sevitt[48] found that of 100 patients with FES, 25 developed symptoms within the first 12 h following injury, 75 showed symptoms within 36 h, and 85 had clinical evidence of FES 48 h following the insult. Certain characteristics of fat embolism may assist in its early diagnosis. Clinical evidence of respiratory insufficiency is present in more than 75% of patients,[17] and more than 90% have arterial hypoxemia.[49] The onset of symptoms is often sudden, characterized by dyspnea, followed by restlessness, agitation, and disorientation. Patients may be combative and difficult to manage. They are often hyperdynamic, tachypneic, and sometimes cyanotic. Pyrexia is a constant finding and, according to Muller et al.,[46] is the direct consequence of purpura cerebri with subsequent decompensation of the thermoregulatory center. Auscultation of the lung fields generally reveals diffuse rales, rhonchi, and wheezing, and occasionally a pleural friction rub is audible. The full neurologic manifestations of FES usually develop after respiratory insufficiency has become

clinically apparent.[17] However, evidence of neurologic involvement can actually precede the signs of pulmonary insufficiency and occasionally represent the sole manifestation of FES.[50,51] Mental status deterioration is often followed by further evidence of neurologic involvement, including long track signs, decorticate and decerebrate posturing, and major motor seizures. Oliguria is not uncommon, and urinary incontinence may occur despite the patient's apparent well-being.[52] The classic rash usually develops by the second or third day in 30–60% of patients.[47,48] It is generally described as showers of petechiae occurring on the upper chest and along the root of the neck and in the axillary folds. The rash is often fleeting and is easily missed during cursory examinations.[21,52] The buccal and conjunctival petechiae, so characteristic of the syndrome, are sharp, well-defined, and easily identified by rolling back the lower lip and lower eyelid, respectively (Fig. 25.1).

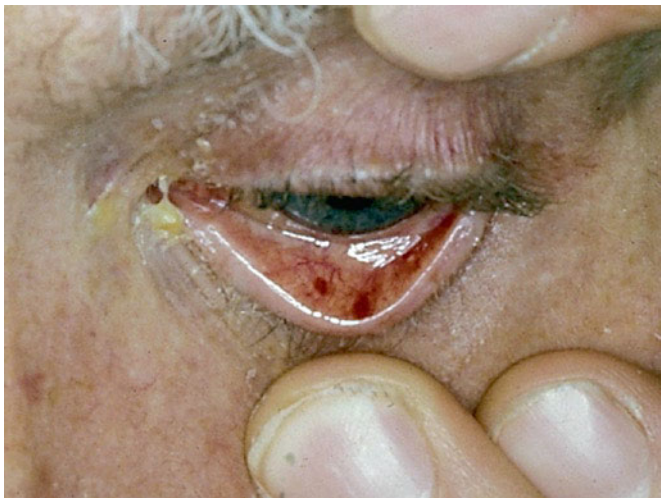

FIG. 25.1. Subconjunctival petechiae with fat embolism.

A funduscopic examination may demonstrate lesions in up to 50% of patients, generally presenting as exudates, edematous patches, cotton-wool spots, petechial hemorrhages, and intravascular fat globules (Fig. 25.2). Patients suffering from blunt chest trauma and fat emboli may manifest a similar but more dramatic form of retinopathy (Purtscher's retinopathy).[53]

Investigations

Laboratory studies may support the diagnosis of FES but none are pathognomonic. Alveolar hemorrhage and mild hemolysis may result in a precipitous drop in hemoglobin concentration.[21] Platelets and fibrinogen are often decreased and abnormal clotting studies are not unusual, but they rarely result in a bleeding diathesis.[54] Fibrinogen, an acute phase reactant, generally rebounds after 3 or 4 days. Calcium levels are also decreased, but serum triglyceride, cholesterol, and lipase concentrations have no association with FES.[54] Serial arterial blood gases most consistently demonstrate worsening refractory hypoxemia and a respiratory alkalemia. The electrocardiogram often shows a sinus tachycardia and non-specific ST–T wave changes[21]; but the right heart strain pattern of cor pulmonale may be present, and conduction abnormalities, including complete heart block, have been reported.[55] The chest radiograph may be initially unremarkable but, as the syndrome develops, up to 50% of patients demonstrate progressive, bilateral, interstitial, and alveolar infiltrates, described as having a "snowstorm" appearance and occupying the dependent lung fields, generally sparing the apices.[56] Ventilation/perfusion lung scans have been advocated by some and may show subsegmental perfusion defects thought suggestive of the FES.[57,58] Skarzynski et al. found that the scans often showed ventilation/perfusion matching and entertained the passage of

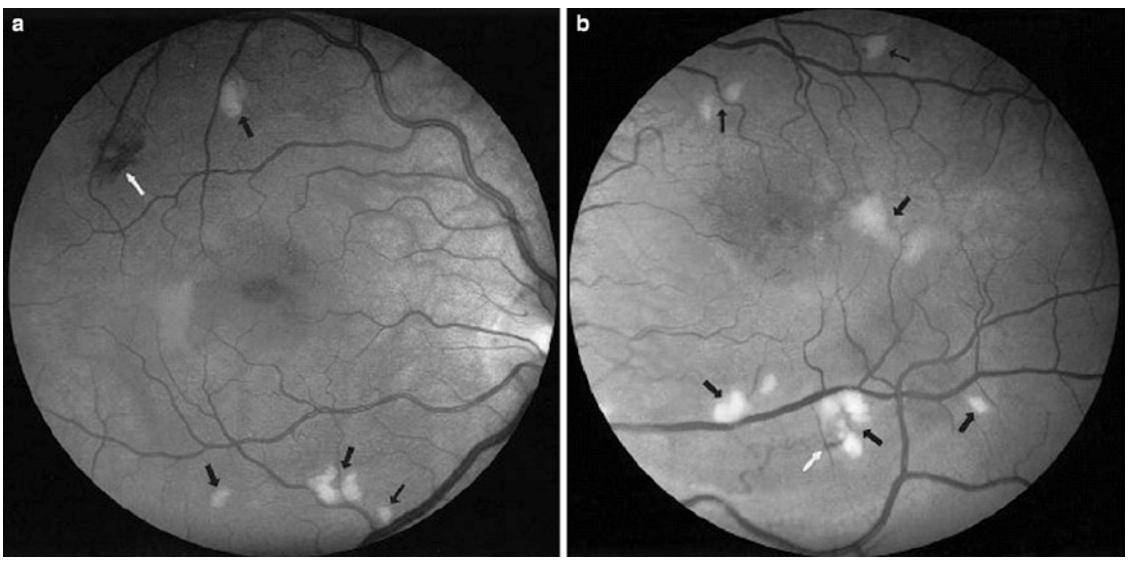

FIG. 25.2. Fundus photographs of the right (**a**) and left (**b**) eyes showing multiple cotton wool spots (*black arrows*) and small areas of superficial hemorrhages (*white arrows*).

lipid across the capillary wall and into the alveolus.[59] Bulger et al.,[47] who performed scans on 10 patients, found the scans helpful for excluding pulmonary emboli but not particularly useful for diagnosing fat emboli because the particles were generally thought to be too small to be detected. Gallardo et al. described chest computerized axial tomography (CT) scans in five patients who met the clinical criteria for FES.[60] The radiologic features differed and included alveolar opacities, ground-glass opacities, and nodules less than 1 cm with ill-defined margins and centrilobular and subpleural distribution. The nodular pattern on CT scan was thought to have helped in supporting the diagnosis of FES and has been described by others.[61,62]

Diagnosis

Because there is no specific diagnostic test for FES, most have continued to rely on the classic clinical criteria of Gurd and Wilson[49] (Table 25.2).

Lindeque et al.[28] argued that the criteria of Gurd and Wilson is too insensitive because blood gas analysis is not included, and hypoxemia may precede clinical signs in early FES. He subsequently based the diagnosis solely on gas exchange abnormalities and tachypnea, which he claimed to be more accurate indicators. The scoring criteria of Schonfeld and associates[63] include skin lesions, mental status, and blood gas abnormalities (Table 25.3).

A retrospective review of 27 patients by Bulger et al. suggested that diagnosis of FES should be one of exclusion.[47] In her study, 96% of patients were hypoxemic, lending support for the diagnosis when no other etiology was apparent. Petechiae, believed by some to be pathognomonic when associated with mental status changes and hypoxemia,[17] were found in only 33% of patients. Treugut et al.[64] reviewed chest radiographs of trauma patients and attempted to identify a diagnostic indicator based on radiographic morphology. Even though they found the radiographic pattern to be very nonspecific, they were able to roughly correlate the time of appearance with specific etiologies. Infiltrates appearing within hours of the insult were thought to be due to contusion or aspiration, while those developing after 24 h were more likely secondary to FES or the acute respiratory distress syndrome. The identification of fat droplets within cells recovered by bronchial alveolar lavage (BAL) was advocated by Chastre et al.[65] as a rapid and specific means of establishing the diagnosis of FES. Two other studies, however, found this practice to be non-specific and hence it could not be recommended.[66,67] Gitin and colleagues[68] were unable to correlate the amount of pulmonary blood fat with the severity of respiratory failure, and numerous other studies have shown that fat analysis of the sputum, urine, and cerebral spinal fluid is an insensitive and non-specific marker for FES.[21,47] Recently, Karagiorga analyzed the protein and neutral lipid content (cholesterol and its esters) in BAL samples from patients with acute respiratory failure (ARF) and controls. He found that the higher levels were predominantly in the patients with ARF believed secondary to FES as compared to those patients with ARF due to other causes.[69]

For over 10 years, there have been case reports utilizing T1, T2, and diffusion-weighted magnetic resonance imaging (MRI) as an alternative to CT scans for diagnosing cerebral fat emboli, and some feel that it is now the procedure of choice.[50,70,71] Magnetic resonance imaging may detect abnormalities in the presence of a normal CT scan.[72] Specific lesions include low density areas on T1-weighted images and high density areas on T2-weighted images[73] with a distribution that usually involves the deep white matter, basal ganglia, corpus callosum, cerebellar hemispheres, and watershed areas (Fig. 25.3).

TABLE 25.2. Gurd and Wilson's diagnosis of FES.

Major features (at least one)	Minor features (at least four)	Laboratory features (at least # 1)
1. Respiratory insufficiency macroglobulinemia	1. Pyrexia	1. Fat
2. Cerebral involvement	2. Tachycardia	2. Anemia
3. Petechial rash	3. Retinal changes	3. Thrombocytopenia
4. Renal changes	4. High sedimentation rate	
5. Jaundice		

TABLE 25.3. Diagnosis of fat embolism using a fat embolism index.[58]

Symptom	Score
Petechiae	5
Diffuse alveolar infiltrates	4
Hypoxemia	3
Confusion	1
Fever > 38°C	1
Heart rate > 120 beats/min	1
Respiratory rate > 30/min	1

A score > 5 is diagnostic.

Management

The treatment as well as prevention of FES is centered on the support of failing organ systems. Oxygen should be administered immediately by mask, and the severity of pulmonary insufficiency assessed with arterial blood gases. Even though some advocate the use of continuous positive pressure by mask and non-invasive ventilation as the next step in the attempt to restore gas exchange, many of these patients are uncooperative or obtunded, making this approach less desirable. Refractory hypoxemia often mandates intubation and the initiation of mechanical ventilation and positive end expiratory pressure. The employment of mechanical ventilatory techniques that incorporate spontaneous breathing are encouraged in order to improve ventilation perfusion matching, alveolar recruitment, and cardiac function. Airway Pressure Release Ventilation has been adopted in some centers for managing

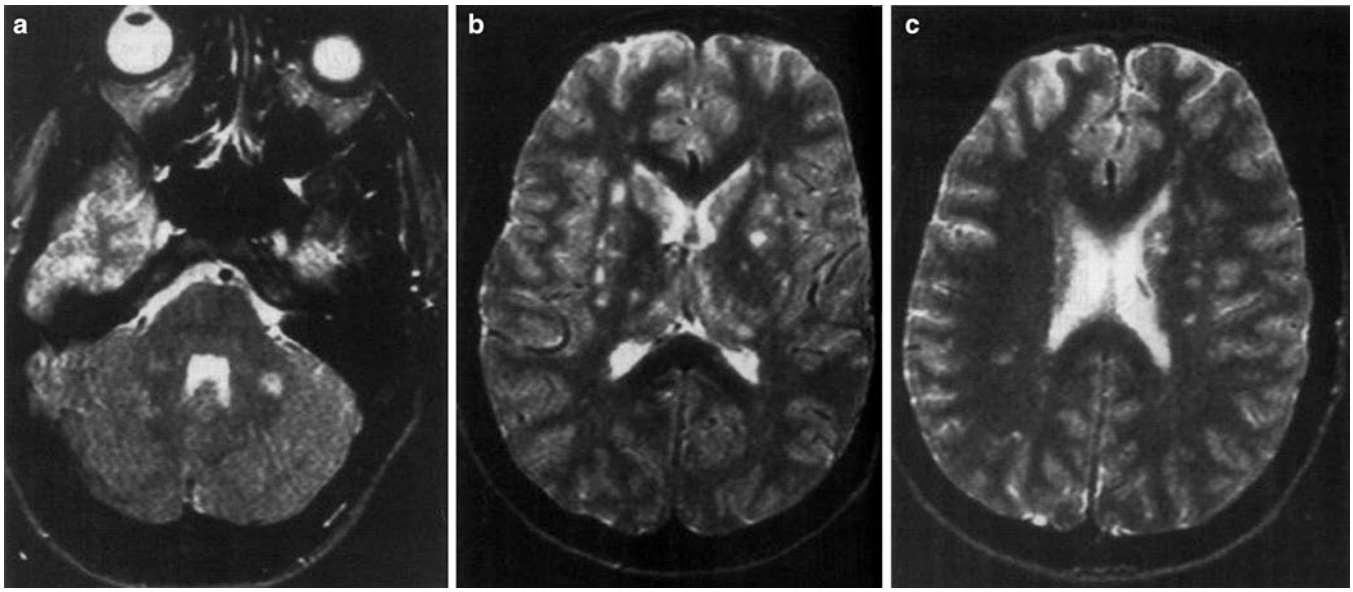

FIG. 25.3. Axial T2W images on post ictal day 3 demonstrating multiple hyperintense foci in (**a**) the middle cerebellar penduncles, (**b**) thalami, basal ganglia, internal and external capsules, and (**c**) periventricular white matter.

the multiple trauma patients with FES.[74] Animal model studies have supported the practice of maintaining adequate intravascular volume in patients suffering from FES, reinforcing the clinical observation that the severity of respiratory failure appears directly related to the degree and duration of hemodynamic instability.[17,49,75–77] Aggressive fluid resuscitation should be initiated early, and invasive hemodynamic monitoring is often required to optimize cardiac function while subsequently avoiding volume overload. Fulminant FES with cardiovascular collapse has been managed with extracorporeal membrane oxygenation.[78,79] A recent meta-analysis of albumin therapy showed improved outcome in critically ill patients[80] and some have advocated the use of albumin with FES because of its ability to bind oleic acid in the animal model, thereby decreasing the fatty acid's inflammatory effect on target organs.[81] Goodman demonstrated several free fatty acid (FFA) binding sites on the albumin molecule, and estimated that each gram of albumin could bind with up to 110 mg of long chain fatty acid.[82] Meticulous pain control may also decrease endogenous catecholamine release and attenuate the rise in FFA.[83,84]

Numerous pharmacologic manipulations have been attempted with limited success. Ethanol infusions were suggested at one time because of the agent's ability to act as an emulsifier and inhibit serum lipase activity.[85] This practice was supported by the observation that the FES appeared to occur less frequently in alcohol-intoxicated patients than the sober ones. However, there seems to be no correlation between blood alcohol levels and free fatty acid levels and the development of the FES. The early use of heparin was based on its ability to stimulate circulating lipoprotein lipase, resulting in the breakdown of embolic neutral fat. This practice has since fallen into disfavor because bleeding complications were common and free fatty acids were toxic to lung parenchyma.[86] Aprotinin, a protease inhibitor, decreases platelet aggregation as well as the release of serotonin, and it has been advocated by some as a means for improving outcome. At this time, however, no well-designed studies are available to support its use.[87] Similar trials with hypertonic glucose, sodium bicarbonate solution, low-molecular-weight dextran, choline, and clofibrate have also been disappointing.[15,17,21] Considerable controversy remains regarding the use of corticosteroids. First introduced in 1966 by Ashbaugh and Petty,[88] this practice gained rapid popularity for patients at risk for developing fat emboli. Subsequently, numerous randomized studies have produced conflicting results regarding the efficacy of corticosteroids in FES. The mechanism of action appears to be the inhibition of the inflammatory reaction associated with white cell and platelet aggregation, and some studies have shown improvement in oxygenation and a lowering of FFA levels. At present, it is uncertain as to whether or not corticosteroids have a prophylactic or therapeutic role in the treatment of FES.[28,89–91]

No aspect of management has been more controversial than the timing and specific technique of orthopedic procedures. Early fracture fixation has been advocated by some as a means of decreasing the pulmonary complications associated with long bone trauma.[92] Bone et al.[93] compared early (less than 24 h) and late (more than 48 h) stabilization in 178 patients with femoral fractures and found the incidence of respiratory complications, including the FES, to be greater when stabilization was delayed. Some researchers have challenged this concept, claiming that early intramedullary rodding may worsen existing respiratory failure.[94] Bulger et al.[46] found no difference in the incidence of the FES in those patients who received operative fixation within 24 h compared with those

undergoing surgery later in their hospital course. Despite these conflicting reports, most orthopedic surgeons agree that the FES is best avoided by minimizing the extent of intramedullary hypertension when preparing the femoral canal, during the cementing of prosthetic devices, and during intramedullary nailing.[95]

Prognosis

Despite our increasing knowledge of the pathophysiology and advances in organ system support, the mortality associated with FES remains between 5 and 15%.[46,92] While most patients succumb to respiratory failure and associated injuries, long-term morbidity is best correlated with neurologic defects as a result of the acute fulminant FES generally seen in trauma patients.[33,96] Persistent cognitive dysfunction has been well documented and any suspicion of intellectual impairment during recovery should prompt formal neuropsychological testing.[97] Cognitive rehabilitation can improve memory loss, attentional deficits, judgement, and overall quality of life.[98]

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26
Venous Air Embolism

Carl J. Borromeo

Definitions

Gas embolism refers to the abnormal presence of gas within the circulatory system. It is a known complication of various surgical, therapeutic, and diagnostic procedures. It can also occur as a result of trauma. Gas embolism may be asymptomatic or may even result in immediate cardiovascular collapse. The type and severity of sequelae depend on the composition and amount of gas, the rate and location of entry, and on patient characteristics such as size, cardiopulmonary reserve, and presence of an intracardiac right–left communication. An understanding of the etiologies and pathophysiology of gas embolism is important in order to recognize, treat, and, most importantly, *prevent* this potentially catastrophic complication.

Gas enters the circulation when two conditions co-exist: (1) a communication between a gas source and the vascular system, and (2) a pressure gradient that favors gas entry into the vasculature. When the atmosphere is the source of gas, then this condition is termed air embolism. Gas can be entrained into open veins or venous sinuses, insufflated into traumatized vessels, or accidentally infused under pressure through indwelling venous or arterial catheters. Rarely, dissolved gas is released in blood through effervescence caused by rapid re-warming or decompression.[1]

Venous (pulmonary) gas embolism (VGE) refers to gas that gains entry into the venous system and causes morbidity via its effects on the right heart and pulmonary vasculature. Systemic (arterial) gas embolism (SGE) results from gas that is propelled by the left heart and embolizes to systemic arterial beds causing ischemia and infarction. Paradoxical gas embolism (PGE) originates in the venous system and gains access to the arterial system through intracardiac defects or the pulmonary circulation.

Systemic Gas Embolism

Systemic gas embolism (SGE) usually results in devastating cardiac and cerebral compromise and is due to obstruction of medium-sized arteries by small gas bubbles. Entrance of gas is commonly through traumatized pulmonary veins. Positive pressure ventilation is important in the pathogenesis of SGE, providing the necessary pressure gradient for gas entry into the pulmonary venous system. Most cases of SGE result from penetrating chest trauma and blast injuries, but it has also been described after cardiac and thoracic surgery, barotrauma from positive pressure ventilation, needle lung biopsy under general anesthesia, and blunt trauma.[2,3] In a typical scenario, institution of positive pressure ventilation in a patient with penetrating chest trauma and hemoptysis is followed by sudden circulatory collapse or central nervous system dysfunction.[2] The appearance of skin marbling (livedo reticularis),[4,5] and mottling of the tongue (Liebermeister's sign)[2] strengthens the diagnosis. SGE may occur in up to 14% of patients with severe pulmonary trauma.[6] Most cases (>2/3) occur as a result of penetrating chest trauma. Pre-intubation hemoptysis may be the only clue to a traumatic communication between the airway and pulmonary vasculature.[6] Management may require immediate thoracotomy with hilar clamping to prevent further embolization, hemodynamic support, and hyperbaric oxygen therapy. Spontaneous ventilation is preferred in trauma patients who are at high risk for this complication; however, if controlled ventilation is required, lung isolation and/or high frequency may be employed.[2]

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Venous Gas Embolism

Historical Perspective and Etiology

In 1947, Durant et al. summarized the circumstances in which venous air embolism (VAE) occurred: surgery of the head and neck, obstetrical procedures, diagnostic and therapeutic air injections, and accidental air entrance into intravenous catheters.[5] Similar general classifications can be used today.

VAE continues to complicate surgical procedures performed above the heart. The use of sensitive monitors has made its intraoperative detection both practical and accurate in classically high-risk procedures such as sitting craniotomies. In addition, VAE has been described in other procedures in which the gravitational gradient for venous air entrainment is more subtle; VAE as a result of air entrainment has complicated surgeries in the prone, beach chair, and lateral decubitus positions (discussed later in this chapter). VAE has also been reported in pelvic and abdominal surgeries, especially in the Trendelenburg position. While air injections have become relatively obsolete, pressurized gases are now utilized in many modern invasive medical procedures during which VGE has become an infrequent complication. As the trend toward less invasive, scope-based procedures increases, pressurized gases become important for visualization within body cavities, fascial planes, and in endoscopic procedures through natural orifices. Pressurized gases are also frequently utilized in modern dissecting, hemostatic, and ablative surgical instruments. Not surprisingly, incidents of VGE have accompanied their use. Finally, frequent use of central venous catheters has resulted in an increased documentation of air embolism through intravenous equipment over the last 30 years.[7–10] Therapeutic and diagnostic automated intravenous infusion devices are probably responsible for a small percentage of VAE through intravenous catheters, with most occurring during placement, use, and removal of central venous lines. Table 26.1 lists the ever-broadening clinical settings in which VGE has been reported. Each circumstance has added to our understanding of VGE, as the following sections will show.

Table 26.1. Circumstances in which VAE has been reported.

Gravitational pressure gradient	Medical uses of pressurized gases	Intravenous catheterization
Craniotomies[11–14]	Laparoscopy[28–33]	Central venous catheters[7–10]
Neck surgery[15]	Hysteroscopy[33–36]	Pressure infusion devices[53–55]
Shoulder arthroscopy[16,17]	Mechanical ventilation[3,4,37]	
Surgery on the spine[18,19]	Cavitron ultrasonic surgical aspirator® for hepatic resection[38,39]	
Total hip arthroplasty[20]	Argon beam coagulator[40–42]	
Cesarean delivery[21]	YAG laser[34]	
Prostate surgery[22,23]	Endoscopic vein harvesting[43–45]	
Liver surgery[24–26]	Endoscopy[46–48]	
Eye surgery[27]	Use of hydrogen peroxide[49–52]	

Table 26.2. Monitors to detect VAE, ordered by decreasing sensitivity.

Monitor	Comment
Transesophageal echocardiography	Can detect PFO and air in the right or left heart
Doppler ultrasound	Probe placement important Electrocautery causes interference
End tidal CO_2 End tidal nitrogen	Decrease can also be due to diminished cardiac output Mass or Raman spectrography
Pulmonary artery pressures	Semi-quantitative
Blood pressure	Late sign

Surgery Above the Heart

The intravascular venous pressure eventually becomes subatmospheric at some level above the right atrium. A low central venous pressure (due to hypovolemia or venous pooling in the sitting position) will act to lower the height at which intravenous pressure is below ambient pressure. If veins at this level are opened, then VAE occurs. The flow rate of the entrained air depends largely on the pressure gradient and size of the venous opening.[11] Gravitational pressure gradients of 60 cmH_2O in the sitting position, 18 cm in the supine and lateral positions, and 7.5 cm in the prone position have been reported.[11] Pressure gradients as low as 5 cmH_2O are sufficient to cause VAE clinically,[11] and theoretically can entrain close to 100 cc/s of air through a 14-gauge catheter.[9,15] Reported lethal volumes of air in humans range from 200 to 500 cc [47,56] and it is postulated that smaller volumes are more dangerous when entrained closer to the heart.[56]

VAE has also been reported in patients in the prone position, especially when supports allowing the abdomen to hang freely are used. It is postulated that this position *may exacerbate* the subatmospheric pressure in the inferior vena cava, thereby increasing the likelihood of VAE.[19] VAE has also been reported during abdominal and pelvic surgery when the operative field is above the heart (Trendelenburg position), for prostate surgery[23], or while the uterus is exteriorized during cesarean delivery[56] and when pelvic veins or the inferior vena cava are open to air.[26] Hatano et al. theorized that during hepatic resection surgery, focal intracaval pressure can be made subatmospheric by manual compression and resultant flow-dependent Venturi effect.[57] Air can then be entrained through adjacent, open hepatic veins that do not collapse easily.

In the operating room, monitors to detect VAE are routinely used in high-risk procedures. These are listed in Table 26.2 in decreasing order of sensitivity. Echocardiography may become more important in the diagnosis of VAE outside the operating room as expertise and equipment availability increase in the critical care environment.[7]

Procedures Utilizing Pressurized Gases

Minimally invasive procedures performed within body cavities (laparoscopy, thoracoscopy) or through natural orifices (endoscopy) frequently require pressurized gases to help visualization via scope-mounted cameras. Laparoscopic abdominal procedures can be performed with intra-abdominal pressures of around 15 mmHg, while laparoscopic pelvic procedures may require pressures up to 25 mmHg. Extraperitoneal procedures are typically accomplished with slightly lower insufflation pressures (roughly 12 mmHg).[58] These pressures can easily exceed venous pressure depending on the patient's volume status and position. Because insufflation during gastrointestinal endoscopy is intermittent and low pressure, the risk of VAE is low. However, factors such as active Crohn's disease, bleeding ulcer, duodenocaval fistula, varices, performance of a sphincterotomy, and insufflation within a blind loop of bowel all increase the risk of VAE during endoscopy.[48] Pressurized gas is used in hysteroscopy to maintain the distending pressure established by the irrigating fluid.[33] In an argon beam coagulator, a jet of argon gas delivers an ionized electrofulguration arc to the bleeding tissue, clearing debris and blood[40] and potentially insufflating argon into open vessels. The neodymium:yttrium–aluminum–garnet (YAG) laser requires the use of high flow air, CO_2, or N_2 as a coolant because of the high temperatures generated by the instrument tip.[21] The Cavitron Ultrasonic Surgical Aspirator® uses ultrasonic mechanical energy to vaporize fluid within cells, causing the cells to fragment and release vapor.[59] The use of hydrogen peroxide is another example of generated gas capable of causing embolism. Hydrogen peroxide undergoes catabolism by the ubiquitous enzyme catalase to produce water and oxygen.[52] When used as a surgical irrigant or as an aid to localize fistulous tracts, oxygen embolism can occur.[49–52] It is more likely that hydrogen peroxide is directly absorbed in vascularized closed spaces, resulting in intravascular catabolism and evaporation of oxygen.[50]

The composition of the offending gas can affect the severity of VGE. Gases that are more soluble in plasma lower the risk of VGE.[60,61] CO_2 is used for pneumoperitoneum partially because of its high plasma solubility (0.495 ml/ml blood),[60] ensuring rapid dissolution should VGE occur. Additionally, the lungs function as a filter for gas emboli, with gas bubbles diffusing into alveoli based on its partial pressure gradient. As such, with the patient breathing room air, CO_2 emboli (high partial pressure gradient) decrease in size more rapidly than air emboli (no partial pressure gradient)[62] In dogs, the lethal dose of intravenous CO_2 is at least five times greater than the lethal dose of air.[61] Despite these advantages, episodes of massive CO_2 embolism have been fatal.[28,63] The solubilities of other gases implicated in SGE are as follows: argon 0.029 ml/ml blood; nitrogen (the predominant gas in air) 0.014 ml/ml blood[58]; and oxygen 0.003 ml/ml blood (at normal P_AO_2).

Intravenous Catheterization

VAE occurring in the critical care setting most likely stems from complications of central venous catheterization.[64] The incidence of VAE in the ICU is unknown and despite a mortality that may approach 50%,[65] its significance is probably underappreciated.[66]

VAE may occur during the placement, maintenance, and removal of central venous catheters (CVC), with the majority of cases probably occurring during catheter use.[10] The theoretical rates of air entrainment are governed by Poiseuille's formula and depend on the pressure gradient and certain characteristics of the communication (internal diameter and length of the catheter).[9] The fixed components of the pressure gradient – vertical height above the right atrium and central venous pressure (CVP) – were discussed in a previous section. In a spontaneously breathing patient, the dynamic component becomes important. During inspiration, the negative pleural and intrathoracic pressure increases the pressure gradient favoring air entrainment. Hyperventilation and obstructive pulmonary disease further augment (i.e., makes more negative) this negative inspiratory pressure.[62] In fact, it has been reported that labored breathing may produce negative intrathoracic vein pressures of 25 mmHg.[15] Therefore, the head up position, hypovolemia, and spontaneous, labored ventilation (which coexist commonly in the intensive care unit), all facilitate VAE in the presence of an open vein.

In the past, anesthesiologists have raised the concern that the large bore sheaths used for Swan–Ganz (SG) and pacing catheters may increase the risk of VAE.[64,67] Malfunction of the introducer valve[68,69] and disconnection of the two-part sheath and side-port/valve mechanism[70] have been implicated in reports of massive VAE. Despite the subsequent manufacture of one-piece introducers[70] and standard self-sealing valves,[64] some still recommend that an introducer is not left in place after the removal of the SG or pacing catheter.

There are numerous reports of VAE after the removal of CVCs.[7,65–67,71–74] Surveys of physicians-in-training and critical care nurses have shown a lack of awareness of the potential for VAE after catheter removal.[66,72] Formation of a fibrin sleeve has been shown within 24 h of CVC placement,[75] providing a potentially patent tract for VAE to occur. Possible contributing factors for VAE after CVC removal include upright patient position during or immediately after removal, coughing or straining, coagulopathy, and the use of a non-occlusive dressing.[7,65–67,72–74]

Clinical Presentation

Making the diagnosis of VGE outside the operating room is frequently difficult because the symptoms and signs are nonspecific and may mimic more familiar causes of sudden circulatory and/or pulmonary compromise. Knowledge of the presentation of VGE, the settings in which it occurs, and an

understanding of its pathophysiology are important in its diagnosis and prevention.

Symptoms

Symptoms of VGE in awake-patients may include chest pain, dyspnea, fear of impending death, light-headedness, or dizziness. One patient reported a "crunching sensation" in her chest.[66] Of these symptoms, dyspnea may be the most consistent.[64]

Slow, continuous VGE during spontaneous respiration may elicit a characteristic, reflexive gasp, described in dogs under experimental conditions[76] and clinically in humans.[77] The gasp/cough reflex may be caused by acute hypoxemia[47] or bronchostriction caused by the endothelial thrombo-inflammatory response to the gas embolism.[78] The possible role that this reflex plays in exacerbating VAE by inducing increased negative intrathoracic pressure has been speculated.[76] In contrast, rapid pulmonary embolism of a large volume of gas results in apnea followed by irregular respirations.[79]

Signs

After significant VGE, patients may become pale or cyanotic, diaphoretic, and tachypneic. Neurologic signs ranging from altered mental status to coma are not uncommon.[64] Physical examination may reveal tachycardia, hypotension, wheezing, and the classic mill wheel murmur. Rales and other physical evidence of pulmonary edema may be heard later.

Laboratory Studies and Hemodynamic Monitoring

The electrocardiogram may be normal or show sinus tachycardia, bradycardia, atrial fibrillation, ventricular fibrillation, ST-segment and T-wave changes, or evidence of right heart strain.[33,64,66] These electrocardiographic changes have sometimes been associated with pulseless electrical activity.[64,66]

The initial chest radiograph is usually normal. Rarely, air can be demonstrated in the right heart or central pulmonary artery.[9,64] Later, bilateral interstitial and alveolar infiltrates without cardiomegaly may develop.[77,80] Arterial blood gas commonly shows hypoxia. Hypocarbia[69] or, more typically, hypercarbia[62,64,81] and acidosis may also be seen.

The hemodynamic changes and severity of clinical effects caused by VGE depend primarily on the rate of air infusion and amount infused.[5,76] Based on experiments with dogs, large boluses of air cause a mechanical "air lock" in the right heart and pulmonary outflow tract.[5,76] Slow, continuous infusion of smaller bubbles causes mechanical and vasoconstrictive obstruction more distally in the pulmonary arterial tree.[5,76] Therefore, hemodynamic changes measured by invasive monitors reflect the type of embolism and location of obstruction. Two patterns are seen: (1) In slow infusion VGE, there is an increase in CVP, pulmonary arterial pressure (PAP), and (possibly) cardiac output. There is also a decrease in systemic blood pressure (MAP) due primarily to a decrease in systemic vascular resistance.[76] (2) In rapid bolus VGE, there is a dose-dependent increase in CVP. Once a large, threshold dose is administered, precipitous decreases in PAP and MAP are observed.[76] Without resuscitative measures, these changes usually progress rapidly to cause death.

Pathophysiology

Circulation

As discussed in the previous section, the primary disturbance caused by VGE is obstruction of pulmonary blood flow. Immediate cardiovascular collapse after VGE is likely due to a large vortex of compressible froth that impedes flow in the right heart or renders right ventricular ejection inefficient. This "air trap" or "air lock" mechanism was first proposed by Durant et al.[5] in 1947 and has been supported experimentally,[76] radiographically,[8,9] and by direct[33] and postmortem[8,76] examination. This may present as pulseless electrical activity as a result of obstruction to right ventricular ejection while cardiac electrical activity is preserved.[64]

A study on dogs[82] to evaluate the effect of repositioning on VAE found *no* evidence of this air lock mechanism in "massive" VAE. However, the intravenous infusions of air were relatively slow (boluses over an average of 14 s) and in amounts that were less than previous studies.[5,76] The air infusions in this study resulted in no immediate deaths and in only 5/18 subacute fatalities. All dogs became hypotensive, demonstrated marked elevations in PAP and CVP (consistent with results of previous experiments studying slow infusions),[6] and showed evidence of RV ischemia. These investigators showed that, in dogs, repositioning to partial left lateral decubitus (Durant's position) after VAE resulted in no improvement of hemodynamics as measured by echocardiography.[82] They also introduced an important concept: that subacute circulatory collapse and death after VAE *may* also result from the vicious cycle established by pulmonary hypertension, subsequent elevation of CVP, systemic hypotension, and RV ischemia.[82]

As such, smaller bubbles associated with slow continuous VGE will not cause an air lock in the right ventricular outflow tract, but rather distribute further downstream in the pulmonary arterial tree based on gas buoyancy and preexisting pulmonary flow characteristics.[83] The intravascular gas causes mechanical obstruction and effectively decreases the size of the pulmonary arterial bed. More importantly, neutrophil infiltration[84,85] and release of vasoactive substances results in pulmonary vasoconstriction further obstructing pulmonary blood flow. Pulmonary angiography demonstrates diffuse, bilateral "corkscrewing" and delayed contrast emptying, confirming this pulmonary vasoconstrictive response after VGE.[62] An air-blood interface clumped with fibrin, aggregated platelets, red cells, and fat[86] provides indirect histological evidence of an environment rich with cytokines and other vasoactive substances. Possible mediators include thromboxane A2, thromboxane B2, endothelin-1, histamine, serotonin, leukotrienes,[87] and complement anaphylatoxins, especially C5a.[85]

The cause of hypotension after slow, continuous VGE is multifactorial. Geissler et al.[82] echocardiographically demonstrated decreased left ventricular filling after VAE – presumably from the mechanical and vasoconstrictive pulmonary vascular obstruction. Another study showed that after slow infusion VAE, there was a decrease in peripheral vascular resistance that was associated with an increase in heart rate and cardiac output.[76] It is postulated that right heart stretch- or baro-receptors, responding to dilation or strain, reflexively trigger a vasodilatory autonomic response.[82] As mentioned earlier, progressive hypotension or subacute decompensation may also result from the vicious cycle of pulmonary hypertension, CVP elevation, systemic hypotension, and RV ischemia. In fact, survival after non-air-lock (slow, continuous) VGE is most likely dependent on right ventricular adaptability to the acute increase in pulmonary vascular resistance.[79]

Pulmonary Changes

Hypoxemia is a hallmark of VGE. Air bubbles at the alveolar–capillary interface serve as a barrier to gas exchange,[61] decreasing the pulmonary diffusing capacity. Additionally, marked ventilation–perfusion (V/Q) mismatch has been demonstrated by multiple inert gas elimination techniques in animals during slow VAE.[88] Animal studies have also shown an association between VAE-induced pulmonary hypertension and the development of intrapulmonary shunting.[89] Angiographic studies in dogs suggest the presence of pulmonary arteriovenous anastomoses after VAE.[62] These intrapulmonary right–left shunts explain not only the hypoxemia after VGE, but also the reports of PGE in the absence of intracardiac defects (see section "Neurological Changes").

Partial and dynamic obstruction to pulmonary blood flow leads to a marked increase of regions with high V/Q,[79] effectively increasing the physiologic dead space. This was demonstrated in *rabbits* after slow VAE by an increase in *V*D/*V*T, calculated using the Bohr equation.[90] The decrease in end tidal-CO2 during clinically significant VGE reflects this increase in high V/Q areas and effective physiologic dead space.

Pulmonary edema may occur after a prolonged, occult episode of VGE[81,91] or after multiple, documented episodes,[77,80,92] suggesting that this is a dose-dependent response. Animal studies seem to confirm this impression, with pulmonary edema seen only after prolonged, slow VAE[88] or after near-lethal VAE.[93] The pulmonary edema fluid is characteristically protein-rich[85] despite no evidence of an increase in microvascular protein permeability.[94] It is postulated that the expected increase in lymphatic flow and protein clearance due to edema may be attenuated after VGE, resulting in the high-protein character of the edema fluid.[94] The edema can occur despite low pulmonary capillary wedge pressures, reflecting increased microvascular water permeability. Neutrophil-dependent,[85,95] oxygen radical-mediated[96] damage to both the alveolar epithelium[97] and microvascular endothelium[98] probably underlies this VGE-induced hyperpermeability to water. The pulmonary edema is typically self-limited, although rarely it can progress to adult respiratory distress syndrome.[72]

An animal study utilizing echocardiography suggested another mechanism that can potentially cause pulmonary edema during VAE.[99] Transthoracic echocardiography demonstrated diastolic septal shift and left ventricular compression due to elevated right heart pressures. The authors postulated that this diastolic dysfunction might *potentially* elevate left ventricular filling pressure to levels resulting in a transudative pulmonary edema; however, this has not been clinically documented.

Bronchospasm can also follow VGE. The exact mechanism has yet to be elucidated. Similar vasoconstrictive and bronchospastic responses are seen after pulmonary thromboembolism. Activation of platelets and the coagulation cascade, as well as specific vasoactive substances, have been implicated[62,82] in the pathogenesis of VGE- and PE-induced bronchospasm and vasoconstriction.

Neurological Changes

The neurological manifestations of VGE are usually due to hypoxia or hypotension, and include global changes such as dizziness, light-headedness, confusion, or loss of consciousness. Rarely, VGE may result in paradoxical embolism, producing disastrous consequences. Focal neurologic deficits and myocardial infarction may result from even small amounts of systemic air. Access of air into the systemic circulation is gained through an intracardiac defect or through the pulmonary circulation.

Probe-patent foramen ovale (PFO) is common in the general population, with a prevalence of 27–35%.[100] In the presence of a PFO, a pressure gradient that promotes right–left shunting must be established for passage of air to the left side of the heart. This condition may be met after VGE, with the observed elevation in right heart pressures and underfilling of the left heart. Coughing, Valsalva maneuver, the sitting position, positive end-expiratory pressure, and preexisting respiratory illness or pulmonary hypertension may exacerbate the gradient and increase the risk of paradoxical gas embolism (PGE).[99,100]

However, in a report of 11 cases of PGE, 6 patients were found to have no evidence of an intracardiac defect.[100] This suggests intravascular transpulmonary passage of embolized air. Animal studies have documented that when the intravascular delivery of gas exceeds the lungs' threshold for elimination, gas will "breakthrough" to the systemic circulation. This breakthrough is preceded by an increase in PAP and may be enhanced by agents such as halothane[100] and aminophylline.[62] It is believed that lungs harbor pulmonary arteriovenous shunts that are normally nonfunctional and that these shunts open during VGE under conditions that are currently not well-understood.[99] In contrast, as many as 40% of patients with severe liver disease demonstrate echocardiographic evidence of functional, always-open pulmonary arteriovenous shunts.[101] This pathologic intrapulmonary vasodilation is an important cause of hypoxemia in cirrhotic patients and underlies not only the hepatopulmonary syndrome but also the increased risk of PGE during liver transplantation and hepatic resection, even with a relatively small volume gas embolus.

An alternate mechanism for venous gas to produce neurological injury has recently been submitted.[102] Based on a bench study and a critical radiologic review of case reports of paradoxical cerebral air embolism, the authors suggest that air bubbles may ascend retrograde into the cerebral venous circulation based on buoyancy, bubble size, and venous flow velocities. Review of head CT scans from cases of PAE *supports* their hypothesis, as the air seen is lodged in vessels whose diameters are more consistent with larger cerebral veins.[102]

Treatment

Once gas embolism is suspected, the entrance of more gas into the vasculature must be disrupted. Execution of this vital step depends on the source of gas and location of the vascular communication. Factors that favor the movement of gas intravascularly must be modified promptly, and oxygen at the highest concentration delivered to the patient.

Durant's Position

In a study undertaken to elucidate the mechanism of death from rapid bolus VAE, Durant et al.[5] found that repositioning the animals left side down improved hemodynamics and increased survival, presumably by displacing the offending air lock away from the right ventricular outflow tract. However, two subsequent studies failed to show a beneficial effect of repositioning[76,82] after venous infusions of air that were more consistent with slow, continuous VAE. Therefore, Durant's position, although cumbersome and, at times impractical to undertake, may at least be beneficial in patients with VAE-induced sudden circulatory collapse due to massive VGE and an air lock mechanism.

Closed-Chest Cardiac Massage

Ericsson et al.[103] first reported the successful use of closed-chest cardiac massage in 5/5 patients with VAE occurring during neurosurgical procedures. It was initially proposed as a rapid and practical means of forcing the air lock from the right heart and into the pulmonary circulation. A study of dogs found closed-chest compression as *effective* in improving survival as the use of Durant's position or the aspiration of intracardiac air.[104]

Aspiration of Air

The use of right atrial catheters for air retrieval in sitting neurosurgical procedures has been standard since its value in resuscitation after VAE was established.[105] A subsequent study using an in vitro heart model defined the optimal catheter (multi-orifice) and catheter position (distal orifice 2 cm below the superior vena cava-right atrial junction) for aspiration of air during VAE in the sitting position.[106] These findings were later confirmed in a study of dogs that also showed that survival after VAE improved with air aspiration.[107] Another study showed that resuscitation after VAE was faster after air aspiration compared to chest compression and Durant's maneuver, although survival rates did not differ between the groups.[104] It should be noted that a catheter in this "optimal" position loses some of its effectiveness for air retrieval if the patient's position (prone, lateral decubitus, supine) and the source of VGE (inferior vena cava) are varied.[108]

Supportive Measures and Oxygen Therapy

Rapid resuscitation is important in the successful treatment of massive VGE.[103] Resuscitative measures may include both hemodynamic and ventilatory support. It has been suggested that the successful modern management of VGE addresses not only arterial hypotension but also pulmonary hypertension.[82] The importance of right ventricular ischemia in the pathogenesis of VGE-induced circulatory collapse has been recently emphasized.[79,82] As such, the pharmacologic therapy of VGE has mainly been focused on the interrelated processes of right ventricular dysfunction and pulmonary arterial vasoconstriction. Studies of pulmonary embolism in animals report beneficial effects of both dobutamine[109] and norepinephrine[110] infusions, but epinephrine may be the catecholamine of choice for hemodynamic support after VGE.[79] Experimentally, inhaled nitric oxide improved hemodynamics via its effects on pulmonary vascular resistance in dogs after massive VAE.[111] A study in rabbits suggests that any hope of a favorable physiological response to VAE requires an intact endogenous production of nitric oxide, as blockade of this system resulted in universal fatalities.[112] In dogs, antagonism of endothelin-1, a vasoactive mediator released after pulmonary embolism, attenuated both the decrease in mean arterial pressure and the increase in pulmonary vascular resistance seen after VAE. [87] Anecdotally, inhaled epoprostenol has been used successfully after carbon dioxide embolism, resulting in prompt normalization of PAP.[45]

Positive pressure ventilation should be provided when needed after VGE, with the appreciation that high levels of positive end-expiratory pressure may establish a gradient that promotes right–left shunting through a PFO.

Administration of 100% O_2 after VAE attenuates the air load in the pulmonary vasculature by hastening the elimination of the nitrogen through the capillary–alveolar barrier. Nitrogen will "wash out" into the alveoli based on its partial pressure gradient; administration of O_2 denitrogenates the alveoli, establishing a gradient that is conducive for the elimination of nitrogen from the pulmonary microvasculature.

The use of hyperbaric oxygen therapy for gas embolism has focused primarily on SGE patients with neurologic injury. *Timing* of therapy is important; longer delays may decrease the likelihood of improvement.[62] The theoretical benefits of hyperbaric oxygen are: (1) increased oxygen delivery (via increased arterial partial pressure of O2); (2) decreased air/gas volume (compression effect), decreasing the obstruction

to blood flow; and (3) high alveolar partial pressure of oxygen, increasing nitrogen/gas washout.[62]

Experimental Therapies

Perfluorocarbon emulsions (PFCE) contain fluorine-substituted hydrocarbons that are characterized by low viscosity and greatly enhanced capacity for dissolving gases (solubility for gases roughly 100,000 times that of plasma).[56] Experiments in animals show that pretreatment with PFCE decreased mortality,[113] decreased infarct size,[114] and improved hemodynamics[115] after VAE. These effects are thought to be due to the ability of PFCE to reduce bubble size,[116] increase oxygen delivery,[115] and increase respiratory washout of nitrogen.[115]

Experiments in animals have also sought to modify the neutrophil-induced endothelial injury and resulting increased vascular permeability after VGE. Antagonism of the anaphylatoxin C5a by monoclonal antibodies in rabbits attenuated neutrophil infiltration of the endothelium after slow, continuous VGE. However, this response was not specific to anti-C5a, as non-specific antibody-treated animals also showed a trend toward diminished infiltration.[86]

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Part V
Infectious Diseases, Sepsis, MODS

27
Sepsis

Patricia Mello and R. Phillip Dellinger

Epidemiology

Sepsis represents the *body's response* to an infectious insult. It is characterized by the dysregulation of the inflammatory response and of the coagulation homeostasis leading to a pro-inflammatory, prothrombotic, and antifibrinolysis state. Depending on the host's predisposition and comorbidities, as well as on the nature and intensity of the insult, sepsis may progress to severe sepsis, which may be associated with circulatory shock, cellular dysfunction, multiple organ failure, and death.

Severe sepsis has become one of the most important diagnoses in intensive care units (ICUs) worldwide. This condition carries alarming morbidity and mortality rates and increases hospital costs significantly. Sepsis is the *leading cause* of death in critically ill patients in the United States. Current estimates are that approximately 750,000 people develop sepsis and more than 200,000 die annually in the United States from this condition. The reported mortality rate in patients with severe sepsis in the United States ranges from 28 to 50%.[1,2] Dombrovskiy et al. reviewed rates of hospitalization, mortality, and hospital case fatality for severe sepsis in the United States from 1993 to 2003. The report revealed that more than 8,403,766 patients were hospitalized with sepsis. This represents a much greater number than previously predicted. The percentage of severe sepsis cases among all sepsis cases increased from 25.6% in 1993 to 43.8% in 2003 ($p<0.001$). Age-adjusted rates for severe-sepsis hospitalization and mortality increased annually by 8.2% ($p<0.001$) and 5.6% ($p<0.001$), respectively, whereas the case fatality rate decreased by 1.4% ($p<0.001$).[3]

Most studies report estimates that the incidence of severe sepsis is about $10\pm4\%$ of ICU patients with a population incidence of 1 ± 0.5 cases per 1,000. Martin et al. reported an annual increase in sepsis incidence of 8.7% and observed that despite the increase in the number of sepsis-related deaths, there was a decline in the overall mortality rate among patients with sepsis from 1979 to 2000. They also reported the predominance of gram-positive bacteria as the microorganism involved in the syndrome since 1987 and an increase of a staggering 207% in the rate of sepsis caused by fungal infections. An increased incidence and mortality rate is observed in males and in nonwhite patients as compared to female and white patient populations.[4]

The incidence of severe sepsis is expected to continue to rise, with its rate of increase *outpacing* the rate of increase of the U.S. population. The differential in growth rate is likely to be a result of age shifts in the U.S. population over the next 50 years and increased complexity of critically ill patients.[1,5] As pointed out by Linde-Zwirble and Angus,[2] "Importantly, the availability of ICU services may well determine the number of treated cases of severe sepsis, and it seems clear that these studies are reporting the treated incidence, *not* the incidence, of severe sepsis."

Known cases of severe sepsis probably represent only the tip of the iceberg. Severe sepsis is likely underdiagnosed and underreported. It is not contagious and does not require notification of authorities. It is possibly underreported as a primary

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diagnosis because it occurs in association with other disorders and is coded as a complication of those disorders (e.g., pneumonia or cancer). Such expressions as "looks septic" and "becoming septic" are still common and reflect the *uncertainty* present in the actual diagnostic criteria of this disorder.

Despite this likely underdiagnosing, severe sepsis and its resulting mortality are *higher* than reported occurrences of and mortality from breast cancer and acquired immunodeficiency syndrome (AIDS). The occurrence of severe sepsis is also greater than the occurrence of acute myocardial infarction (AMI), and its mortality rate stays only slightly behind deaths caused by the first AMI.[1,6,7] To better understand the precise mortality of severe sepsis, improved diagnostic criteria are needed not only to have uniform entry criteria and interpretation of research results but also for better application of diagnostic and therapeutic guidelines in the management of patients.

Definitions in Sepsis

The word 'sepsis' originates from Greek, meaning "putrefaction." Long after the word was developed, Pasteur made the association between the presence of bacteria and putrefaction.

In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) published a Consensus Conference statement introducing the term "systemic inflammatory response syndrome" (SIRS) (Fig. 27.1). The syndrome is considered to be present when patients have more than one of the following clinical findings[8]:

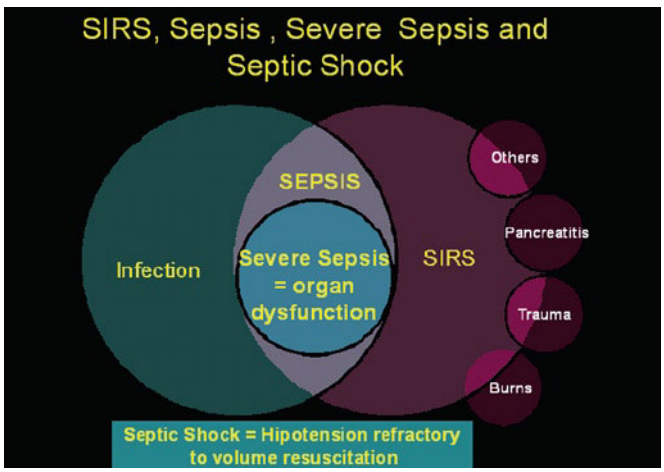

FIG. 27.1. Sepsis diagram. This Venn diagram illustrates the interrelationship of the various components of sepsis. As shown, the overlap between infection and systemic inflammatory response syndrome (SIRS) constitutes sepsis; the concomitant presence of multiple organ dysfunction syndrome (MODS) establishes the diagnosis of severe sepsis. If one were to place septic shock in this diagram, it would appear as the bull's eye in the center of the severe-sepsis circle. The tight link between inflammation and hemostasis was not included in this diagram from the 1992 ACCP/SCCM Consensus Conference because the interrelationship was not fully appreciated at the time.[8,9] Adapted with permission from ref. 8.

- Body temperature >38 or <36°C
- Heart rate >90 min^{-1}
- Hyperventilation evidenced by a respiratory rate of >20 min^{-1}, or a pressure of carbon dioxide (PaCO2) of <32 mmHg
- A white blood cell count of >12,000°cells μL^{-1} or <4,000°µL or >immature 10% neutrophils.[8]

A problem with the SIRS criteria is the lack of specificity for sepsis because these findings may occur in response to a variety of different insults (e.g., infection, trauma, thermal injury, or sterile inflammatory processes such as acute pancreatitis). Therefore, if the nature of the insult triggering SIRS is thought to be infectious, sepsis is present. The Consensus Conference also defined "severe sepsis" as sepsis causing organ dysfunction, sepsis-induced tissue hypoperfusion as sepsis-induced oliguria, and elevated lactate or hypotension (systolic blood pressure <90 mmHg or a decrease from baseline of 40 mmHg or greater) and "septic shock" as sepsis with hypotension persisting after "adequate" volume resuscitation.

The problem with the 1992 Consensus Conference definition of sepsis is that both a previously healthy 15-year-old with paronychia, fever, and tachycardia as well as an elderly patient who is a heavy smoker with diabetes, pneumonia, fever, and tachycardia would both be labeled as having sepsis. It also does not help the identification of patients who will develop organ failure.[9,10] Nevertheless, this definition does encourage the identification of patients with systemic manifestations of infection who should be targeted for more aggressive monitoring and lactate measurement.

The definition of severe sepsis requires the presence of organ dysfunction, but consensus on the threshold for what should be considered "organ dysfunction" in each organic system is still lacking. Thresholds established were somewhat arbitrary. With regard to the definition of shock, the focus is still on the presence of refractory hypotension following fluid resuscitation that requires vasopressor therapy. However, tissue hypoperfusion is *not* just about blood pressure. Concentrating solely on blood pressure could lead physicians to underestimate the need to direct more aggressive therapy toward correction of the cellular oxygen deficit and optimization of the oxygen delivery–oxygen uptake (DO2–VO2) relationship with normalization of both flow and cellular use of oxygen.

The definitions were revisited in 2002, with few changes.[11] One change was the broadening of signs, symptoms, and laboratory findings signaling the possibility of the presence of sepsis (Table 27.1). The second change was the inclusion of PIRO (see the next section). Organ dysfunction and the severity of organ dysfunction can be defined using the definitions developed by Marshall et al.[12] or the definitions used for the Sequential Organ Failure Assessment (SOFA) score.[13] Septic shock is still defined as persistent arterial hypotension – systolic blood pressure (SBP) <90 mmHg, mean arterial pressure (MAP<60), or a reduction in systolic blood pressure of >40 mmHg from baseline – despite adequate volume resuscitation, in the absence of other causes of hypotension.

TABLE 27.1. Coagulopathic criteria for sepsis.[11]

General variables	Inflammatory variables	Hemodynamic variables	Organ-dysfunction variables	Tissue-perfusion variables
Fever (core temperature >38.3°C)	Leukocytosis (WBC count >12,000 μL^{-1})	Arterial hypotension[b] (SBP < 90 mmHg, MAP <70, or an SBP decrease >40 mmHg in adults or <2 sd below normal for age)	Arterial hypoxemia (PaO_2/FiO_2 <300)	Hyperlactatemia (upper limits lab normal)
Hypothermia (core temperature <36°C)	Leukopenia (WBC count <4,000 μL^{-1})	SO_2 >70%[b]	Acute oliguria (urine output <0.5 mL $kg^{-1} h^{-1}$ or 45 mmol/L for at least 2 h)	Decreased capillary refill or mottling
Heart rate >90 min^{-1} or >2 sd above the normal value for age	Normal WBC count with >10% immature forms	Cardiac index >3.5 L $min^{-1} M^{-23}$	Creatinine increase >0.5 mg/dL	hypotension, $ScvO_2$
Tachypnea	Plasma C-reactive protein, INR, aPTT >2 sd above the normal value		Coagulation abnormalities (INR >1.5 or aPTT >60 s)	
Altered mental status	Plasma procalcitonin >2 sd above the normal value		Ileus (absent bowel sounds)	
Significant edema or positive fluid balance (>20 mL/kg over 24 h)			Thrombocytopenia (platelet count <100,000 μL^{-1})	
Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes			Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)	

Adapted from Levy M, Fink MP, Marshall JC. et al. For the International Sepsis Definitions Conference. Crit Care Med 2003;31(4):1250–1256, by permission of Wolters Kluwer Health.

WBC white blood cell; *SBP* systolic blood pressure; *MAP* mean arterial blood pressure; *Svo_2* mixed venous oxygen saturation; *INR* international normalized ratio; *aPTT* activated partial thromboplastin time.

Infection, documented or suspected, and some of the following:

[a]Infection defined as a pathologic process induced by a microorganism;[b]Svo_2 sat >70% is normal in children (normally, 75–80%), and CI 3.5–5.5 is normal in children; therefore, NEITHER should be used as signs of sepsis in newborns or children; [c]diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5 or <35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

PIRO

Sepsis, like cancer, has variable causes, clinical courses, and therapeutic responses, generating a very complex and heterogeneous patient population. In sepsis, there is dysregulation of the mechanisms that control inflammation and coagulation, while in cancer there is a dysregulation of normal cellular growth and differentiation. Both conditions have their prognosis strongly influenced by genetic predisposition of the host, individual host response mechanisms, and presence of comorbidities. That is why the same infectious insult may cause pneumonia in one group of patients, severe sepsis in another group, and septic shock in a third group.

The creation of a stratification model has been proposed to better identify the various subgroups of patients with severe sepsis and provide a formal process similar to that of the oncology tumor/nodes/metastasis (TNM) model. The PIRO model – where P stands for predisposition; I for infection; R for response and O for organ dysfunction – considers the heterogeneity of the patients who develop sepsis and the heterogeneity of the insult itself. PIRO could make possible the assignment of viable prognostic "scores" for these patients [11,14] (see Fig. 27.2 and Table 27.2).

There is a strong belief that the future of classification of septic patients and decisions on aligning the best therapeutic interventions for those patients rests with biochemical and immunological criteria.[15,16] Biomarkers and biomarker profiles, rather than clinical criteria, would be used to characterize the inflammatory response, allowing us to differentiate patients with SIRS caused by sepsis from patients with SIRS caused by other insults, as well as to help identify patients with sepsis that will progress to severe sepsis and shock. Much work is being done in this area, but currently this capability does not exist.[13]

The biomarker profile of septic patients could be used in a similar fashion as tumor markers or histopathology are used in cancer.

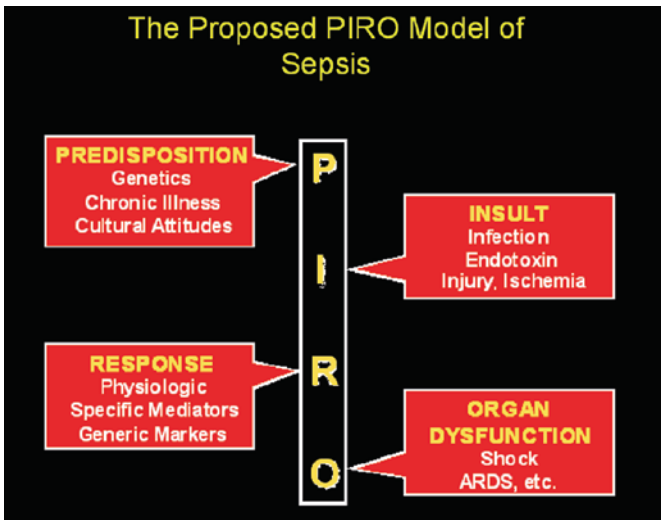

FIG. 27.2. The proposed PIRO model of sepsis. Slide from ref. 14. Copyright © Society of Critical Care Medicine. Reproduced by permission of the publisher.

Table 27.2. Example of PIRO classification.[14]

Stage 1 sepsis
P1: Absence of chronic comorbidities
I1: Abdominal infection without source control issues
R1: Immune response activation (↑ WBC, C-reactive protein, ↑ procalcitonin)
O0: Absence of hypotension, improved with volume resuscitation

WBC white blood cell.

It would be inconceivable to initiate a patient on chemotherapy based on unspecific data (significant weight loss, anorexia, the presence of a lung mass) and the assumption that "most likely" a patient with this triad has cancer. But, in sepsis, we still use SIRS to identify patients with sepsis and use the same "bundle of interventions" for all patients, even though we understand that septic patients do not all respond in the same way. The presence of different "response profiles" in septic patients is likely an important cause for the failure seen in multiple immunotherapy trials targeting the inflammatory and coagulation cascade. We may have individuals who need antagonization of tumor necrosis factor (TNF) production, having their outcome improved by an anti-TNF agent, but there are others who do not benefit or may even be harmed by it. However, other studies suggest a beneficial impact in severe sepsis within specific subgroups.[17]

Good evidence exists that *genetic differences* in immune responses may affect susceptibility to and outcome of septic shock. Investigators have identified, in both experimental and clinical studies, genetic polymorphism in important inflammatory mediators such as TNFa and also in toll-like receptors (TLR4) that are associated with clinical phenotypes. The presence of genetic alteration of the TNFa promoter (TNFa2) gene at position 308 is associated with individuals predisposed to an exacerbated inflammatory response.[18] These patients may have a lower chance of becoming infected, but, once infected, mount a more aggressive response that may put them at increased risk from the pro-inflammatory response than from the intruder itself.

Optimization of therapy will only be feasible through identification of useful sepsis markers and more homogeneous subgroups of patients in order to better guide prognosis and therapy. Future immunotherapy directed to modulating the inflammatory and coagulation cascade probably will be individualized. Therefore, the PIRO model may help this become possible.

Pathogenesis

Inflammation, Coagulation, and Immune Dysfunction

Once microbial products like lipopolysaccharides are identified by toll-like receptors (TLRs), cellular activation is induced and a series of events are triggered. Immune cells (e.g., neutrophils, monocytes, macrophages, and lymphocytes) are activated and an inflammatory response initiated with the release of pro-inflammatory cytokines. This is followed by a compensatory antiinflammatory response syndrome. In severe sepsis, the activation of the inflammatory pathways occurs in a dysregulated manner, leading to the onset of organ damage and, eventually, to a refractory state characterized by a down-regulation of the capacity of mononuclear cells to produce pro-inflammatory cytokines on stimulation ex vivo. The coagulation is also activated through the tissue factor pathway concomitant with changes in the expression of various adhesion molecules, leading to alteration of the balance between the anticoagulant and prothrombotic state of various endothelial cells with increased thrombin generation and fibrin deposition.

Investigators have detected elevated circulating levels of several cytokines in patients with severe sepsis, and new cytokines continue to be identified. Elevated levels of interleukin 6 (IL-6),[19] C-reactive protein,[20,21] and procalcitonin[22–24] seem to be useful as markers of the presence of inflammation; and procalcitonin also may be useful as a marker of active ongoing infection.

An early and significant elevation of TNFa, IL-1, and nitric oxide (NO) has triggered the development of a number of trials aiming to block pro-inflammatory pathways action (TNF antagonists[25,26]; IL-1–receptor antagonists[27,28]). Benefit from this strategy has not been demonstrated, and in some studies increased mortality was observed.[25,29] Elevated levels of macrophage inhibitory factor (MIF) and endogenous high-mobility group box 1 (HMGB1) have been associated with increased mortality of septic patients; and some early phase studies have suggested a potential benefit of inhibiting these cytokines.[30,31] The continuing evolution of the complex molecular biological interactions is fascinating. A representative summary of current understanding is shown in Fig. 27.3.[32]

The alterations in the coagulation, inflammation, and immune function have a dynamic pattern in sepsis. That pattern varies according to genetic predisposing factors, the infecting organism, local factors, and even organ-to-organ in the same patient. This may be the best explanation of why agents targeting the clinical syndrome of severe sepsis have generally failed to reduce mortality in these patients and reinforces the need for aiming the development of *individualized therapy* based on the patient's individual "biochemical response profile."

Macrocirculation and Microcirculation

The hemodynamic profile of the septic patient will vary according to the stage of the disease, status of resuscitation and with the patient's comorbidities. A myriad of physiologic changes occur with severe sepsis. Massive cytokine release triggering vasodilating properties (e.g., nitric oxide) leads to a significant decrease in afterload. Hypotension and decreased preload occur as a result of vasodilation and loss of normal vascular tone, external fluid losses, and internal fluid redistribution.

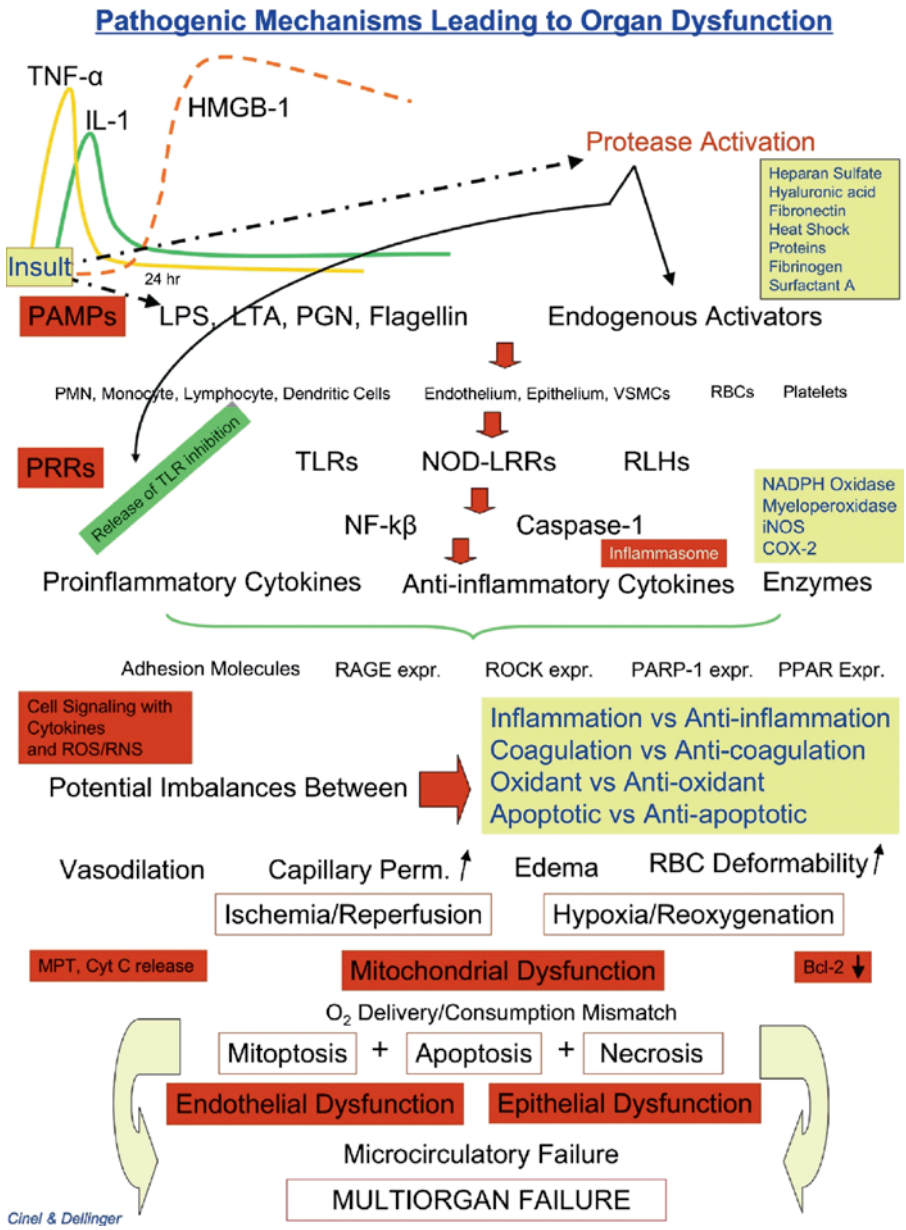

FIG. 27.3. Pathogenic mechanisms leading to organ dysfunction. Courtesy of Ismail Cinel, MD, PhD, Camden, New Jersey and reprinted with permission from ref. 32, Review, Lippincott.

Cardiac output (CO) tends to be increased following fluid resuscitation. It is important to recognize that this hyperdynamic pattern is only seen in well-resuscitated patients, because profound hypovolemia existing at the time of presentation in many patients caused by capillary leak may be associated with a decreased cardiac output. It is now recognized that at the time of presentation septic patients may be hypodynamic with poorly filled left ventricles and low cardiac output. Cytokine release may also lead to myocardial depression. Table 27.3 shows hemodynamic alterations that might be found in patients in the various stages.[33,34] This presentation can evolve over time from "pre-shock" to "warm," and then to "cold" shock. Notably, these stages are not obligatory and patients do not necessarily pass from warm to cold shock. Other changes that can occur in patients with septic shock include loss of autoregulatory mechanisms and decreased vascular sensitivity to catecholamines.[33]

In the absence of clinically overt shock, hypoperfusion and microcirculation failure can be demonstrated through lactate elevation despite the presence of normal systemic pressures. More recently, perturbations on microcirculatory flow have been demonstrated through direct visualization

TABLE 27.3. Hemodynamic alterations of septic shock.[33]

Parameter	Severe sepsis prior to fluid resuscitation	Severe sepsis after fluid resuscitation
Heart rate	↑	↑
Blood pressure	↓	↓
Systemic vascular resistance	↓↓	↓↓
Cardiac output	↓	↑
Pulmonary artery occlusive pressure	↓	

of microcirculation with Orthogonal Polarization Spectral (OPS) Imaging.[35]

We now understand that the microcirculation represents an immense invisible stage where oxygen and nutrients are delivered to the cells. The vascular endothelium functions as an "organ" capable of adjusting its vasomotor tone, hemostatic balance adhesion properties, and cell survival/apoptosis pathways. It responds to several neurohumoral substances, oxygen, CO2, lactate, lipopolysaccharide (LPS), cytokines, reactive oxygen metabolites, thrombin, and flow. Its structure and function is heterogeneous and varies in different organs. Its response to the various stimuli varies in space and time, producing phenotypic heterogeneity in the response to sepsis. The endothelium has an important role in the regulation of the release of hemostatic factors, including von Willebrand's factor (vWF), tissue factor (TF), thrombin receptor (TR), plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (t-PA), tissue factor pathway inhibitor (TFPI), thrombomodulin, and protein C receptor.[36,37]

Nitric oxide is released from endothelial cells following hypoxia and cytokine stimulation, causing vasodilation,[38,39] and represents an important regulator of microcirculatory flow. In sepsis, this occurs as a heterogeneous expression of inducible nitric oxide synthase (iNOS), potentially altering distribution of flow.[40,41] Areas where iNOS is poorly expressed will lead to hypoxia and elevation of lactate concentration. Tissue hypoperfusion in specific vascular beds may be present despite normal values of systemic oxygen variables (SvO2, ScvO2). In addition to the disturbed coagulation and loss of ability of endothelial cells to control smooth muscle tone,[42,43] the red blood cells become less deformable and aggregate more.[44] Activation of leukocytes generates reactive oxygen species that directly disrupt microcirculatory structures, cellular interactions, and coagulatory function.[45–47] Severe microcirculatory dysfunction may ensue, leading to hypoperfusion, oxygen extraction deficit, and cellular respiration distress.[40,41,48]

It is well known that despite normalization of blood flow and systemic pressures and optimization of oxygen delivery, lactate production may continuously point to ongoing cellular distress. In this scenario, it is also observed that mixed venous saturation remains elevated, signaling a problem with oxygen extraction as opposed to a problem with oxygen delivery. Cellular respiration is affected profoundly and metabolic failure ensues. This has been called cytopathic hypoxia. Its occurrence is intrinsically related to the microcirculatory failure and probably plays an important role in the development of multiple organ dysfunction. The microcirculatory and cellular derangements in sepsis have made common a new medical term: Microcirculatory and Mitochondrial Distress Syndrome (MMDS).

It has been postulated that the metabolic failure seen in these patients could potentially represent a natural defense mechanism of cell survival. The cell would enter into a hibernating state upon sensing that delivery of nutrients is scarce. This theory is supported by several studies that show that, even though there is an important mitochondrial derangement in sepsis, cell death is not a major finding in its pathogenesis. Cell death would be the expected finding if this were a consequence of a "cell failure" process as opposed to a "cell protection" mechanism.[49]

Diagnosis and Treatment

Once the diagnosis of severe sepsis is made, early and aggressive diagnostic and therapeutic measures must be implemented in order to *minimize* progression of organ dysfunction. Multiple interventions must be started simultaneously to achieve hemodynamic stabilization with optimization of the volume status and oxygen delivery, bacterial killing, source control, and adjuvant support measures. In selected cases, the use of recent, trial-supported innovative therapy is warranted in order to limit the cellular and organ damage that would lead to multiple organ failure and eventual death.

Source Control and Antibiotics

Early and appropriate initial empirical *antibiotic therapy* is crucial for better outcomes. The empirical coverage should be broad and modified by local data and adjusted with subsequent culture results to minimize the potential to increase bacterial resistance patterns. *Antibiotics* should be started immediately after the drawing of appropriate cultures and within a few hours of clinical diagnosis. Studies have shown that the mortality of these patients can increase significantly if delays on the first antibiotic dose occur.[50] Mortality is also increased if the initial empirical coverage is inappropriate. This impact on mortality is not improved even if the antibiotic regimen is adjusted after availability of culture results. This highlights the need for early and correct initiation of antibiotic coverage.[51] *Identification* of the likely focus or foci is essential because it helps guide the specific diagnostic workup as well as the appropriate choice of empirical antibiotic. It is important to know the microbiological patterns as well as the antibiograms from the hospital setting in which the patient acquired the infection because they may vary greatly from ICUs in the same hospital or from hospital to hospital. Therapy principles should include the use of antibiotics that penetrate to the site of infection and the use of the correct dose and route with coverage matching the microorganism sensitivities.

Short courses should be used if good clinical response is obtained[52]; prolonged combination therapy should be avoided, and a de-escalating strategy based on culture results is recommended. Early drainage of abscesses and removal of infected devices is *key* for a good outcome. Unnecessary delays for surgical drainages should be avoided.

Hemodynamic Support and Optimization of Oxygen Delivery

The initial approach to treating patients who have severe sepsis requires evaluation and support of the ABCs of resuscitation: airway, breathing, and circulation. It is imperative to optimize every determinant of oxygen delivery; evaluating and optimizing the determinants of adequate oxygen content (e.g., hemoglobin, arterial oxygen saturation) and of cardiac output (heart rate and stroke volume) (Fig. 27.4). Optimization of stroke volume requires accurate assessment of its determinants (preload, contractility, and afterload); and, in refractory cases, *invasive monitoring* is recommended to track the response of fluid resuscitation, inotropic agents, and vasoactive amines on filling pressures, volumes, and cardiac output. Elective intubation and early ventilatory support in the presence of respiratory distress can ease the work of breathing and help support adequate oxygenation to other tissues. A lung-protective strategy with low plateau pressures (equal to or lower than 30 cmH2O) and low tidal volumes (6 mL/kg ideal body weight or less) for mechanically ventilated patients is recommended in cases of sepsis-induced acute lung injury. Elevated PaCO2 levels may be *permitted* while limiting tidal volumes and plateau pressures (Pplat) as long as pH is ≥7.21. The exception would be in patients with coexisting elevated intracranial pressure. Circulatory support involves early assessment and correction of compromised intravascular volume status, usually requiring aggressive fluid resuscitation. In the event of tissue hypoperfusion persisting even after initial fluid bolus of 20 mL/kg crystalloid or colloid equivalent or serum lactate 4.0 mmol/L, monitoring of filling pressures (e.g., central venous pressure [CVP] or pulmonary artery pressures) is recommended. Resuscitation should be targeted to a urine output of 0.5 mL/kg/h or greater and central venous or mixed venous saturation of 70 and 65%, respectively.

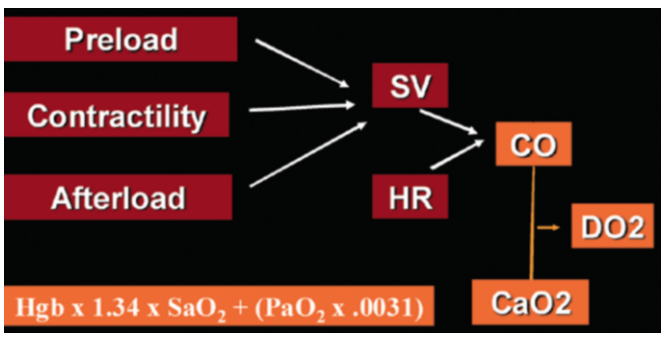

FIG. 27.4. Determinants of effective tissue perfusion. *SV* systolic volume; *HR* heart rate; *CO* cardiac output; *DO2* oxygen delivery; *CaO2* arterial oxygen content.

The mean arterial pressure (MAP) should be maintained at 65 mmHg and higher in patients with a history of hypertension. Following adequate fluid resuscitation, persistent hypotension is caused by a combination of decreased contractility and arteriolar vasodilation. Dopamine and norepinephrine, as combined inotrope/vasopressors, are recommended as the first-line drugs to maintain MAP at 65 mmHg. Despite the frequent use of these drugs, very few studies are available comparing them in the setting of septic shock. In a small, randomized, double-blind trial, Martin et al. compared norepinephrine to dopamine in 32 patients with septic shock.[53] The expected elevation in both MAP and cardiac index (CI) was achieved in 93% of patients started on norepinephrine versus only 31% of patients started on dopamine ($p<0.001$). Furthermore, ten of 11 patients who did not respond to dopamine were successfully treated with the subsequent addition of norepinephrine. These findings suggest that *norepinephrine may be more effective* and reliable at reversing hypotension in septic-shock patients. In 2000, Martin et al. published a later prospective, observational cohort, nonrandomized study, comparing norepinephrine to dopamine in 97 adult patients with septic shock.[54] Using stepwise logistic regression analysis, norepinephrine was found to be the only factor associated with significantly improved survival ($p=0.03$) and this is the only study that suggested better outcomes with the use of norepinephrine than with dopamine. The 57 patients who were treated with norepinephrine had significantly lower hospital mortality (62% vs. 82%, $p<0.001$; relative risk = 0.68; 95% confidence interval = 0.54–0.87) than the 40 patients using dopamine or epinephrine or both.

Some studies suggest that dopamine can affect the production of hormones depending on the hypophyseal–hypothalamic axis.[55] Dopamine may increase intracranial pressures (ICP) in severely head-injured patients[56]; it may cause more splanchnic hypoperfusion[57]; and it is more likely to produce tachycardia when compared to norepinephrine.[58] The use of low-dose (2 µg/kg/min) dopamine as a strategy to protect renal function is not indicated. It may increase urine output, but it does not improve kidney perfusion and it does not decrease the need for hemodialysis.[59] Nonetheless, to this date, no large study has compared both drugs, and either one may be considered as a first choice of vasopressor in sepsis-induced hypotension.

Epinephrine is recommended as the second-tier inotrope/vasopressor for sepsis-induced hypotension. A recent prospective, multicenter, randomized, double-blind study compared the use of norepinephrine plus dobutamine with the use of epinephrine alone in 330 patients with septic shock.[60] The drugs were titrated to keep a MAP at 70 mmHg or above. The rates of serious adverse effects were similar in both groups; and no significant differences in mortality rates or in the time to hemodynamic success, time to vasopressor withdrawal, and time course of SOFA score were observed. Although this suggests that both epinephrine alone and norepinephrine plus

dobutamine may be considered equally safe and efficacious in the hemodynamic support of septic patients, the mortality in the epinephrine group at 28 days was 40% versus 34% in the norepinephrine-plus-dobutamine group; and there is a possibility that the study was underpowered to show benefit of norepinephrine plus dobutamine through 28 days.

Serum vasopressin is often found to be depleted in patients with septic shock but not in patients with cardiogenic or hypovolemic shock.[34] After an initial spike of vasopressin in septic shock, normal levels are found within 24–48 h despite the presence of persistent hypotension.[61] This has been termed "relative vasopressin deficiency." Small studies have demonstrated potential hemodynamic benefit with the use of low doses of vasopressin in cases of refractory shock and have shown vasopressin to increase not only MAP but also urine output.[62–66] Recently, the Vasopressin in Septic Shock Trial (VASST) – a randomized, controlled trial that compared the use of norepinephrine alone to the use of norepinephrine plus vasopressin at 0.03 units/min – showed no difference in outcome in the intent to treat the population. In a subgroup analysis, however, patients receiving less than 15 μg/min of norepinephrine at the time of randomization showed a survival benefit in the group treated with norepinephrine and vasopressin.[67] It should be noted that the rationale for the stratification to norepinephrine requirement below 15 μg/min was the possibility of benefit in the higher norepinephrine subgroup, not in the lower-dosed group. The results of this subgroup analysis should, therefore, be viewed with caution. Care should be taken when vasopressin is initiated, particularly at doses higher than 0.04 units/min because administration has been associated with significant vasoconstriction in the coronary, splanchnic, and skin circulation.[68]

A randomized, non-blind trial by Rivers et al.[69] in septic patients with systolic blood pressure £90 mmHg after 20 mL/kg of crystalloids or a lactate ³4 mmol/L demonstrated improved outcome with, what in this study was called, early goal-directed therapy (EGDT), where the *early resuscitation* (first 6 h) was guided by specific formulas for volume, inotrope/vasopressor drugs, and blood transfusion. By titrating therapy not only to optimize filling pressures but also for optimization of systemic oxygenation parameters, the investigators were able to demonstrate benefit in survival. Hospital mortality was decreased markedly (30.5% vs. 46.5%; $p=0.009$), as was mortality at 28 days (33.3% vs. 49.2%; $p=0.01$) and at 60 days (44.3% vs. 56.9%; $p=0.03$). Although the formula for aggressive resuscitation used in this study is not necessarily the only or the optimal early aggressive resuscitation formula, this study has served as a model for the importance of early identification and aggressive resuscitation during the critical initial hours of presentation of sepsis-induced tissue hypoperfusion.

The challenge of early adequate assessment of intravascular volume status is great. How one judges fluid responsiveness, hemodynamic profile, and perfusion status at bedside is *not* easy. The correct use and interpretation of available tools is key. Monitoring of filling pressures is limited in the presence of preexisting decreased ventricular compliance, in patients on mechanical ventilation, or with increased intra-abdominal pressures. Nonetheless, these measures are important tools in the resuscitation of these patients as they are generally available and encourage more aggressive fluid resuscitation, especially by physicians who have less experience with these patients. In patients with normal intrathoracic and intra-abdominal pressure and normally compliant left ventricles (normal wall thickness and diastolic resistance) a central venous pressure of 8–12 mmHg is recommended. Higher filling pressures are recommended when these circumstances do not exist. Trends in the filling-pressure values are likely more important than their absolute values; and *surveillance* of the patient's responses (increases in arterial pressure, decreases in heart rate, or improvements in tissue perfusion) is crucial for optimizing use of bedside hemodynamic monitoring.

Studies by Harvey et al. and Wheeler et al. have failed to demonstrate the utility of the pulmonary artery catheter (PAC) in improving outcome in septic shock.[70,71] Neither of these studies evaluated the use of the attached PACs to apply a specific treatment protocol. Despite the lack of randomized trials showing the benefit of PAC use in septic shock, monitoring with PAC allows measurements of intracardiac pressures, determination of cardiac output (CO) with thermodilution, and measurement of mixed venous oxygen saturation (SvO2), which offers objective assessment of the patient's hemodynamic profile and changes in response to therapeutic interventions. Volumetric catheters allow evaluation of end-diastolic volume that may represent more reliable assessment of intravascular volume than pulmonary artery occlusion pressure (PAOP) in the absence of pulmonary artery hypotension. Intracardiac volume can also be monitored with a transpulmonary thermodilution and pulse contour analysis system (e.g., PiCCO™ system) through the calculation of intrathoracic and intravascular fluid volume.[72,73] Continuous monitoring of stroke volume is also possible with pulse contour analysis referenced to measurement of cardiac output with either dye-dilution or lithium-dilution measurement of cardiac output.[74–76] In addition, in mechanically ventilated patients, the use of esophageal Doppler allows the tracking of effect of resuscitation intervention on cardiac output.[77]

A normal systemic pressure does not guarantee adequate tissue perfusion. *Optimization* of systemic oxygenation parameters with a target of central venous oxygen saturation ($ScvO_2$) of 70% or higher, or mixed venous oxygen saturation (SvO_2) of 65% or higher, is recommended in patients with persistent sepsis-induced hypotension (vasopressor requiring) or lactate 4.0 mmol/L. Even normal or high SvO_2 is not a guarantee of adequate resuscitation because it reflects global oxygenation and regional hypoperfusion may still be present. Nonetheless, a low SvO_2 should trigger aggressive interventions to increase oxygen delivery to the tissues and to minimize sepsis-induced tissue hypoperfusion. An association between good clinical outcome in septic shock and MAP >65 mmHg as well as SvO_2 of >70% has been demonstrated.[78] Both crystalloid and colloid solutions *may be* adequate for fluid resuscitation because no studies to date

have demonstrated the benefits of one over the other.[79,80] The Saline versus Albumin Fluid Evaluation (SAFE) trial compared resuscitation with albumin versus resuscitation with crystalloid solutions and there was *no difference* in outcome.[81] Nonetheless, in a hypothesis-generating post hoc subset analysis of this study, patients with severe sepsis had better survival with the use of albumin.

Other Supportive Therapy

In addition to respiratory and hemodynamic stabilization, attention should be given to several important *adjunct therapies* aiming to prevent further damage and improve prognosis. They include deep venous thrombosis and gastrointestinal bleeding prophylaxis, and maintenance of glucose-level concentrations between 80 and 150 mg/dL. Patients who develop renal failure should be considered candidates for early and aggressive hemodialysis therapy.[82]

Activated Protein C

Endogenous-activated protein C has anti-inflammatory, anticoagulant, and profibrinolytic properties. It modulates the inflammatory response to infection by inhibiting tumor necrosis factor alpha (TNFα) production by monocytes, by blocking leukocyte adhesion to selectins, and by limiting the thrombin-induced inflammatory response within the microvasculature. In addition, it exhibits antithrombosis effect by inhibiting coagulation factors Va and VIIIa, and prevents amplification of the coagulation process by downregulating thrombin generation as well as profibrinolysis by inhibiting PAI-1. It also limits the generation of activated thrombin-activatable fibrinolysis inhibitor (TAFI).

A large, multicenter, randomized trial supported a mortality benefit with the use of activated protein C for patients with severe sepsis who are at high risk of death – Acute Physiology and Chronic Health evaluation (APACHE) II score ≥25 – or multiple organ failure.[17] As of 2008, endogenous-activated protein C is the only therapy targeting the inflammatory and coagulation cascade that has been approved by the U.S. Food and Drug Administration (FDA). Activated protein C may cause serious bleeding, so appropriate timing and patient selection are key for improved outcomes with this therapy.[83,84] It is not recommended in patients with low risk of death caused by severe sepsis.[85] It is also not recommended in children[86–88] or in adults with severe sepsis and a clinical assessment of low risk of death (defined by an APACHE II score <25 or single-organ failure). Its benefit in postoperative patients is also not clear.

Steroids

Initial studies suggest a benefit in septic-shock mortality with the use of stress doses of hydrocortisone (200 mg daily either in four divided doses or by continuous infusion) targeting a state of relative adrenal insufficiency (adrenal glands no longer able to produce adequate amounts of steroids despite the body's signal to do so).[89] This is clinically defined as blood pressure poorly responsive to adequate fluid resuscitation and vasopressor therapy. A recent randomized, multicenter study using corticosteroids to treat septic shock supports that there was no survival benefit in the patient population enrolled in this study (shock not as severe as that in the patients in the previously cited study and treated later) – despite shock-reversal benefits of steroids.[90] Because steroids were available for use as an option to clinical-trial enrollment, the potential for selection bias also existed. The earlier shock-reversal effect occurred independent of adrenocorticotropic hormone (ACTH) stimulation test response. Furthermore, even though there was no increased incidence of polyneuropathy, an increased incidence of superinfection and new septic shock occurred in the steroid group.[90] However, it should be recognized that the increased incidence of superinfection and new septic shock in this study was contrary to that found in three other studies that used similar steroid-dosing regimens in late Acute Respiratory Distress Syndrome (ARDS), early ARDS, and severe community-acquired pneumonia. Although steroids should *not* be used routinely in septic shock, they should be considered for patients whose blood pressure remains poorly responsive to aggressive fluid therapy and vasopressors.[91]

Surviving Sepsis Campaign

The Surviving Sepsis Campaign (SSC) represents a collaborative effort by international critical care organizations with the purpose to improve recognition and treatment of severe sepsis, and to reduce the high mortality rate associated with this condition. Key recommendations of the guidelines were identified and included in a performance-improvement program (in collaboration with the Institute of Healthcare Improvement). This "sepsis bundles" approach identifies key performance indicators (goals) to be accomplished in order to improve outcome in the patient with severe sepsis (Table 27.4).[82,91,92]

Novel, Controversial, and Future Therapies

The search for ways to improve outcome in severe sepsis continues. Many novel compounds and novel approaches are in either preclinical development or clinical trials. These various approaches are targeting the *toxins* initiating sepsis and the *mediators* driving sepsis, as well as the sepsis-driven tissue-bed modifications. Therapies targeting toxins primarily concentrate on anti-endotoxin strategies.[93] Therapies targeting mediators include a variety of anti-inflammatory therapies targeting a variety of layers of pro-inflammatory stimulation.[17,30,31,94] Tissue-bed strategies are hallmarked by investigations of effects of various therapies on the sublingual circulation.[95–97]

TABLE 27.4. Surviving sepsis campaign recommendations.[91]

Resuscitation bundle (to be accomplished as soon as possible and scored over the first 6 h)	Management bundle (to be accomplished as soon as possible and scored over the first 24 h)
Serum lactate measured	Low-dose steroids considered for septic shock in accordance with a standardized hospital policy
Blood cultures obtained prior to antibiotics administered	Drotrecogin alfa (activated) considered in accordance with a standardized hospital policy
From the time of presentation, broad-spectrum antibiotics within 3 h for ED admissions and 1 h for non-ED ICU admissions	Glucose control maintained ≥80 mg/dL (lower limit of normal), but <150 mg/dL (8.3 mmol/L)
For hypotension or lactate or both >4 mmol/L:	Inspiratory plateau pressures <30 cmH_2O for mechanically ventilated patients
Deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent)	
Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain MAP ≥65 mmHg	
For persistent hypotension despite fluid resuscitation (septic shock) or lactate or both >4 mmol/L:	
Achieve CVP ≥ 8 mmHg	
Achieve $ScvO_2$ of ≥70% (or SvO_2 of ≥65%)	

ED emergency department; *ICU* intensive care unit; *CVP* central venous pressure; $ScvO_2$ central venous oxygen saturation; SvO_2 mixed venous oxygen saturation. Reprinted with permission from ref. 91 Hospital das Clínicas, Faculty of Medicine, University of São Paulo. For more information, please visit www.ihi.org/IHI/Topics/CriticalCare/Sepsis/.

Conclusion

Like most diseases, more *precise identification* of the population of interest will transition to better care. The use of biomarkers and genetic predisposition is likely to enable clinicians to predict patients at risk and target therapy more appropriately to patients with severe sepsis.

Unlike the treatment for multisystem trauma and acute myocardial infarction, the standardized treatment strategy for severe sepsis is more of a work in progress. However, treatment strategies based on a multitude of positive clinical trials in severe sepsis are beginning to make a difference in this area. The importance of the *early use of antibiotics* and *early resuscitation* of the cardiovascular system are now recognized as paramount. The best ways to guide early cardiovascular resuscitation are not yet defined, but it appears that any close attention to early resuscitation is likely to improve outcome.

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28
Vascular Catheter-Related Bloodstream Infections

Nikolaos Zias, Alexandra Chroneou, John F. Beamis, and Donald E. Craven

Introduction

Intravascular catheter insertion is an integral part of the care received by almost every patient admitted to a hospital. Patients in intensive care units (ICU) may have multiple types of catheters placed during their hospital stay (Table 28.1). Each year millions of intravascular catheters are inserted into patients for administration of medications, fluids, or hemodynamic monitoring.[1] Although intravascular catheter insertion is a common practice, it alters natural host defenses against infection, which increases the risk of local infection or bacteremia with more serious complications, such as osteomyelitis or endocarditis.

The incidence of catheter-related bloodstream infections (CR-BSI) varies considerably by the type of catheter, frequency of catheter manipulation, and patient-related factors, such as underlying disease and acuity of illness.[2] Peripheral venous catheters are the devices most frequently used for vascular access. Although the incidence of local and or bloodstream infections (BSI) associated with peripheral venous catheters is usually low, serious infectious complications produce considerable annual morbidity because of the *frequency* with which such catheters are used. The majority of serious catheter-related infections (CRI) are associated with central venous catheters (CVC), especially those that are placed in critically ill patients in the ICU. Vascular access, not inserted carefully or that is needed for a more extended period of time, is at greater risk of colonization or infection with a spectrum of hospital-acquired organisms, most commonly coagulase-negative staphylococci, *Staphylococcus aureus*, the aerobic gram-negative bacilli, and *Candida albicans*.[3]

This chapter will provide an overview of CRIs with an emphasis on CR-BSI pathogenesis, management principles, and targets for prevention. Evidence-based data, published in guidelines and other key references, will be emphasized along with emerging concepts and controversies over management and prevention.

Terminology and Epidemiology

In the United States, it is estimated that up to 150 million intravascular devices are inserted annually in hospitalized patients, and that more than 200,000 nosocomial bloodstream infections occur each year.[1,4,5] There are 17,000 deaths annually, directly related to catheter-associated infections[6] (Fig. 28.1). Different types of intravascular devices are used to administer intravenous fluids, medications, blood products, and parenteral nutrition fluids, as well as to monitor hemodynamic status and to provide hemodialysis[1](Fig. 28.2). An overview of the terminology used to identify different types of catheters is summarized in Table 28.1. Other special characteristics of the catheter terminology include the presence or absence of a cuff; impregnation with heparin, antibiotics, or antiseptics; and the number of lumens.

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TABLE 28.1. Types of intravascular devices and comments for patient care and risk of infections or complication. (Adapted from Ref. [38].)

Type of catheter	Comments
Peripheral venous catheters	Usually inserted into the veins of the forearm or hand; most commonly used short-term, intravascular device; rarely associated with bloodstream infection, if placed aseptically, are not manipulated, and are removed within 72–96 h or if there is pain or signs of inflammation
Peripheral arterial catheters	Short-term, commonly used to monitor hemodynamic status and for blood gas determinations in critically ill patients; low risk of local catheter infection and bloodstream infection when placed with sterile techniques and caution advised when inserted in the femoral artery
Midline catheters	A 3- to 8-in. peripheral catheter, inserted via the antecubital fossa into the proximal basilic or cephalic veins, or distal subclavian vein, that does not enter central veins; lower rates of phlebitis and infection than central catheters; medications that may cause phlebitis may need PICC line for better dilution
Non-tunneled central venous catheters (CVCs)	Most commonly used CVCs; account for an estimated 90% of all catheter-related bloodstream infections; increased risk of infection by site of insertion (e.g., internal jugular > subclavian vein)
Pulmonary artery catheters or Swan Ganz catheters	Inserted through a Teflon introducer and typically remain in place an average of only 3 days; most catheters are heparin bonded to reduce catheter thrombosis and microbial adherence to the catheter
Pressure monitoring systems	Used in conjunction with arterial catheter; associated with both epidemic and endemic nosocomial bloodstream infections; source often the fluid column in the tubing between the patient's intravascular catheter and the pressure monitoring apparatus, contaminated infusate, or non-disposable transducers
Peripherally inserted central catheters	Peripherally inserted central catheters (PICCs) provide an alternative to subclavian or jugular vein catheterization; are inserted via a peripheral vein into the superior vena cava by way of the cephalic and basilar veins (or femoral vein into the inferior vena cava); easier to maintain and associated with fewer mechanical complications (e.g., thrombosis, hemothorax)
Tunneled, central venous catheters	Surgically implanted central venous catheters with a tunneled portion exiting the skin and a Dacron cuff just inside the exit site (Hickman, Broviac, Groshong, and Quinton); cuff inhibits migration of organisms into the catheter tract by stimulating growth of the surrounding tissue, thus sealing the catheter tract; used to provide vascular access to patients requiring prolonged IV chemotherapy, home-infusion therapy, or hemodialysis
Totally implantable devices (TIDs)	Tunneled beneath the skin with subcutaneous port or reservoir with a self-sealing septum; is accessed by needle through intact skin; low rates of infection

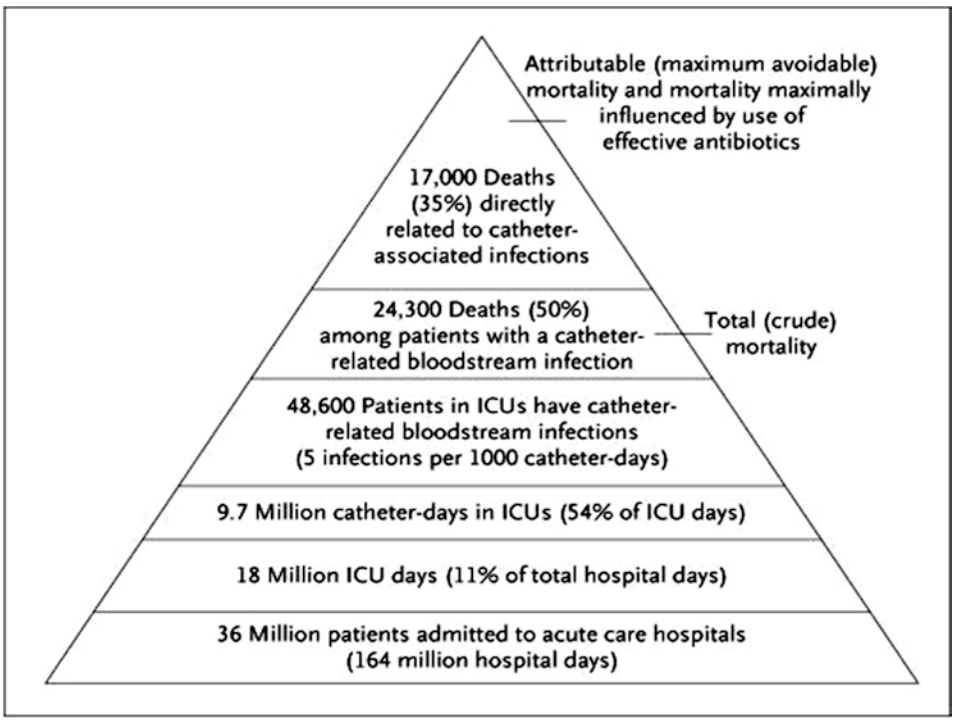

FIG. 28.1. Summary of the epidemiology of catheter-associated infections and outcomes in the United States. Reprinted with permission from Wenzel RP, Edmond MB. Team-based prevention of catheter-related infections. N Engl J Med 2006;355(26):2781–2783.

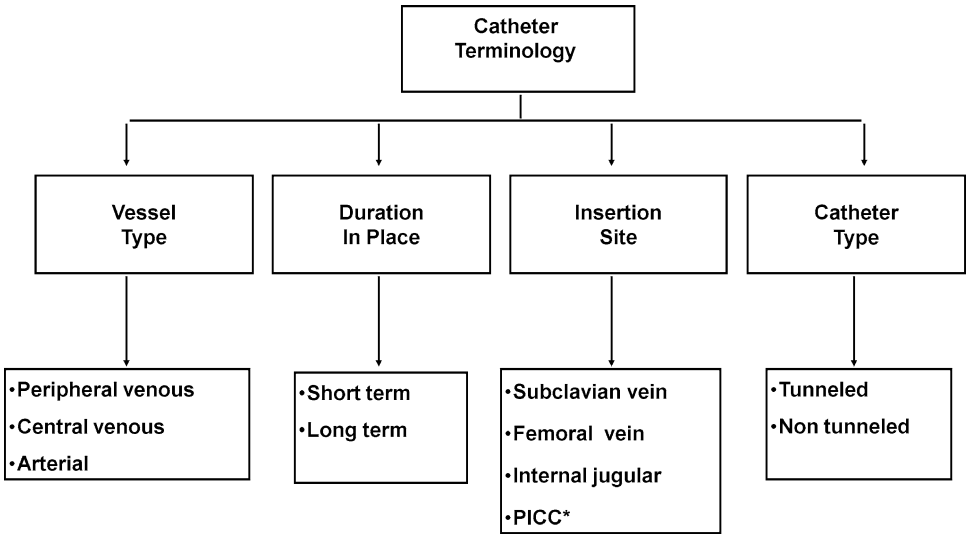

FIG. 28.2. Catheter terminology according to vessel type, duration in place, insertion site, and catheter type.

Most CR-BSIs in ICUs are substantially higher in patients with central venous catheters (CVC)[1,4] than for those with peripheral lines.[7] Non-tunneled central catheters, the most commonly used catheters, account for an estimated 90% of all CR-BSIs.[1] Intravenous catheter device-related infection increases hospital costs, length of stay, and patient morbidity.[8] In a recent meta-analysis of 2,573 CR-BSIs, the case fatality rate was 14%; and 19% of these deaths were attributed to the CRIs. Mortality rates vary by pathogen and rates for *S. aureus* bacteremia are significantly higher than for coagulase-negative staphylococci.

Etiologic Agents Causing CR-BSIs

Recent data suggest that the microorganisms most commonly associated with peripheral vascular and CVC infections are coagulase-negative staphylococci, *S. aureus*, different species of aerobic gram-negative bacilli, and *Candida albicans*[1] (Table 28.2). Thus, a patient with blood cultures positive for *S. aureus*, coagulase-negative staphylococci, or *Candida* spp. – in the absence of any other identifiable source of infection – should be strongly suspected for CR- BSI.[9–11] Other less common organisms isolated from blood cultures or pull-back cultures from the catheter (Table 28.2) should also raise the possibility of CR-BSI.

Pathogenesis

As shown in Fig. 28.3, CRI can occur by[5]:

1. Colonization of the external surface of the catheter by skin microbes entering the puncture site
2. Intraluminal contamination via contamination of hubs/stopcocks
3. Infusion of contaminated intravenous fluid or
4. Secondary seeding of the catheter due to bacteremia originating from a distant site

TABLE 28.2. Etiologic agents causing CR-BSI[3]: common vs. uncommon microorganisms.

Common bacterial pathogens	
Coagulase-negative staphylococci	
Staphylococcous aureus	
Gram-negative bacilli	*Pseudomonas aeruginosa*, *Enterobacter* spp., *Serratia marcescens* and *Serratia* spp., *Acinetobacter* spp., *Klebsiella* spp., *Escherichia coli*, *Stenotrophomonas maltophilia*
Candida spp.	*Candida albicans*
Uncommon pathogens	
Bacterial	*Micrococcus* species, *Achromobacter* species, rapidly growing *Mycobacteria* species (*M. chelonei*, *M. fortuitum*)
Fungi	*Malassezia furfur*, *Rhodotorula*, *Fusarium*, or *Trichosporon*

External catheter contamination is more common in peripheral, non-tunneled, short-term catheters. Contamination of the catheter hub and intraluminal infection is the most common route of infection with surgically implanted, tunneled CVCs or implantable devices.[1,10]

There are numerous risk factors augmenting the occurrence of CR-BSIs that include host factors, catheter type, and the specific pathogen.[1,4,10] Host-related factors include impaired host immunity, poor personal hygiene, occlusive dressing, *S. aureus* nasal carriage, older age, diabetes mellitus, recent hospitalization, and high cumulative dose of intravenous iron. A number of studies have identified neutropenia or an underlying malignant disorder as a risk factor for CR-BSI.[12–14]

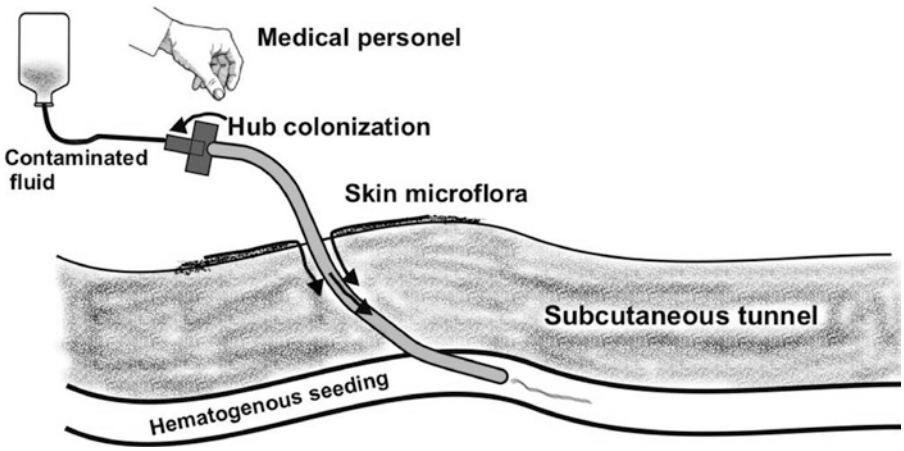

FIG. 28.3. Mechanisms for intravenous catheter colonization and infection: extraluminal from skin microflora, intraluminal from hub colonization and less commonly from hematogenous spread or contaminated intravenous fluids. Each of these mechanisms is a target for prevention strategies.

The intensity of immunosuppressive therapy may contribute to overall risk of developing catheter-associated bloodstream infection. Patients with malignant hematologic disorders and acquired immunodeficiency syndrome (AIDS) have a fourfold increased risk of CRI versus an 11-fold increased risk for patients with neutropenia.[14] Hematopoietic stem cell transplantation was found to be a significant risk factor after adjustment for underlying diagnosis in a large prospective observational study of hematology and oncology patients.[15]

CR-BSI risk factors include the site of insertion, increased duration of catheter use, history of bacteremia, colonization of catheter tip and cutaneous tract with skin flora, catheter lumen contamination, hematogenous seeding of the catheter from another infection source, contamination of lumen with infusate, and lack of aseptic precautions during catheter insertion. Catheter composition can also impact the risk of infection. Polymers such as polyurethane (without hydromer) and polyvinylchloride tend to be more thrombogenic than others. Thrombosis may also increase the risk of infection.[16,17]

Pathogen-related factors include the biofilm formation, resistance to antibiotic therapy, bacterial virulence, and contiguous infection. Virtually, all implantable devices eventually become encased in a biofilm.[18] The biofilm is composed of a fibrous glycocalix and several host proteins, such as fibronectin and laminin, and can support the adherence of several microbial species (Fig. 28.4). In addition, attachment is augmented by production of an extracellular polysaccharide by some types of microbes. The biofilm represents a protective environment for the microbes and reduces the ability of host defense mechanisms to eradicate them. Also, the bacteria can communicate with each other by chemical "quorum sensing"[19–21] and regulate their reproduction. The fact that *Candida* species and coagulase-negative staphylococci produce extracellular polysaccharide and that *S. aureus* can bind to several biofilm proteins helps explain the increased incidence of CR-BSIs due to these organisms. Prevention of biofilm formation has also been used as prevention strategy for nosocomial infections.[19,22]

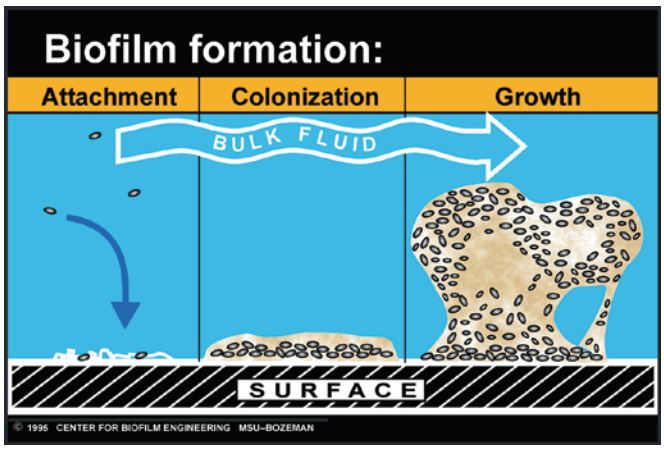

FIG. 28.4. Bacterial colonization and attachment results in biofilm formation in the catheter lumen and increases over time. Biofilm reduces antibiotic penetration, and protection from killing by host phagocytes, antibody and complement. Illustration used with permission from Dirckx P, Montana State University Center for Biofilm Engineering, Bozeman, Montana.

Diagnosis

Clinical findings are *unreliable* for establishing the diagnosis of intravascular device-related infection due to their poor specificity and sensitivity. For example, the most sensitive clinical findings – such as fever, with or without chills – have poor specificity; and inflammation or purulence around the intravascular device combined with BSI have greater specificity, but poor sensitivity.[1]

The use of the Gram stain may be helpful in diagnosing local infections, but is significantly less sensitive than quantitative methods for diagnosing CRI.[23] Semiquantitative (roll plate) or quantitative catheter culture techniques (vortex or sonication methods) are the most reliable diagnostic methodologies, as

both methods have greater specificity in identifying CRIs than do qualitative cultures, where a single contaminating microbe can result in a positive catheter culture.[24,25]

The roll-plate method needs removal of the catheter, and the tip or the 5-cm intradermal segment is aseptically cut and rolled back and forth on a blood agar plate four times. The plate is incubated for 24–48 h and colony-forming units (CFU) are counted. Growth of ≥15 CFU is considered significant.[25] This method only samples the external surface of the catheter; thus, infections due to organisms within the lumen of the catheter may be overlooked. However, because the semiquantitative, roll-plate method is fast and easy to perform, it continues to be the most popular technique for catheter culture. Quantitative culture of the catheter segment requires flushing the segment with broth, or centrifuging, vortexing, or sonicating it in broth followed by serial dilutions and surface plating on blood agar.[25–27] Sonication and flushing of the lumen can increase diagnostic sensitivity.[27] Growth of >15 CFU from a catheter by semiquantitative culture or growth of $>10^2$ CFU from a catheter by quantitative culture, with accompanying signs of local or systemic infection, is indicative of catheter-related infection.

The predictive value of quantitative or semiquantitative culture methods may vary depending on the type and location of the catheter, the culture methodology used, and the source of catheter colonization.[28] For example, a recently inserted catheter (e.g., duration of placement less than a week) is most commonly colonized from a skin microorganism along the external surface of the catheter, so that the roll plate method will be quite sensitive in identifying such colonization. For longer dwelling catheters (e.g., in place for more than 1 week), in which intraluminal spread from the hub is the dominant mechanism for catheter colonization, the roll plate method is less sensitive, and methods that obtain cultures of both the internal and external surfaces will be more sensitive.[28] As the use of antimicrobial-coated catheters becomes more prevalent, existing definitions of catheter colonization and catheter-related infection may need to be modified, since such coatings may lead to false negative cultures.[29,30]

Paired Blood and Intravenous Catheter Blood Cultures

Patients with suspected intravenous CRI should have two sets of blood cultures drawn, with at least one set drawn percutaneously. The clinical utility of blood cultures drawn from an indwelling CVC was assessed in hospitalized cancer patients.[31] In this study, the positive predictive value of catheter and peripheral blood cultures was 63 and 73%, respectively; and the negative predictive value was 99 and 98%, respectively. Thus, a positive blood culture drawn through the catheter needs clinical interpretation; but a negative blood culture has a high negative predictive value and is, therefore, very helpful in excluding catheter-related bloodstream infection as a source of fever or suspected infection.

Quantitative Blood Cultures: Peripheral Blood and CVC

With quantitative blood cultures drawn from the catheter and from peripheral venipuncture, it is possible to diagnose CRI with the catheter left in place.[32] However, the technique requires specific blood culture systems and sophisticated logistics and therefore, has not been widely used in clinical practice. Quantitative blood culturing techniques have been developed as an alternative for diagnosis of CRBSI in patients where catheter removal is undesirable because of limited vascular access. This technique relies on quantitative culture of paired blood samples, one obtained through the central catheter hub and the other from a peripheral venipuncture site. In most studies, a colony count of the blood obtained from the CVC that is at least five- to ten-fold greater than the colony count from the blood obtained from a peripheral vein was predictive of CRBSI.[33] Among tunneled catheters, for which the method is more accurate, a quantitative blood culture from the CVC with at least 100 CFU/ml may be diagnostic without a companion culture of peripheral blood.[32]

Differential Time to Positivity for CVC vs. Peripheral Blood Cultures

A very elegant method has been described using the differential time to positivity (DTP) of blood cultures drawn simultaneously from peripheral veins and central lines.[34] Using a cut-off of 2 h for DTP, Blot et al. showed that this method has excellent sensitivity and specificity, as well as positive and negative predictive values.[35] Blot and colleagues[34,35] reported that the measurement of differential time to positivity between blood cultures drawn through the central venous catheter and those drawn from the peripheral vein is highly diagnostic of CRBSI in patients with long-term catheters. DTP is defined as the difference in time needed for blood cultures drawn simultaneously through the central venous catheter and from a peripheral vein to become positive. DTP was considered positive (that is, suggestive of CRBSI) if the blood culture drawn through the central venous catheter became positive at least 120 min earlier than a positive culture drawn simultaneously from a peripheral vein. A time differential of >120 min between the catheter and peripheral blood cultures has a 91% sensitivity and 94% specificity for CRI.[35] However, all of the studies reported so far have included a very small number of evaluable patients who had positive simultaneous blood cultures from both the central venous catheter and the peripheral vein.[36,37] When studied in tunneled catheters, this method has offered comparable accuracy to quantitative blood cultures and had greater cost-effectiveness.[34,35] In one study using DTP, a definite diagnosis of catheter-related bacteremia could be made in 16 of the 17 patients who had a CVC blood culture that was positive at least 2 h earlier than the peripheral blood cultures; the overall sensitivity was 91% and specificity was 94%.[34] Most hospitals do not have quantitative blood culture methodologies, but many will be able to use DTP for diagnosis.

Further studies are needed to evaluate the utility of this method under different clinical conditions.

Therapy

Guidelines for the management of CR-BSI were published in 2001 and revised guidelines are expected in early 2009.[38] Figures 28.5–28.7 summarize current guidelines for empiric antimicrobial therapy and criteria for removal of an infected intravascular device, depending on the specific pathogen type of catheter involved.[39] Antibiotic treatment options and doses for specific pathogens are shown in Table 28.3.

Non-tunneled Catheters

A common problem in the ICU is the febrile patient with a central venous catheter. If there are no local signs of infection, the chances of the catheter being the cause of the fever are only 10%.[40] If the patient develops CR-BSI, appropriate empiric systemic antibiotic therapy for a suspected pathogen is shown in Fig. 28.5. If the patient is critically ill or has

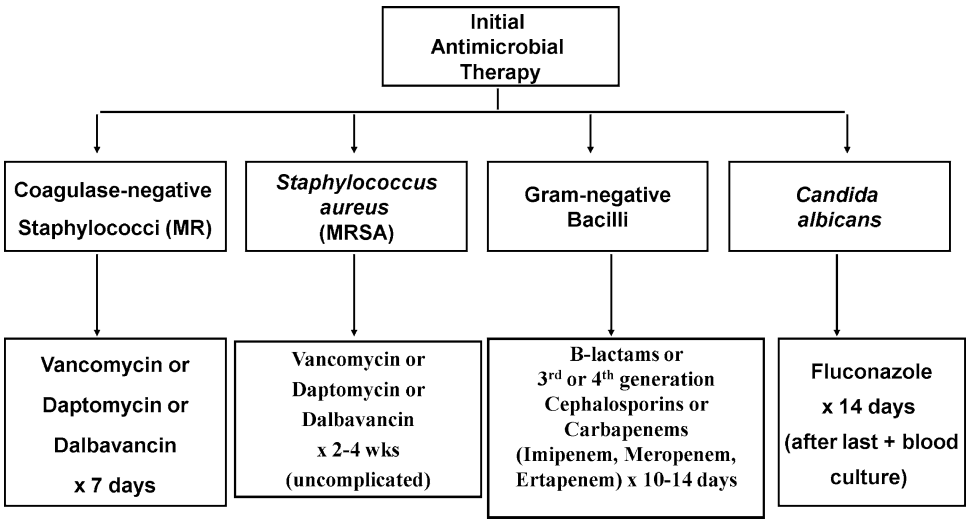

FIG. 28.5. Antimicrobial therapy options for pathogens commonly associated with catheter-related bloodstream infections.

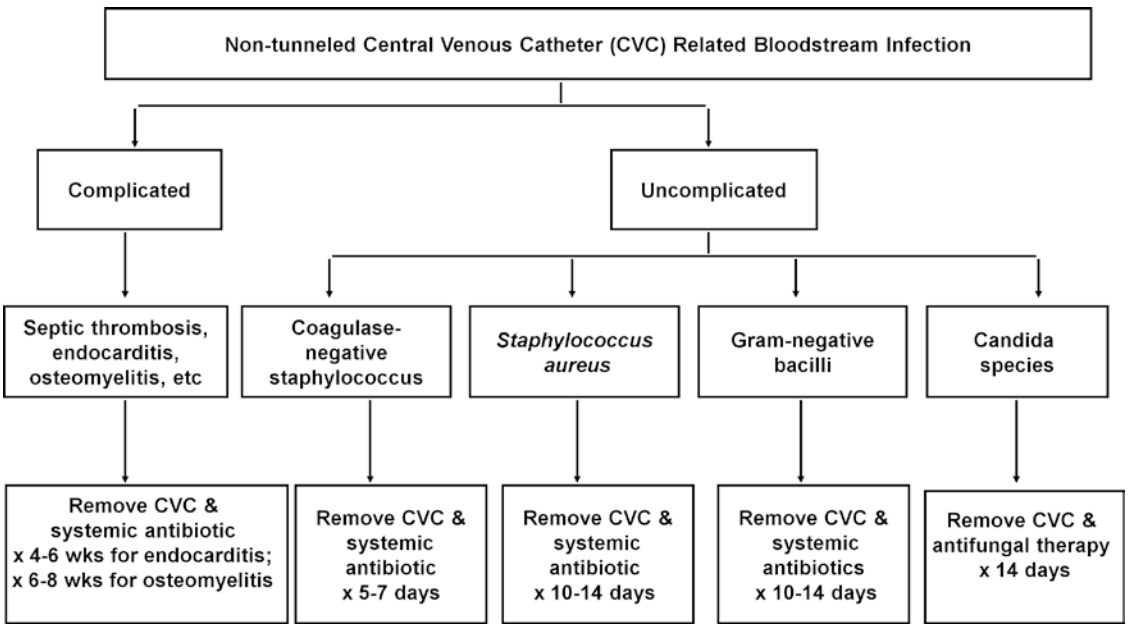

FIG. 28.6. Management of non-tunneled, removable catheter-related bloodstream infections caused by specific pathogens. With the exception of coagulase-negative staphylococci, the catheter should be removed and systemic antibiotic therapy initiated.

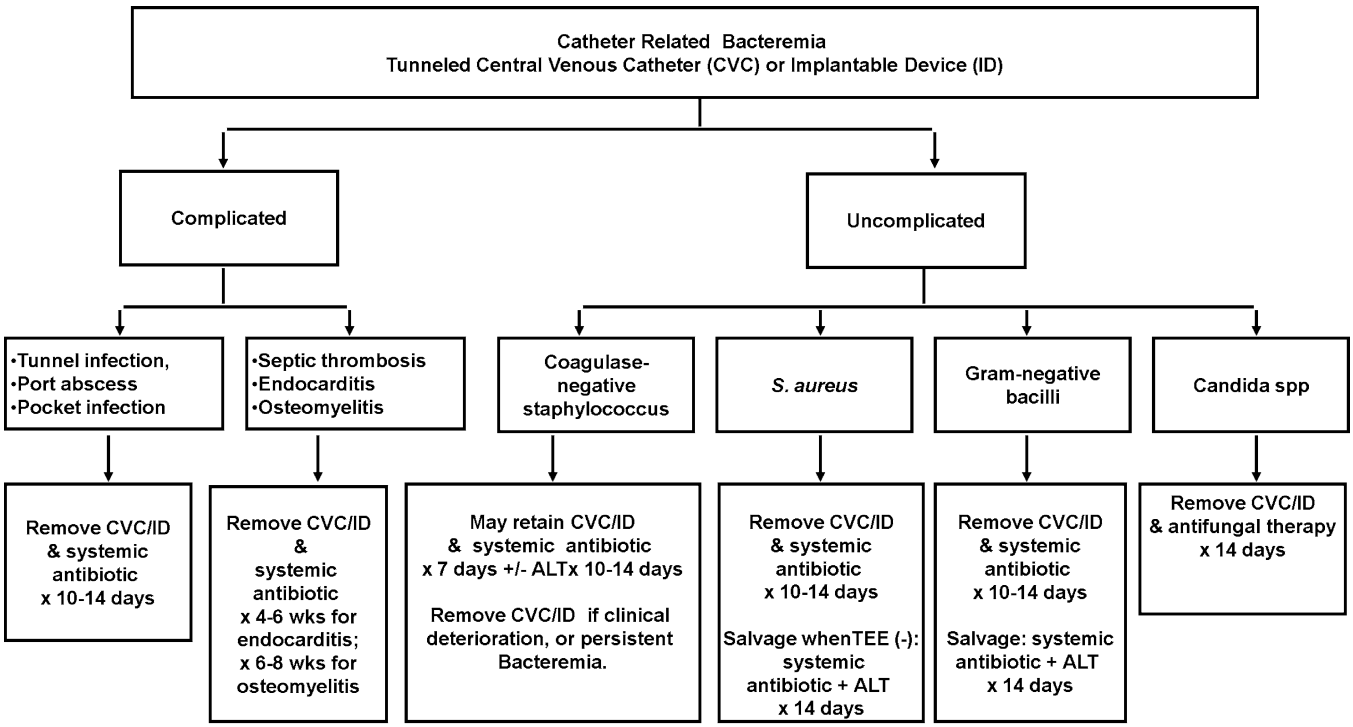

FIG. 28.7. Management of infected tunneled catheters and implantable devices, complicated by bacteremia. Intraluminal infection with possible biofilm formation should be considered. Treatment may include the use of systemic antibiotic therapy and removal of the device or salvage therapy. Salvage therapy included infusion of intravenous antibiotics through the catheter plus locking high concentration of antibiotics into the catheter lumen over time, antibiotic lock therapy (ALT) as described in the text.

signs of sepsis, broad-spectrum, empiric coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) and aerobic gram-negative bacilli is recommended. If the patient is also immunosuppressed or at risk for opportunistic fungi infection, anti-fungal therapy should be added as well.

Once the peripheral blood or pull-back blood culture pathogen and antibiotic sensitivity data are available, antibiotic therapy can be de-escalated and the duration of therapy determined (Fig. 28.6). CR-BSI due to *S. aureus*, gram-negative bacilli and *Candida* species are usually more severe and have a higher mortality than CR-BSI due to coagulase-negative staphylococcus. With the exception of coagulase-negative staphylococcus CR-BSI, non-tunneled catheters should be removed. Similar recommendations are suggested for patients with coagulase-negative staphylococcus CR-BSI, if the patient has a prosthetic device present.

Efforts to assess the patient for metastatic foci is particularly important for *S. aureus*. Also, because of the rapid increase in MRSA in the community and hospital, empiric therapy with vancomycin or daptomycin is recommended until identification and sensitivity data are available. Recommendations for choice and duration of therapy for MRSA will depend on the patients and clinical evidence available.

Initial empiric antimicrobial therapy should be given intravenously to cover likely pathogens such as coagulase-negative staphylococci or *S. aureus*, or possibly aerobic gram-negative bacilli. The management of some common pathogens is discussed below.

Coagulase-Negative Staphylococci

Most coagulase-negative staphylococci are resistant to b-lactam antibiotics, such as oxacillin or a first-generation cephalosporin (e.g., cefazolin) and therefore, require treatment with a glycopeptide (e.g., vancomycin) or a cyclic lipopeptide (e.g., daptomycin). The optimal duration of treatment is not established, but most experts recommend antibiotic treatment for 7–10 days. Special care must be taken in patients with prosthetic devices that may have been seeded. In the absence of prosthetic devices or persistent bacteremia, removal of the catheter without antibiotic therapy has been successful.

S. aureus

For an uncomplicated *S. aureus* CR-BSI, some authors have argued that a relative short course of therapy (10–14 days) is adequate.[41] If fever or bacteremia persists beyond 3 days, a longer duration of antibiotic therapy is often needed along with an extensive work-up to exclude endocarditis, a deep-seated infection or seeding of a prosthetic device.[42]

Vancomycin is often given initially in cases of suspected or established *S. aureus* CRI, but daptomycin is also highly

TABLE 28.3. Antimicrobial treatment for intravenous catheter-related bloodstream infections in adults by specific pathogen isolated. Presented dosages are for normal renal function.

Pathogen	Antibiotic class	Suggested regimens	Dosage (IV)
Staphylococcus aureus and coagulase-negative staphylococci			
Methicillin-susceptible	Penicillinase-resistant penicillin or	Nafcillin (or Oxacillin)	2 g → q4h
	First-generation cephalosporin	Cefazolin	2 g → q8h
Methicillin-resistant	Glycopeptide or	Vancomycin	1 g → q12h
	Cyclic lipopeptide or	Daptomycin	6 mg/kg → q24h
	Lipoglycopeptide or	Dalbavancin	500 mg → q24h (1 g the first day)
	Streptogramin (groups B and A)	Quinupristin/dalfopristin	7.5 mg/kg → q8h
Gram-negative bacilli			
Escherichia coli	Third-generation cephalosporin or	Ceftriaxone	1–2 g → q24h
Klebsiella, Enterobacter,	Second-generation fluoroquinolone or	Ciprofloxacin (or ofloxacin)	400 mg → q12h
Serratia spp.	Monobactam	Aztreonam	2 g → q8h
	Carbapenem	Imipenem/meropenem/ertapenem	500 mg → q6h/1 g → q8h/1 g → q24h
	Aminoglycosides	Gentamicin, tobramycin, amikacin	
	Second-generation fluoroquinolone	Ciprofloxacin, ofloxacin	7 mg/kg/7 mg/kg//15 mg/kg → q24h 400 mg → q12h
ESBL+gram-negative bacilli (*E. coli*, *Klebsiella*, *Enterobacter* spp.)	Carbepenem	See above	
Acinetobacter spp.	Carbapenem ± aminoglycoside	See above	See above
Stenotrophomonas maltophilia	Trimethaprim-sulfamethoxazole	Trimethaprim-sulfamethoxazole	3–5 mg/kg → q8h
	Second-generation floroquinolone	Ciprofloxacin (or ofloxacin)	400 mg → q12h
Pseudomonas aeruginosa	Third-generation cephalosporin or	Ceftazidime	2 g → q8h
	Fourth-generation cephalosporin or	Cefepime	2 g → q12h
	Carbapenem	Imipenem/meropenem	See above
	Antipseudomonal β-lactam	TicarcillinSee above	3 g → q4h
	Aminoglycoside		
Fungi			
Candida albicans	Azoles	FluconazoleAmpotericin B	400–600 mg → q24h
	Amphotericin B		0.3–1 mg/kg → q24h
Candida spp. (resistant to fluconazole)	Azoles	Voriconazole	Load: 6 mg/kg q12h × 1 day 4 mg/kg q12 h
	Echinocandins	Caspofungin	50 mg → q24h (70 mg first day)
		Micafungin	100 mg → q24h
	Amphotericin B	See above	

effective. However, both of these agents are generally reserved for MRSA infections for patients who are allergic to b-lactams. Otherwise, penicillinase-resistant penicillins (such as nafcillin or oxacillin) or a cephalosporin (such as cefazolin) should be used.

S. aureus infections should be treated with appropriate antibiotics given intravenously for at least 2 weeks and perhaps as long as 4 weeks. However, in cases of complicated infections, such as endocarditis, 4–6 weeks of therapy may be needed; and perhaps 6–8 weeks are needed for osteomyelitis.[38]

Daptomycin, quinoprustin/dalfopristin, and linezolid have been used to treat MRSA. Daptomycin has the advantage of once-a-day dosing by weight and there is no need to monitor therapeutic levels.[43,44] Quinoprustin/dalfopristin has not been widely used due to some adverse effects. Linezolid has the advantage of oral dosing that is equivalent to intravenous dosing, but should not be used to treat CR-BSI.

Gram-Negative Bacilli

Gram-negative infections may include a wide range of pathogens and have to be treated according to culture results and antimicrobial susceptibility testing. There are no data available on the optimal duration of therapy, but treatment period of 7–10 days might be sufficient in most cases. In severely immunocompromised patients and CR-BSI with gram-negative bacilli, coverage for *P. aeruginosa* should be considered; and initial therapy would include a third-generation cephalosporin (i.e., ceftazidime) or fourth-generation agent (i.e., cefepime), an aminoglycoside (gentamicin, tobramycin, or amikacin), an extended spectrum beta-lactam (i.e., ticarcillin or piperacillin) or a carbapenem (i.e., imipenem, meropenem). For ESBL+gram-negative bacilli, a carbapenem or aminoglycoside would be effective. For *Acinetobacter* infections, either a carbapenem, an aminoglycoside or polymyxin is suggested. If the organism or

sensitivity of the organism is known, fluoroquinolone therapy (i.e., ciprofloxacin or levofloxacin) would be effective and can be given orally.

Candida Species

Patients who developed catheter-associated fungemia should receive systemic antifungal therapy as they are at high risk for developing complications. Retention of a catheter increases the risk for persistence of fungemia.[45] Nearly all isolates are sensitive to fluconazole. Currently, intravenous fluconazole is the drug of choice for CR-BSI due to *Candida* spp.[46] All *Candida albicans* are sensitive to fluconazole, a 14-day course (400 mg/day) is recommended. For *Candida* species that are resistant to fluconazole (such as *Candida glabrata* and *Candida krusei*), treatment options would include the newly developed echinocandin class, such as micafungin or caspofungin[47] or voriconazole that has intravenous and oral options, or amphotericin B, which has been used effectively in the past. Treatment is usually for 14 days after the last positive blood culture, and usually the infected intravenous device is removed. Consideration should be made for the extension of anti-fungal therapy if signs of deep-seated infection become manifest.

Tunneled Catheters

Before removing a tunneled catheter or implantable device, there should be reasonable evidence of infection and that another catheter site is available once the BSI has cleared (Fig. 28.7). Specific antibiotics for therapy are discussed above. Catheters with evidence of extraluminal infection (e.g., inflammation over the tunnel, pocket infectons, or infected totally implanted devices) need to be removed.[28]

One reason for treatment failures of vascular catheter infections is the inability of most antibiotics in therapeutically achievable concentrations to kill microorganisms growing in a biofilm.[48–53] Antibiotic concentrations must be 100–1,000 times greater to kill biofilm bacteria than for in solution bacteria.[48–53] A potential solution to this problem is based on the fact that the majority of infections in tunneled catheters arise from the catheter hub and spread to the catheter lumen.[54]

In cases when the catheter cannot be removed, antibiotic lock therapy (ALT) has been tried. This involves filling the catheter lumen with high concentrations of an antibiotic or ethanol (~30–50%) and leaving it there for hours or days.[48,54–56] Antibiotic solutions containing the desired antimicrobial concentration (usually 10- to 100-fold greater than the serum concentration) may be mixed with 50–100 units of heparin (or normal saline) in sufficient volume to fill the catheter lumen and "locked" into the catheter lumen.[48,54,55,57–60] For example, vancomycin has been used at concentrations of 1–5 mg/ml, gentamicin and amikacin at 1–2 mg/ml, and ciprofloxacin at 1–2 mg/ml. The volume of installed antibiotic is then removed prior to infusing the next dose of antibiotic or intravenous medication.

Current guidelines have suggested the use of ALT plus systemic antibiotics for salvage of tunneled central venous catheters or implantable devices infected with coagulase-negative staphylococci, *S. aureus*, or gram-negative bacilli. Salvage therapy should only be used in selected patients with limited options, uncomplicated infections, and in the absence of tunnel or pocket infections.

Complications

Uncomplicated infections at the insertion site should resolve quickly. If the patient's condition does not improve after 48 h, consideration should be directed at the cause: *wrong drug*, *wrong bug*, or *wrong diagnosis*; or a *complication*, such as an undrained abscess, septic thrombophlebitis, or other metastatic foci. Among patients with CR-BSI, blood cultures should be negative after 48 h of initiating appropriate treatment. If bacteremia persists beyond 48 h a re-evaluation for the possibility of deep-seated infection, such as endocarditis or metastatic abscess, should be considered.[61]

Prevention

The majority of infections associated with the use of intravascular devices in critically ill patients requiring short-term catheterization are preventable. Prevention relies first on a strict observation of the basic rules of hygiene, of which *hand hygiene* represents the first and most important. More specific measures, including the use of maximal sterile barriers during insertion, optimal insertion site preparation, detailed guidelines for catheter replacement, and defining particular situations in which the use of antiseptic- or antibiotic-coated devices may be used have been studied in detail in hundreds of clinical studies. Strategies for CR-BSI prevention are summarized in Table 28.4.

TABLE 28.4. Prevention strategies for CR-BSI.

Strategy	Comments
Skin preparation	Rigorous cleansing/disinfection, sterile barrier precautions during insertion, hair-cutting
Site of insertion	Subclavian vein → jugular vein → femoral vein
Dressing	Chlorhexidine patches. If semi-permeable dressing is used renew every 48–72 h
Catheter handling	Avoid often hub manipulation. Replace administrations sets every 72 h
Catheter replacement	Routine change of catheters is not proven to be associated with reduced rates of infection
Antibiotic/antiseptic-coated catheters	Use chlorexidine/silver sulfadiazine or minocycline/rifampin impregnated catheters
Antibiotic lock therapy	Effective in biofilm growing microorganisms and salvage of tunneled catheters
Anticoagulants	Heparin or warfarin reduce the rate of catheter thrombosis and infection
Silver impregnated collagen cuff	May reduce density of bacterial growth, further studies needed

Skin Preparation

The skin is a major reservoir for bacteria. Rigorous cleansing and disinfection of the insertion site are critical. Povidone iodine 10% and alcohol 70% are effective, but aqueous chlorhexidine 2% has been shown to be superior in preventing central venous catheter colonization.[68] An alcohol-based preparation of chlorhexidine gluconate (0.5%) may combine the advantages of a broader antimicrobial spectrum and a very rapid killing of skin microorganisms and drying time at low cost. Topical antimicrobial ointments have been used to prevent catheter colonization, but they favor colonization with resistant organisms and are thus no longer recommended.[2,11] Skin preparation should include hair-cutting rather than shaving.[64] Maximal sterile barrier precautions during insertion – including not only fenestrated drapes and the use of sterile gloves, but also gown, cap, mask, and a large drape – can minimize catheter colonization and subsequent CRI.[69]

Site of Insertion

It has been repeatedly shown that central lines inserted in the jugular site are more likely to be colonized than those inserted by the subclavian route. This could be related to factors favoring skin colonization such as proximity of oropharyngeal secretions, higher skin temperature, and difficulty in immobilizing the catheter and maintaining an optimal dressing.[29] Among the possible insertion sites for central venous catheters, the subclavian vein is associated with the lowest risk of infection.[11]

Although the femoral route offers potentially less severe complications related to their insertion and an intermediate rate of infectious complications, untunneled catheters are associated with a higher frequency of infection and deep venous thrombosis. Data from recent studies suggest that the use of *tunneled catheters* in the internal jugular[70] or femoral[71] position *reduce the risk* of CR-BSI when compared to untunneled catheters inserted in the same site. For the internal jugular catheters, the exit site is the infraclavicular area. Use of tunneled subclavian catheters does not appear to reduce the risk of infection. For arterial catheters, an association between site of insertion and infection has not been observed, but insertion method, maintenance, and duration left in place are important risk factors for infection.

"Hands off" catheters and single versus multilumen catheters seemto have a favorable effect in lowering the rate of CR-BSI. Careful fixation of the catheter at the skin exit-site may avoid complications such as leakage of the fixing device and movement through the intradermic portion. Topical agents applied to catheter exit sites have included povidone iodine, muripocin, and polysporin.[72–74]

Dressing

Catheter-site dressing has generated considerable literature for decades, yielding to debates and contradictory findings. Semi-permeable transparent dressings are widely used. They are simple to place, allow continuous observation of the skin insertion site, and reduce the risk of extrinsic contamination. However, they may promote moisture and bacterial proliferation under the cover and have been associated with higher CRI rates when compared with traditional gauze dressings.[75]

Catheter Handling

Currently, except for blood products and lipid emulsions, administration sets can be safely replaced only every 72 h.[2,11] Antiseptic hub models have been shown to be associated with a significant reduction in catheter-associated bloodstream infections attributed to the hub and may be a valuable measure that should be further evaluated in large randomized trials. Increased hub manipulation will increase catheter colonization and the risk of subsequent CR-BSI.[5,28] Some[78,79] but not all studies[80] have shown that hub protection devices can reduce the risk of CR-BSI when duration of catheterization is in excess of 7 days.

Catheter Replacement

The cumulative risk of CRIs increases the longer the catheter remains in place. As a consequence, many clinicians will routinely change catheters after a predetermined number of days (ranging from 3 to 7). This practice has been called into question by a number of studies where scheduled changes (either via guidewire or insertion at a new site) did not translate into reduced rates of infection.[81–83]

Antibiotic and Antiseptic-Coated Catheters

Prospective, randomized clinical studies and a meta-analysis have shown that the use of central venous catheters impregnated with either chlorhexidine and silver sulfadiazine on the external surface, or with minocycline and rifampin on both external and internal surfaces, are associated with significant reductions in microbiologically documented CRIs.[30,84,85]

However, the *duration* of catheterization may have played a role. Impregnated catheters failed to prevent CRIs in neutropenic cancer patients with a longer mean catheterization time of 20 days, compared to less than 8 days in other studies.[29,30]

Chlorhexidine Patches

Chlorhexidine patches have shown to reduce colonization and infection related to catheter placement.[2,76,77] The precise duration that a dressing can be safely left on a central line is unknown, but it should be systematically renewed every 48–72 h if an earlier change is not clinically indicated.

In a multicenter study, a chlorhexidine-impregnated sponge (Biopatch™) placed over the site of short-term arterial and central venous catheters reduced the risk for catheter colonization and CR-BSI. No adverse systemic effects resulted from the use

of this device.[2] Use of chlorhexidine-impregnated dressing is safe and prevents bacterial infection related to vascular catheters.[76,77]

Antibiotic Lock Therapy for Prevention

This technique, as already described, is more successful for bacteria than *Candida* spp. In one study, when the antibiotic lock technique in addition to standard parenteral therapy for patients with hemodialysis CRIs was used, all 40 CRBIs were cured and the catheter salvaged, including all of 12 cases reported to involve *S. aureus*.[86]

Anticoagulants

Catheter thrombosis is associated with an increased risk of infection. Low doses of warfarin or heparin (either as a flush solution or added to the infusate) will decrease the incidence of thrombosis, although the impact on infection is less clear. For this reason and because of heparin's association with heparin induced-thrombocytopenia, many centers have stopped using heparin flush solutions all together. Heparin also has activity (via ionic bonding to quaternary ammonium surfactants) against a number of gram-positive organisms, but has little effect on gram-negative bacteria. In addition, the antimicrobial activity diminishes by greater than 50% within 24 h of exposure to serum.[87] Heparin that is attached to catheters by covalent end-point bonding has a longer duration of activity and appears to reduce the density of bacterial colonization compared to uncoated catheters.[88]

Silver-Impregnated Collagen Cuff

Since most of the infections associated with short-term catheterization are a result of colonization of the external surface of the catheter, a silver-impregnated collagen cuff was developed that fits around the catheter and resides in a subcutaneous pocket.[89] Although initial studies showed that the cuff reduced the density of bacterial growth on the catheter, there was no effect on CR-BSIs.[89,90] Subsequent studies have failed to demonstrate a reduction in either colonization or CR-BSIs.[91] Seating the cuff in the subcutaneous pocket can be difficult for inexperienced operators and there is a tendency for the cuff to be extruded over time.

Summary

The incidence of CR-BSIs is not negligible and is associated with higher rates of morbidity and mortality, especially with CVCs. The best method to treat catheter-related infections is *prevention*. Adherence to practices that have been proven to reduce the risk of infection should be actively encouraged in every ICU. For those ICUs where the rate of CR-BSIs is still high despite the use of preventive strategies, the use of antiseptic- or antibiotic-impregnated catheters with chlorhexidine dressing is recommended.

Widespread use of prevention strategies, including the use of antibiotic lock therapy,[92] antimicrobial-impregnated catheters,[30] or quinolone prophylaxis[93] by individual centers could influence the rate, etiology, and susceptibility of CR-BSIs, affecting choice of empiric or first-line antimicrobial therapy.

Future Directions

New technologies are emerging to help us prevent CR-BSIs. New catheters that resist colonization with new polymers may have heparin-bonded surfaces, antimicrobial coatings, antiseptic impregnation, ultrasmooth surfaces resistant to biofilm formation, and anti-inflammatory drugs. Also, hubs resistant to contamination and luminal lock solutions are promising for lowering the rate of infections. Despite all the new technology, *prevention*, *surveillance*, and *staff education are the keys to long-term success*.

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29
Pneumonia

Alexandra Chroneou, Nikolaos Zias, Anthony Gray, and Donald E. Craven

Hospital-acquired pneumonia (HAP) is usually caused by bacterial, viral, or fungal pathogens that occur ≥48 h after hospital admission.[1,2] Overall, more than 80% of HAP episodes are related to invasive airway management (in patients with endotracheal intubation or tracheostomy) with mechanical ventilation, which is known as ventilator-associated pneumonia (VAP).[3] VAP is defined as pneumonia developing more than 48 h after intubation and mechanical ventilation. Healthcare-associated pneumonia (HCAP) is part of the continuum of pneumonia, which includes patients who were hospitalized in an acute-care hospital for ≥2 days within 90 days of the infection; resided in a long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic.[1,2] Although this document focuses more on HAP and VAP, many of the principles are also relevant to the management of HCAP. HAP, VAP, and HCAP are the second most common nosocomial infections after urinary tract infection, but are the leading causes of mortality due to hospital-acquired infections.[4,5]

Organisms causing HAP/VAP may originate from the host's endogenous flora, other patients, visitors, hospital staff, or environmental sources. Aspiration and leakage around the endotracheal tube cuff are major risk factors for bacterial entry into the lower respiratory tract (Fig. 29.1).[6,7] Over the past decade, there has been an increase in HAP caused by multidrug-resistant (MDR) pathogens, such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus* (MRSA).[1,2,6,8]

This chapter highlights the changing epidemiology, pathogenesis, and treatment of HAP, VAP, and, to a lesser extent, HCAP. Our primary focus is on bacterial pathogens causing HAP in immunocompetent adults. Readers are referred to other chapters for specific information on pulmonary infections related to immunodeficiency, mycobacteria, viruses, or fungal pathogens. Our major emphasis is on evidence-based patient management (diagnosis and treatment) and prevention strategies to improve patient outcomes.

Epidemiology

Each year there are 5–10 episodes of HAP per 1,000 hospital admissions.[1,2,6] HAP accounts for 15% of all healthcare-associated infections and approximately 25% of all intensive care unit (ICU) infections. Rates of HAP tend to be higher in university versus non-teaching hospitals. VAP rates in the Centers for Disease Control and Prevention's (CDC) National Nosocomial Infections Surveillance (NNIS) system varied by the type of ICU with a pooled mean of 7.3/1,000 ventilator days for medicine versus 13.2 for surgical ICUs. The 50th percentile (median) was 6.0 ventilator days for medicine and 11.6/1,000 ventilator days for surgical ICUs.[9]

Crude mortality rates range between 20 and 50% for VAP and vary by patient population and method of diagnosis.[1,2,6] The mortality attributable to the pneumonia also varies between 10 and 30%, depending on the methodology used. Several studies have demonstrated that rates of VAP increase

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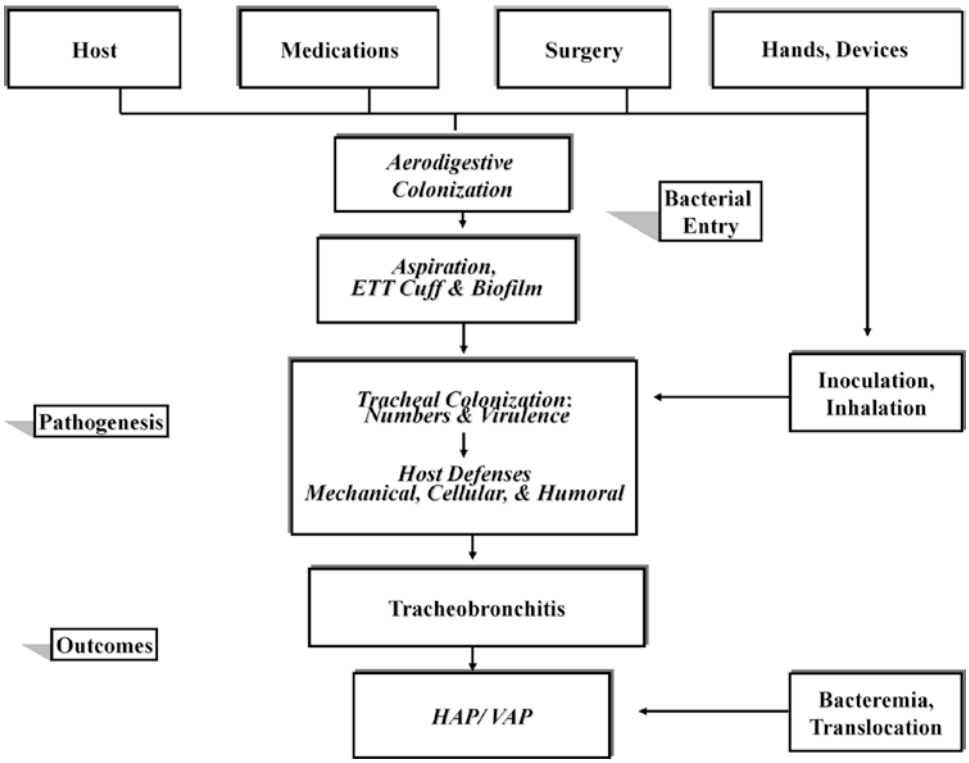

FIG. 29.1. Pathogenesis of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP): (1) Colonization and entry of bacteria into the lower respiratory tract); (2) Bacterial–host defense interactions (bacterial numbers and virulence vs. host mechanical, humoral and cellular defenses); and (3) Outcomes (either tracheobronchitis or HAP/VAP).

with the duration of mechanical ventilation and attack rates have been estimated to be approximately 3% per day during the first 5 days and 2% per day thereafter.[8]

We are entering an era with greater pressure for public reporting of healthcare-associated infections, but rates may depend on the definitions and denominators used. Eggimann et al. examined several ways to report healthcare-associated infection rates and suggested some caveats for benchmarking rates of VAP. In a prospective cohort of 1,068 medical ICU patients, 127 episodes of VAP developed in 106 (23.5%) of 451 mechanically ventilated patients.[10] The incidence of first episode of VAP was 22.8/1,000 patient-days; 29.6/1,000 patient days at risk, 35.7/1,000 ventilator days, and 44.0/1,000 ventilator days at risk. When considering all 127 episodes of VAP, infection rates increased from 22.8 to 27.3 episodes/1,000 ICU days and from 35.7 to 42.8 episodes/1,000 ventilator days. These data demonstrate the importance of the denominator chosen and may differ by as much as 40–60%. These rates have decreased in the past 3 years due to better prevention measures.

Crude mortality rates for VAP pneumonia range from 20 to 60%, reflecting, in large part, the severity of underlying disease, organ failure, and specific pathogen(s) and study populations.[1,2,6,11,12] In two major studies of VAP, the mortality rate varied between 4% in patients without prior antibiotic exposure to 73% in those with VAP due to MDR pathogens (e.g., *P. aeruginosa* or *A. baumannii*), and attributable mortality ranged from 6 to 14%.[13]

Prevention programs for VAP are critically important for patient safety. Preventing VAP not only improves clinical outcomes, but also significantly reduces healthcare costs and liability. Rello et al. demonstrated that an average episode of VAP increased hospitalization by 12 days, mechanical ventilation by 10 days, ventilator days by 6 days, and ICU stay by 6 days at a hospital cost of $40,000; similar results have been reported from a suburban hospital by Warren et al.[12,14]

Pathogenesis

Pathogenesis of HAP involves the direct interaction between the pathogen(s) with the host and epidemiologic variables that facilitate this dynamic. There are several mechanisms that contribute to the pathogenesis of HAP, and the relative contribution of each pathway remains controversial and varies by population at risk and the infecting pathogen(s) (Fig. 29.1).[1,2] Microaspiration in nonventilated patients is the primary route of bacterial entry into the lower respiratory tract.[1,2] In addition, patients who are sedated, postoperative, or have abnormal swallowing are at higher risk for aspiration.[1,2] Direct inoculation, bacteremic spread, or translocation of bacteria from the gastrointestinal tract are less common modes of acquisition.

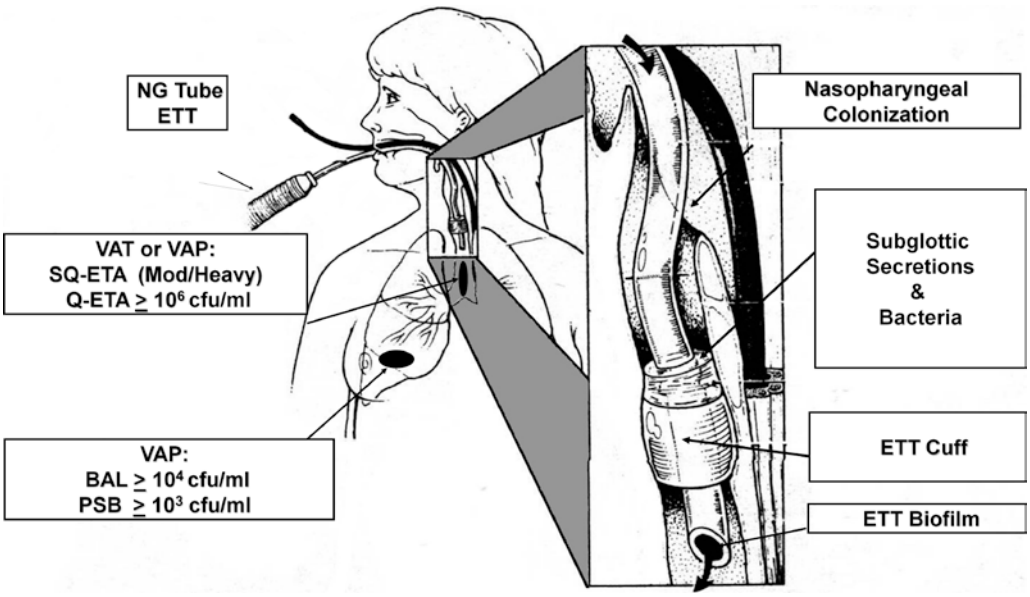

FIG. 29.2. An intubated patient with oropharyngeal colonization. Subglottic secretions pooled above the endotracheal tube (ETT) cuff may leak around the cuff or be introduced directly into the trachea, resulting in either colonization. Depending on level of bacterial colonization, using semiquantitative samples of endotracheal aspirates (SQ-ETA) or quantitative-ETA, a diagnosis of ventilator-associated tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP) can be made. Quantitative diagnostic sampling of the alveolar space by bronchoscopic of non-bronchoscopic, bronchoalveolar lavage (BAL), or protected specimen brush (PSB) may also be used to diagnose VAP. *NG*: nasogastric tube.

High concentrations of bacteria refluxed from the gastric reservoir or infected sinuses may be aspirated and increase levels of bacteria colonizing the oropharynx, but the relative contribution of these sites remains controversial. The current practice of maintaining patients in the semi-upright position, especially while providing enteral feeding, probably reduces the contribution of gastric colonization to VAP. Bacterial adherence and colonization of the oropharynx clearly are important for bacterial entry into the lower respiratory tract.[1,15,16]

Colonization with gram-negative bacilli was present in 16% of moderately ill patients versus 57% of critically ill patients, and rates of pneumonia increased sixfold in ICU patients with bacterial colonization. Host factors, types of bacteria colonizing the pharynx, and the use of antibiotics may alter colonization and adherence of gram-negative bacilli. Oral epithelial cells rich in fibronectin bind gram-positive organisms, such as streptococci and *S. aureus*; conversely, those poor in fibronectin preferentially bind gram-negative bacilli such as *P. aeruginosa.*[16]

In the mechanically ventilated patient, inhalation of aerosols, contaminated tubing condensate, leakage of bacteria, and oral secretions around the endotracheal cuff are routes of bacterial entry into the lower respiratory tract (Fig. 29.2).[18,19] In addition, local trauma and inflammation from the endotracheal tube increase tracheal colonization and reduce clearance of organisms and secretions from the lower respiratory tract. The development of biofilm-encased bacteria over time on the endotracheal tube lumen may increase the risk of bacterial embolization into the alveoli following suctioning or bronchoscopy[20] (Fig. 29.3).

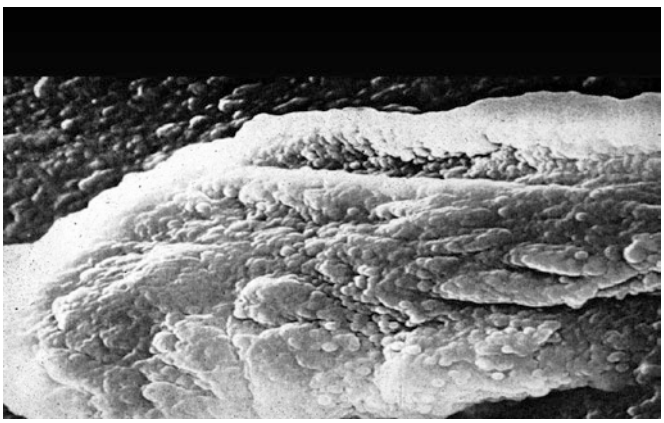

FIG. 29.3. Biofilm-encased bacteria on an endotracheal tube. Note that the bacteria are protected from killing by antibiotics, cellular host defenses, such as macrophages and polymorphonuclear leukocytes, antibodies, and complement.

In mechanically ventilated patients, the stomach and gastrointestinal tract may contribute to oropharyngeal and tracheal colonization with gram-negative bacilli, although some investigators question their importance.[1,15,21–23] The stomach often is sterile when the pH is <2 because of the potent bactericidal activity of hydrochloric acid. An increase in gastric colonization occurs with achlorhydria, and various gastrointestinal diseases, malnutrition, or use of antacids or histamine-2 (H2) blockers. In mechanically ventilated patients, colonization may reach 1–100 million gram-negative bacilli/ml of gastric juice when the pH is >4.[23]

The pathogenesis of lower respiratory tract infections often begins with tracheal colonization, which may progress to ventilator-associated tracheobronchitis (VAT), and, in selected patients, to VAP.[24,25] In addition, discrimination between VAT and VAP may be difficult due to poor and overlapping definitions. VAT is defined as the presence of clinical signs of lower respiratory tract infection (fever, leukocytosis, and purulent sputum) with a quantitative endotracheal sputum sample with more than 106 organisms/ml of a respiratory pathogen, in the absence of a new or progressive infiltrate on chest X-ray (Fig. 29.2). Monitoring endotracheal aspirates used to identify pathogens colonizing the lower airway is needed to diagnose and initiate early, appropriate antibiotic therapy. Recent data suggest that VAT appears to be an important risk factor for VAP and that targeted antibiotic therapy for VAT may be a new paradigm for VAP prevention and better patient outcomes.[24,25]

Immune Defenses in the Lung

The response of pulmonary host defenses to invading microorganisms plays an integral part in the pathogenesis and outcome of infection (Fig. 29.1).[2,6,26,27] Mucociliary and mechanical clearances in the upper airway are important factors in the defense against infection. Bacterial antigens and cytokines that alter the activity and efficacy of ciliary cells in clearing bacteria from the lower airway need further study. The ability of macrophages and polymorphonuclear leukocytes to eliminate bacterial pathogens, and the interaction of these cells with inflammatory cytokines, probably play important roles in the pathogenesis of pneumonia. Cell-mediated immune response is controlled by a complex array of lipids, peptides, and cytokines, including interleukin-1 and -2 interferons, growth factors, and chemotactic factors. Leukotrienes complement components, and platelet-activating factor also assist in the inflammatory response and contribute to the pathogenesis of pneumonia.

Etiologic Agents

The wide spectrum of etiologic agents causing HAP/VAP varies by hospital, type of ICU, and patient population studied, emphasizing the importance of current local surveillance data[1,2,6,9,12,28,29] (Table 29.1). Bacteria causing HAP/VAP may originate from various sources, including the patient's endogenous flora, other patients, staff, contaminated devices, or the environment.[7,30,31] Prior hospitalization, exposure to chronic care facilities, and antibiotic therapy also are important predisposing factors for MDR pathogens.[32–35] In the absence of these factors, early onset HAP, occurring during the first 5 days of the hospital stay, is usually caused by *Streptococcus pneumoniae*, *Moraxella catarrhalis, Haemophilus influenzae,* or anaerobic bacteria (Table 29.1). In comparison, late-onset HAP is more commonly caused by MDR gram-negative bacilli (*Klebsiella pneumoniae* with extended-spectrum beta-lactamases (ESBL+), *A. baumannii*, *P. aeruginosa*) or MRSA.[36]

Table 29.1. Non-multidrug-resistant and multidrug-resistant (MDR) pathogens causing HAP.[150]

Non-MDR pathogens	MDR pathogens	Comments
Gram-positive Cocci		
Staphylococcus aureus	Methicillin-resistant *S. aureus* (MRSA)	MRSA is increasing in hospitals: community-acquired MRSA (CA-MRSA) isolates are rapidly emerging: and less resistant; inducible resistance to clindamycin has been reported
	Vancomycin or glycopeptide-intermediate *S. aureus* (VISA,GISA)	New definitions of vancomycin sensitivity (MICs) may increase prevalence of GISA, VISA isolates, currently rare.
	Vancomycin-resistant *S. aureus* (VRSA)	VRSA currently rare
	Linezolid-resistant *S. aureus (LRSA)*	LRSA strains are rare, but may increase with greater prescribing.
Streptococcus pneumoniae (pneumococcus)	Penicillin-resistant *S. pneumoniae* (PRSP) and multidrug-resistant (MDR)*S. pneumoniae*	Usually early onset HAP; PRSP strains increasing: resistant serotypes changing with use of protein–polysaccharide vaccine in children
Gram-negative Bacilli		
Escherichia coli	Extended-spectrum beta-lactamase (ESBL)+ *E. coli*	Not a common HAP pathogen
Klebsiella pneumoniae	ESBL+ *K. pneumoniae*	ESBL+ strains are increasing in the United States
Enterobacter species		Resistance to cephalosporins may develop on therapy
Serratia marcescens		Some resistant isolates reported
	Pseudomonas aeruginosa	Common MDR pathogen; resistant spectrum common
	Acinetobacter species	Variable; may cause outbreaks of VAP
	Burkholderia cepacia	Uncommon
	Stenotrophomonas maltophilia	Uncommon
Gram-negative Coccobacilli		
Hemophilus influenzae		Early onset HAP: more common chronic lung disease patients; resistant strains usually b-lactamase+
Moraxella catarrhalis		Some resistant strains reported
Special pathogens		
Legionella pneumophila		Check hospital water supply; cooling towers (airborne)

Gram-negative bacilli have been implicated in more than 60% of reported episodes of HAP, and *S. aureus* (often MRSA) accounts for 20–40% of episodes but is increasing rapidly in the United States.[1,5,9] Isolation rates of these bacteria vary considerably depending on the population at risk, location, hospital size, ICU type, and method of diagnosis. However, overall rates of MDR pathogen infections are increasing rapidly in the United States and many other countries.[5,37,38] Most episodes of bacterial nosocomial pneumonia are caused by more than one species of bacteria because of aspiration or leakage of mixed bacterial flora from the oropharynx.[1,2,6,12]

More recently, pneumonia due to community-acquired MRSA (CA-MRSA) has emerged in children and adults.[39–42] In contrast to healthcare-associated (HA)-MRSA, CA-MRSA isolates are genetically distinct and almost uniformly carry the Panton–Valentine leukocidin (PVL), which may be associated with greater virulence. These strains also have been identified as an emerging source of infection spreading within hospitals. There is also concern over the evolution of vancomycin or glycopeptide-intermediate *S. aureus* (VISA/GISA) isolates of *S. aureus* that have been increasing.[39,43]

Diagnosis

Accurate data regarding etiologic agents, epidemiology, and treatment of HAP/VAP are limited by the lack of a diagnostic gold standard. Although clinical criteria and semiquantitative sputum culture criteria for the diagnosis of VAP are the current standard for diagnosis in most hospitals, there are concerns about lack of diagnostic specificity.[2,6,44] Atelectasis, pulmonary edema, pulmonary emboli, neoplastic processes, and some autoimmune diseases can mimic HAP and VAP and, therefore, microbiologic diagnosis is critical. In addition, chest radiographic changes may be difficult to evaluate due to adult respiratory distress syndrome (ARDS) or congestive heart failure, making the clinical diagnosis of pneumonia more difficult (Fig. 29.4a, b). The use of a computerized tomographic (CT) scan improves imaging but quality sputum samples for Gram stain and culture are also of paramount importance for providing clues to possible pathogens. Sputum may be produced spontaneously, induced by nebulized saline, or obtained by bronchoscopy in the non-intubated patient. For patients in mechanically ventilated ICUs, there has been considerable controversy regarding the benefits and risks of clinical diagnosis using semiquantitative evaluation of endotracheal aspirates versus quantitative cultures obtained from either bronchoscopic bronchoalveolar lavage (B-BAL) or protective specimen brush (B-PSB) or non-bronchoscopic BAL/PSB (NB-BAL or NB-PSB).[2] These diagnostic approaches are discussed below.

Clinical Diagnosis

The clinical diagnosis of pneumonia is defined as the presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever>38°C, leukocytosis or leukopenia, and purulent secretions). While sensitivity for the presence of pneumonia is increased if only one criterion is used, specificity is reduced, leading to significantly increased use of antibiotics. Requiring all three clinical criteria is too insensitive, resulting in under-prescribing for patients with HAP.

The clinical pulmonary infection score (CPIS), used in some ICUs, gives points for clinical, radiographic, physiologic (PaO_2/FiO_2), and microbiologic data for a single numerical result.[36] When the CPIS score was greater than 6, good correlation was found with the presence of pneumonia.[45] Singh et al. used a modified CPIS score that did not rely on culture data to guide clinical management.[46] Patients with a low clinical suspicion of VAP (CPIS≤6) were randomized to therapy with ciprofloxacin compared to conventional therapy. The

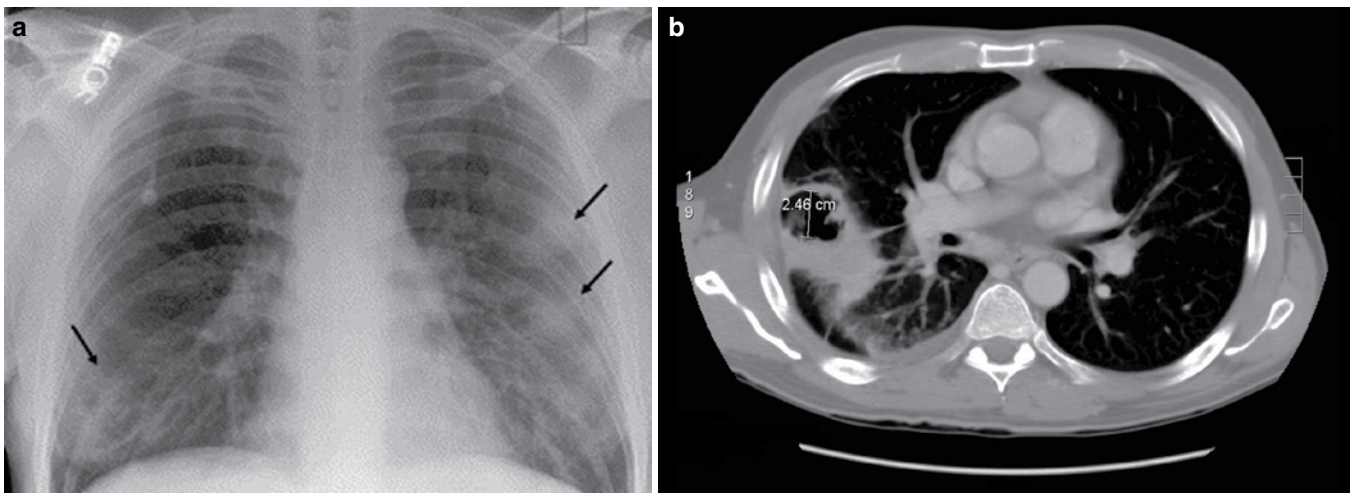

FIG. 29.4. (**a**) Chest radiograph of a patient with vague infiltrate in the *right lower lobe*, which is more clearly identified in (**b**) the computerized tomographic (CT) scan.

ciprofloxacin group had antibiotics discontinued after 3 days if there was no deterioration in their clinical status or CPIS score.[46] The modified CPIS score appears to be an objective measure to define patients who can receive shorter courses of therapy (3 days), achieving better overall outcomes.

Microbiologic Diagnosis

Most microbiology laboratories report sputum culture results in a semiquantitative fashion, describing growth as light, moderate, or heavy. Moderate to heavy growth is most consistent with a diagnosis of VAT or VAP, especially if the Gram stain has many polymorphonuclear leukocytes and bacteria. The presence of bacteria on Gram stain (smear) correlates with 10^5 bacteria/ml by bronchoscopic alveolar lavage (BAL). Also, the morphology of the bacteria is a clue to the offending bacteria (i.e., gram-positive cocci in clusters suggest *S. aureus* and gram-negative bacilli may suggest *Klebsiella spp, E. coli*, or *P. aeruginosa)*. It is also important to correlate these findings with aerobic culture results, because anaerobic cultures are not routinely performed. A Gram stain of sputum or tracheal aspirate without bacteria or inflammatory cells has a strong negative predictive value for VAP and may suggest another cause for the patient's fever, leukocytosis, and infiltrate on chest X-ray.

Use of the endotracheal aspirates for the diagnosis of VAP allows prompt, empiric therapy, and may reduce mortality. However, it may not effectively separate lower airway colonization (purulent tracheobronchitis) from VAP (Table 29.2). Semiquantitative criteria suggesting VAP are moderate to heavy growth.

By comparison, quantitative endotracheal aspirates, or cultures of lower respiratory secretions using bronchoscopic or non-bronchoscopic BAL or PSB to define VAP, are more specific than semiquantitative endotracheal aspirates.[2,6] VAP is defined as growth of $>10^5$–10^6 CFU/ml for endotracheal aspirates, $>10^3$ CFU/ml for PSB, and $>10^3$ CFU/ml for BAL. Growth below the threshold suggests colonization or contamination with some exceptions. For example, patients who have had a recent change in antibiotics may have a false-negative BAL/PSB, perhaps early VAP, inadequate BAL technique, or other causes, such as *Legionella pneumophila*, viruses, or anaerobic bacteria. However, the quantitative approach may improve de-escalation of antibiotics by targeting the specific pathogens that are causing VAP. In one large, prospective, randomized trial of 413 patients with suspected VAP, patients receiving invasive management compared to those managed clinically had a lower mortality rate at day 14 (16 and 25%; $p=0.02$, but not at day 28), lower mean sepsis-related organ failure assessment scores ($p=0.04$), and significantly more antibiotic-free days (11 ± 9 vs. 7 ± 7; $p<0.001$).[47] Multivariate analysis demonstrated significantly reduced mortality (hazards ratio, 1.54 [CI, 1.10–2.16]; $p=0.01$). Although a high percentage of patients in both arms received adequate initial antibiotics, more patients in the invasive group received adequate therapy than in the clinical group, and the impact of this difference on the observed mortality is of concern. This study suggests that the quantitative approach is safe, leads to less antibiotic use, and may potentially reduce mortality.

On the contrary, a recent randomized study by a Canadian Critical Care Trials group compared quantitative and semiquantitative techniques for diagnosing VAP in 740 patients who were randomized to specifically target antibiotic therapy.[48] Although there were many patients excluded from the study, including those with MRSA and *P. aeruginosa* colonization, the clinical outcomes in terms of length of stay in the hospital/ICU and the 28-day mortality were similar between the two groups.

Antimicrobial Management

Current management principles for HAP and VAP summarized in the 2005 American Thoracic Society & Infectious Diseases Society (ATS/IDSA) Guidelines include early, appropriated, initial antibiotic therapy, followed by de-escalating antibiotics based on clinical response and microbiologic data and reducing duration of therapy to 7–8 days in responders.[2] An alternative management strategy has been suggested that focuses on treating VAT before the development of VAP using targeted antibiotic therapy when a quantitative endotracheal aspirate has a pathogen(s) $\geq10^6$ organisms/ml, but such a strategy needs further investigation.[24,25]

Early, Appropriate, and Adequate Initial Empiric Antibiotic Therapy

As soon as HAP/VAP is suspected, the collection of respiratory samples and the prompt initiation of appropriate antibiotics, in adequate doses, are suggested (Fig. 29.5 and Table 29.2). It has been shown that the shorter the time between diagnosis and initiation of treatment the better the impact on prognosis, length of hospital stay, and cost.[49–52] Appropriate therapy means that the pathogen is susceptible to the chosen regimen, whereas adequate therapy means that appropriate drugs, with good lung penetration, are given in optimal doses via the correct route. Choosing an initial, appropriate intravenous antibiotic regimen depends on the likelihood of infection with MDR pathogens, such as *P. aeruginosa, A. baumannii,* ESBL+ *K. pneumonia,* or MRSA.

Risk factors for MDR pathogens include prior hospitalization, late-onset infection, prior antibiotic therapy, and chronic dialysis, and are more for residents of chronic care facilities and for immunocompromised patients. Patients without MDR risk factors and early onset HAP or VAP usually can be treated with a more limited spectrum of antibiotics, such as ceftriaxone plus azithromycin, a third- or fourth-generation quinolone (i.e., levofloxacin), or ampicillin–sulbactam (Table 29.2). By comparison, broader initial antibiotic therapy is suggested if patients are at risk for MDR pathogens (Table 29.3). Finally, it is important to use doses of antibiotics that will achieve adequate concentrations in the lung parenchyma, which are outlined in the ATS/IDSA Guideline.[2]

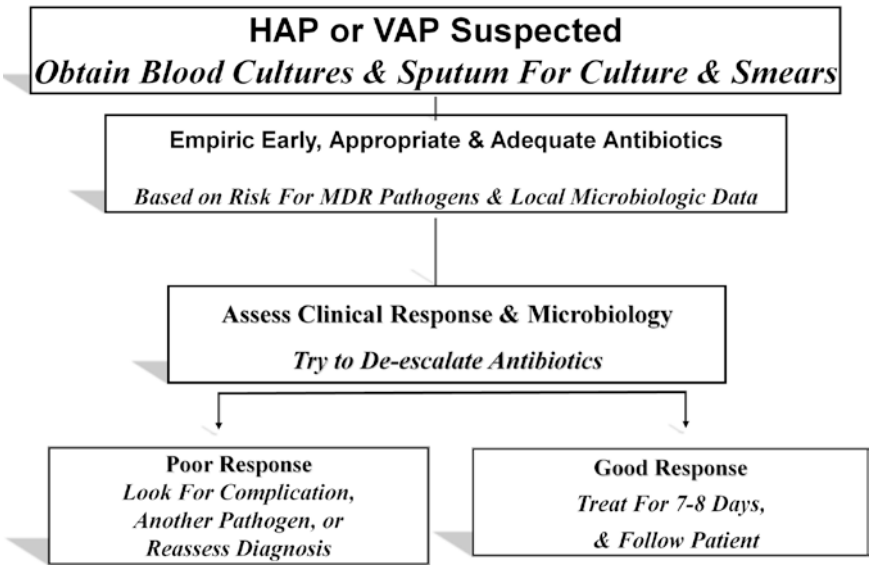

FIG. 29.5. Approach to initial antibiotic therapy and management of HAP/VAP. Based in part on the American Thoracic Society (ATS) & Infectious Diseases Society of America (IDSA) Guideline.[2]

TABLE 29.2. Recommendations for initial broad-spectrum empiric therapy for patients with suspected pneumonia and risk factors for multidrug-resistant (MDR) pathogens.[2]

Potential MDR pathogens	Combination therapy
MDR gram-negative bacilli *Pseudomonas aeruginosa* *Escherichia coli* *Klebsiella pneumoniae*	Anti-pseudomonal cephalosporin e.g., cefepime, ceftazidime *OR* Anti-pseudomonal carbapenem (imipenem or meropenem) *OR* Anti-pseudomonal penicillin (piperacillin–tazobactam) *PLUS* Anti-pseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) *OR* Aminoglycoside (amikacin, gentamicin, or tobramycin)
ESBL+ *Klebsiella pneumoniae*	Carbapenem
Acinetobacter species	Carbapenem + aminoglycoside
Non-MDR gram-negative Bacilli *Legionella pneumophila*	Fluoroquinolone or macrolide (ciprofloxacin, levofloxacin or azithromycin)
MDR gram-positive cocci Methicillin-resistant *Staphylococcus aureus* (MRSA)	Vancomycin or linezolid

TABLE 29.3. Arbitrary risk factors for multidrug-resistant (MDR) pathogens.[1,2]

Antimicrobial therapy in preceding 90 days
Current hospitalization of at least 5 days
High frequency of antibiotic resistance in the community or in the specific hospital unit
Hospitalization for at least 2 days in the preceding 90 days
Residence in a nursing home or extended care facility
Home infusion therapy (including antibiotics)
Chronic dialysis within 30 days
Home wound care
Family member with infection involving MDR pathogen
Immunosuppressive disease and/or therapy

Assessing Clinical Response, Cultures, and Antibiotic De-escalation

While initial antibiotic coverage should be liberal and broad enough to cover all suspected pathogens, de-escalation or streamlining antibiotic therapy, based on the patient's clinical response and microbiologic data, is of critical importance to improve patient outcomes and minimize antibiotic use[2,46] (Fig. 29.5). Patients without evidence of HAP or VAP should have their antibiotics stopped. If necessary, further work-up and treatment for other sources of fever should be initiated.

Limiting Duration of Therapy

In a recent randomized trial of patients with VAP, patients randomized to 8 days of antibiotic therapy had fewer recurrences and less resistance overall than those randomized to 15 days of therapy.[53] No significant differences were noted in mortality or clinical response parameters, but rates of recurrence for those patients with VAP due to *P. aeruginosa* infection were higher in the group treated for 8 rather than 15 days. The ATS/IDSA guideline recommends 7–8 days of therapy for uncomplicated HAP or VAP with close follow-up for any signs of relapse, especially for patients with HAP or VAP due to *P. aeruginosa*[2] (Fig. 29.5).

Management of Selected MDR Pathogens

Pseudomonas Aeruginosa

This pathogen is distinguished by its capacity to develop resistance to all known classes of antibiotics even while the patient is still on therapy. It is unclear if this problem could be avoided with the use of combination therapy.[54,55] The only supporting data comes from a study of *P. aeruginosa* bacteremia (few cases

of which were due to pneumonia), which showed that patients receiving combination therapy were less likely to die.[56]

Cometta et al.,[55] in a prospective study, compared combination therapy of an aminoglycoside and a carbapenem versus monotherapy with carbapenem, which did not show improved outcomes, or a difference in the rate of developing resistance. Of note is that no study has used single daily dosing of the aminoglycoside, or the maximal effective dose recommended by ATS/IDSA. Also, no data are available comparing a fluoroquinolone-based combination therapy, with b-lactam monotherapy. However, if *P. aeruginosa* is isolated, combination therapy should be used until antibiotic sensitivity is available.

Acinetobacter Species

The choices of treatment of *Acinetobacter* species pneumonia are limited because of its native resistance to many classes of antibiotics. Carbapenems, polymyxins, and the sulbactam component of ampicillin–sulbactam are considered the most effective antibiotic classes. Wood and coworkers demonstrated equivalent rates of clinical cure in a population with trauma surgery with ampicillin–sulbactam, compared with imipenem, including patients with imipenem-resistant isolates.[57] The emergence of carbapenem-resistant clones suggests the need for use of optimal doses of carbapenem. Polymyxins are significantly nephrotoxic, limiting their widespread intravenous use; there may be some benefit from aerosolized polymyxin.[58,59]

Extended-Spectrum β-Lactamase Producers

The hallmark of ESBL-producing enterobacteriaceae, such as *Klebsiella pneumoniae, Escherichia coli*, and *Enterobacter species*, is a variable response to cephalosporins, and therefore third- and fourth-generation agents should be avoided as monotherapy when these pathogens are suspected or isolated.[60] Third-generation cephalosporins (e.g., cefotaxime) should not be used for treatment of *Enterobacter* spp. because of the high frequency of resistance of this pathogen to this therapy.[61] The use of the fourth-generation cephalosporin (e.g., cefepime) is also not recommended.[60,62] A most reliable empiric choice is a carbapenem, such as imipenem, meropenem, or etrapenem.[63]

MRSA

Although vancomycin is considered the standard therapy for MRSA pneumonia, clinical trials and studies from different centers have reported clinical failure rates of greater than 40% with a standard dose of 1 g every 12 h.[64–66] This treatment failure may be related to inadequate dosing.[64] Many physicians have therefore tried to achieve a trough concentration of 15 mg/l or more, but without prospective clinical data supporting this practice. Combination therapy with rifampin, aminoglycosides, and other agents has been tried, but without well-documented value.[67] The use of continuous vancomycin infusions has not been proved to be advantageous compared with twice-daily dosing in severe MRSA infections.[68]

Linezolid is another agent that has been used in the treatment of patients with MRSA VAP. Two large multicenter trials demonstrated equivalence to vancomycin in the treatment of these patients.[69,70] When these studies were combined and analyzed by multivariate techniques, linezolid was associated with a better clinical cure and lower mortality. Although the superiority of linezolid over vancomycin needs further validation in randomized trials, it has higher lung penetration, as measured by epithelial lining fluid analysis when compared with vancomycin.[58,71] Linezolid should be considered in patients with renal failure or a documented lack of response to vancomycin. Dosing vancomycin in patients with fluctuating renal function is difficult, and requires frequent monitoring of drug levels. Notably, the presence of renal insufficiency was a significant predictor of vancomycin failure in a multivariate analysis of patients with VAP,[69] and there is also concern about increased nephrotoxicity in patients receiving vancomycin and other nephrotoxic medications, such as aminoglycosides.[68,72,73]

Other approved new agents for nosocomial MRSA infections are quinupristin/dalfopristin. Daptomycin should not be used in the treatment of MRSA pneumonia, as it was found inferior in clinical trials. Tigecycline has excellent activity against MRSA in vitro, and clinical studies of VAP are in progress. Ceftobiprole and dalbavancin also have in vitro activity against MRSA, but are not currently approved for use in the United States.[74–76]

There are also new concerns over the emergence and rapid spread of a new strain of community-acquired MRSA that can cause serious pneumonia in healthy children and adults, and superinfection in individuals with influenza A virus infection.[77–79] Community-acquired MRSA has caused outbreaks in nursing homes, hospitals, schools, prisons, athletic teams, and the military. This strain may continue to spread in the community and is likely to become a major healthcare-associated pathogen.[39,79,80] Community-acquired MRSA isolates have increased virulence that may be related, in part, to the presence of the Panton–Valentine leukocidin. Furthermore, the combination of increasing hospital-acquired MRSA in healthcare settings and the rapid spread of community-acquired MRSA in selected high-risk populations and in acute and chronic healthcare settings requires close attention. Finally, the encapsulated pathogens *S. pneumoniae* and *S. aureus*, which may cause HAP, are common causes of bacterial superinfection following the yearly influenza outbreaks, and there is even greater concern over both hospital-acquired and community-acquired MRSA in the setting of a future bird flu pandemic.[81]

Lack of Response to Initial Therapy

In most patients, clinical improvement takes 24–48 h. Therefore, the selected antimicrobial regimen should not be changed during this time unless there is evidence of progressive deterioration.

Possible causes of rapid deterioration or failure to improve include three possibilities:

1. *Wrong diagnosis* – pulmonary embolism with infarction, atelectasis, pulmonary hemorrhage, neoplastic or connective tissue disease, chemical pneumonitis from aspiration, acute respiratory distress syndrome (ARDS) with diffuse alveolar damage, other source of infection.
2. *Wrong antimicrobial therapy* – drug-resistant pathogen, inadequate dosing, wrong antimicrobial agent.
3. *Wrong pathogen* – tuberculosis, fungal or viral infection, opportunistic infection, Legionella infection – or *complication* of pneumonia (empyema or lung abscess, *Clostridium difficile* colitis, bacterial or *Candida albicans* superinfection, drug fever).[2]

Prevention

Detailed, evidence-based prevention measures are well summarized in the 2004 CDC Healthcare Infection Control Prevention Advisory Committee (HICPAC) and ATS/IDSA Guidelines, as well as several review articles and in Table 29.4.[1,2,82,83]

TABLE 29.4. Selected ventilator-associated pneumonia (VAP) prevention strategies abstracted from recent guidelines; more detailed discussion and references in test.[82,151]

Intervention/strategy	Support/evidence	Comments
Infrastructure		
Multidisciplinary team	Programs developed by team consensus more effective	Input by critical care staff and respiratory therapists crucial
"Champion" of the cause	Recognized leader/expert increases "buy-in" by staff and hospital administration	Leadership needed to set benchmarks, maintain efforts and secure resources
Targeted staff education	Staff education/awareness programs shown to reduce VAP	Such programs are adaptable to local needs and are cost-effective
Infection control	Data supports importance in reducing spread of multidrug-resistant (MDR) organisms	Coordinate with quality improvement efforts; feedback data to staff
Antibiotic control	Reduces inappropriate antibiotic use and associated costs	Designated pharmacist optimal; computer programs good alternative
Adequate staffing	Critical for maintaining patient safety and adherence to protocols	Particularly important in critical care units; current nursing shortages exist
Benchmarking/quality	Current recommendations from ICHI and local multidisciplinary teams	Benchmarks should be evaluated routinely and data communicated
Patient care		
Sedation vacation	Supported by clinical data; accessible and feasible; part of VAP bundle	Implement standard protocols
Semi-upright position	Supported by early data; recent data suggest lower elevation target indicated Part of VAP bundle	Few outcome data; poor compliance with strategy. Further studies needed
Noninvasive positive pressure ventilation	Supported by several clinical trials in recent review by Cochrane	Experience with technique is suggested for patients with COPD and CHF
Oral care	Evidence is limited, but risk and cost are low	Further studies are needed
Stress bleeding prophylaxis	Data support use of proton pump inhibitors (PPIs) and histamine type 2 (H2) blockers; limit to high-risk patients	PPIs and H2 are more effective than sucralfate in preventing bleeding; *C. difficile* may be increases with PPIs
Deep vein thrombosis prophylaxis	Evidence supportive, part of VAP bundle	Recommended in the VAP 100,000 Lives Campaign VAP "bundle"
Standardized protocols for weaning and enteral feedings	Rates of VAP lowered by reduced duration of intubation and enteral feeding	Protocols help standardize implementation and provide standards for monitoring
Chlorhexidine with or without colistin	Randomized controlled trials (RCTs) demonstrate efficacy	More data needed
Selective decontamination of the digestive tract	VAP and mortality decreased with intravenous and topical antibiotics	Concerns about antibiotic resistance limit "routine" use
Targeting ventilator-associated tracheobronchitis (VAT) to prevent VAP	One randomized trial	Further studies are needed on VAT
Orotracheal intubation and use of orogastric tubes	Several small clinical trials report decreased sinusitis	Recommended, but limited impact on VAP
Continuous aspiration of subglottic secretions or	Decreased VAP shown in at least four RCTs	Optional; cost and impact on staffing are of concern
Silver-coated endotracheal tube (ETT)	One randomized trial demonstrated reduced VAP	Cost and identifying high-risk patients are needed

(continued)

Table 29.4. (continued)

Intervention/strategy	Support/evidence	Comments
Heat moisture exchangers	Trend toward decreased VAP	Recommended; eliminates condensate, but decreases humidity
No change of ventilator circuits	Several RCTs support this intervention	Recommended; positive cost and staffing impact
Early tracheostomy	Reports from three RCTs; methodological concerns	Optional; further data from rigorous studies needed
Closed endotracheal suctioning	Three RCTs showed no effect on VAP, but probably reduces environmental contamination	Optional, may reduce environmental spread of MDR pathogens
Discharge issues		
Vaccination	Pneumococcal and influenza vaccination reduce hospitalizations	Recommended, poor routine vaccination rates of high-risk populations
Smoking cessation	Smoking cessation has been demonstrated to reduce morbidity and mortality	Recommended; instructions and referrals should be documented
Nutritional counseling	Obesity is a known risk factor for comorbidities associated with pneumonia	Recommended; instructions and referrals should be documented
Prevention of aspiration	Aspiration is a major risk factor for pneumonia; speech and swallow study helpful	Check sedation, head of the bed; speech and swallow studies, if indicated

General Prevention Strategies

Most hospitals are using the Institute for Healthcare Improvement (IHI) bundles to reduce VAP (Table 29.4). This quality improvement effort, coupled with other measures regarding reduced reimbursement for healthcare-associated infections, has decreased rates of reported VAP in the United States and Europe.

Staff education is needed for all clinicians and staff who manage HAP and VAP. Zack et al.[84] used successfully a self-study module, in-service teaching programs that were coordinated with ICU staff meetings, along with fact sheets and posters, which were placed in the ICU and respiratory care departments. Rates of VAP dropped nearly 58%, and the cost savings were estimated to be between $425,606 and >$4,000,000. Babcock et al., using an extension of this program in an Integrated Health Care System, reported a 46% reduction in VAP over an 18-month period.[85] Staffing in the ICU is important, which is under-appreciated[1,4], and must be sufficient for patient care and compliance with infection control practices.[85–87]

Use of proper isolation techniques and effective infection control practices are cornerstones for prevention of HAP.[1,7,86] Infection control programs have repeatedly demonstrated efficacy in reducing infection and colonization due to MDR organisms.[1,4,30,88–90] Unfortunately, staff compliance with proven infection control measures, such as hand hygiene, remains inconsistent in many hospitals. Also, surveillance of ICU infections to identify and quantify endemic and new MDR organisms with timely feedback of data is critical.[10,88,91–93] Timely communication of current data among clinicial, laboratory, pharmacy, and infection control staff is essential. Organism-specific strategies may need to be complemented by more aggressive eradication methods.[41,43,94]

Studies are beginning to implicate the inanimate environment as an indirect contributor to pathogen acquisition.[86] Special interventions, including targeted environmental sampling and more aggressive environmental disinfection, may be indicated during outbreaks, particularly those involving MDR organisms or organisms that are more resistant to routine cleaning.[95]

Antibiotic stewardship programs play an extremely important role in the overall effort to control healthcare-associated infections, reduce emergence of MDR organisms, and control spiraling healthcare costs.[96] Antibiotic stewardship should be focused, dynamic, and carefully monitored in order to adjust for specific MDR pathogens.[23,97] An infectious disease pharmacist in the ICU, or a computerized decision support program to optimize drug regimens, has reduced inappropriate antibiotic use.[1,2] By comparison, antibiotic cycling or rotation programs are more difficult to evaluate because of study design issues.[2,97–100]

Modifiable Risk Factors

Risk factors for the development of HAP can be differentiated into modifiable and non-modifiable conditions as will be discussed later. Aspiration – the primary route of bacterial entry into the lung – is common and increased during hospitalization, with sedation, neuromuscular blockers, head trauma, intubation, enteral feeding, and following surgery.[1,101–105] Supine patient positioning may facilitate aspiration, which can be decreased by maintaining a semirecumbent patient position. One randomized trial demonstrated a threefold reduction in the incidence of ICU-acquired VAP in patients kept in a semirecumbent position versus supine position.[106] VAP rates reached 50% in patients maintained in the supine position while simultaneously receiving enteral nutrition.

Although maintaining mechanically ventilated and/or enterally fed patients in a 30–45° position continues to be strongly recommended,[1,2,106] recent studies have suggested that this may not be practical, at least at the levels currently recommended. A study by van Nieuwenhoven et al. in ventilated patients who were randomly assigned to backrest elevation of 45° versus the standard of 10°, demonstrated barriers to implementing this strategy.[107] The targeted backrest elevation of 45° was not reached and the actual achieved difference was 28° versus 10°, which did not reduce VAP. Perhaps, further studies measuring the impact of maintaining ventilated and/or enterally fed patients in a semirecumbent position are more attainable targets.

Modulation of Bacterial Colonization

Oral Care

Oral care has been studied and recommended to prevent VAP.[108–111] In a recent study, Mori et al. compared rates of VAP in a nonrandomized group compared to historic controls.[112] The incidence of VAP in the oral care group was 3.9 episodes/1,000 days versus 10.4 in the control group. Although there are concerns about the study design, oral care has intuitive benefits and limited cost, but more randomized, controlled studies are needed.

Antiseptics

Oropharyngeal colonization is the primary source of pathogens causing HAP and VAP, and therefore reducing levels of colonization or eliminating potential pathogens is an obvious risk-reduction strategy. In a randomized trial, DeRiso et al. demonstrated that the use of the oral antiseptic chlorhexidine (CHX) significantly reduced rates of hospital-acquired infections in patients undergoing coronary artery bypass graft surgery.[113] Although topical antiseptics, such as chlorhexidine (CHX), provide an attractive alternative to antibiotics, the initial reported success in patients who have undergone cardiac surgery could not be confirmed by other studies. A recent study by Koeman et al. provides important data from a multicenter, double-blind, randomized clinical trial of VAP outcomes for subjects treated with 2% CHX paste versus patients randomized to 2% CHX + 2% colistin (COL) paste to provide greater activity against gram-negative bacilli compared to placebo.[114] Compared to the placebo group, the daily risk of VAP was reduced by 65% in the CHX group ($p = 0.01$) and 55% in the CHX–COL group ($p < 0.03$). This impressive result for an inexpensive, nontoxic, topically applied modality warrants further attention, but is difficult to reconcile with the absence of effect on ventilator days, length of stay, or mortality. It is important to measure how prophylactic use of CHX and CHX–COL complement other effective prevention strategies, and resistance could become an important issue over time.

Data from seven randomized controlled trials by Chan et al., involving 2,144 patients, showed that topical antiseptics are beneficial in preventing VAP; the benefit is most marked in patients who have undergone cardiac surgery.[115] These findings are comparable to those of another recently published review study[116] (limited to topical CHX), which also included seven trials but only 1,650 patients. However, both reviews found that oropharyngeal antiseptics had no impact on mortality or length of stay in the intensive care unit.

Antibiotic Prophylaxis Strategies

Modulation of oropharyngeal colonization by combinations of oral antibiotics, with or without systemic therapy, or selective decontamination of the digestive tract (SDD) is effective in preventing HAP/VAP, although the methodologic study quality, specific regimens used, study populations, and clinical impact differ widely among studies.[1,2,108,110,117,118]

In two recently published prospective randomized trials, SDD was associated with a higher ICU survival among patients receiving SDD.[118,119] Also, in two meta-analyses and one additional study, decreased mortality was demonstrated in critically ill surgical patients receiving SDD, including both systemic and local prophylactic antibiotics,[117,120,121] raising questions about the relative importance of systemic rather than non-absorbed antibiotics.

Preventive effects of intravenous antibiotics were evaluated in only one randomized trial: Administration of cefuroxime for 24 h at the time of intubation reduced the incidence of early onset HAP in patients with closed head injury.[122] The role of the gastrointestinal tract in the pathogenesis of VAP and the clinical evidence for the efficacy of SDD were recently reviewed by Kallet and Quinn[123] and in a Cochrane review by Liberati et al.[117] In the latter study, the authors concluded that for topical and systemic antibiotic prophylaxis, five patients would need to be treated to prevent one infection and 21 patients would need to be treated to prevent one death. No recommendation was made for topical prophylaxis. In a large study of SDD by de Jonge et al. in 2003, SDD was highly effective in preventing pneumonia without an increase in antibiotic resistance.[119] However, citing concerns over rapid increases in antimicrobial resistance in the hospital setting, coupled with the association between MDR pathogens and poorer patient outcomes, recent guidelines have suggested that SDD should be considered for selected ICU populations and in targeted clinical scenarios, but not be employed "routinely" for VAP prevention.[1,2,124]

Since VAT appears to be a precursor to VAP, recently there has been greater interest in collecting serial endotracheal aspirates and using targeted antibiotic therapy to treat VAT as a method of preventing VAP and not delaying therapy in patients with chest X-rays that are difficult to interpret.[24,25] Although these approaches need further investigation, they could be a new paradigm for early treatment, VAP prevention, and better patient outcomes.

Endotracheal Tube and Mechanical Ventilation

Several devices have been identified as risk factors for HAP. Many of these devices are used in mechanically ventilated patients and increase the risk of VAP; intervention strategies are summarized in several review articles.[1,2,125]

Subglottic Secretion Drainage

Continuous aspiration of subglottic secretions (CASS) through use of specially designed endotracheal tubes (ETTs) with a wider elliptic hole helps facilitate drainage (Fig. 29.3) and has significantly reduced the incidence of early onset VAP in several studies.[1,2] In a recent meta-analysis, CASS reduced the incidence of VAP by half (risk ratio 0.51, 95% CI 1.7–2.3), shortened ICU stay by 3 days (95% CI 2.1–3.9), and delayed the onset of VAP by 6 days. CASS also was cost effective,

saving $4,992 per episode of VAP prevented or $1,872 per patient, but mortality was not affected.[126]

Silver

Biofilm-encased bacteria that form on the ETT and are protected against killing by antibiotics and host defenses may be a risk factor for VAP. A large, randomized study of 1,509 patients intubated for more that 24 h compared the use of colloidal silver-coated ETT (Bard Pharmaceuticals) – designed to prevent endotracheal tube colonization and biofilm formation – to a conventional ETT.[127] Diagnosis of VAP required confirmation of VAP by a BAL $^3 10^4$ organisms/ml. The silver-ETT group had a lower incidence of VAP (4.8% vs. 7.5%, $p=0.03$), with a relative risk reduction of 35.9% and an absolute reduction of 2.7%, but did not reduce mortality rates, duration of intubation, ICU stay, or hospital stay. Like CASS, the silver-ETT delayed the onset of VAP, had its greatest effect in patients ventilated for more than 48 h, and was highly active against pathogens, such as *P. aeruginosa* and MRSA.

Non-invasive Positive Pressure Ventilation

Non-invasive positive pressure ventilation (NPPV) provides ventilatory support without the need for intubation and for earlier removal of the endotracheal tube to reduce complications related to prolonged intubation. NPPV using a face mask is an attractive alternative for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) or acute hypoxemic respiratory failure, and for some immunosuppressed patients with pulmonary infiltrates and respiratory failure.[1,2] Burns et al., in a recent Cochrane review, reported significant benefits: decreased mortality (RR 0.41, 95% CI 0.22–0.76), lower rates of VAP (RR 0.28, 95% CI 0.90–0.85), decreased length of ICU stay and shorter hospital stays, and lower duration of mechanical support.[128] The impact of NPPV is greater in patients with COPD exacerbations or congestive heart failure than for patients with VAP. Recent data also indicate that NPPV may not be a good strategy to avoid re-intubation after initial extubation and is recommended for hospitals with staff who are experienced in this technique.[129]

Sedation and Weaning

Efforts to reduce the likelihood of aspiration of oropharyngeal bacteria around the endotracheal tube cuff into the lower respiratory tract include limiting the use of sedative and paralytic agents that depress cough and other host-protective mechanisms, and maintaining endotracheal cuff pressure at >20 cm H_2O.[130] Re-intubation should be avoided, if possible, as it increases the risk of VAP.[131] Efforts to reduce acute lung injury by using smaller tidal volumes and lower pressures have been suggested.[132] Other strategies to reduce the duration of mechanical ventilation include improved methods of sedation and the use of protocols to facilitate and accelerate weaning.[1,133–135] These interventions clearly are dependent on adequate ICU staffing.[136,137] Dries et al., using a standardized weaning protocol, reduced the proportion of days of mechanical ventilation (total ICU days) from 0.47 to 0.33%, number of patients failing extubation (25 vs. 43), and the rates of VAP (15–5%).[138] Schweickert et al. evaluated seven complications in 128 patients receiving mechanical ventilation and continuous infusions of sedative drug, who were randomized to daily interruption of sedative infusions ($N=66$) versus sedation directed by the MICU team without this strategy ($N=60$).[7,133] Daily interrupted sedative infusions reduced the length of stay in ICU (6.2 days vs. 9.9, $p<0.01$), duration of mechanical ventilation (4.8 vs. 7.3 days, $p<0.003$), and the incidence of complications per patient (13/12 patients vs. 26/19 patients, $p<0.04$).

Miscellaneous Strategies

Enteral Feeding

Enteral nutrition has been considered a risk factor for the development of HAP, mainly secondary to the increased risk of aspiration of gastric contents.[1,139] Parenteral nutrition is associated with a higher risk of intravascular-device-associated infection and complications from central venous catheter insertion, higher costs, and loss of intestinal villous architecture, which may facilitate enteral microbial translocation. Accurate assessment of the patient's nutritional status and the use of enteral feeding, rather than parenteral nutrition, appear to reduce the risk of HAP.[1,140] Early initiation of enteral feeding may help maintain the gastrointestinal epithelium and prevent bacterial translocation, but it is not without risk. Enteral feeding protocols have been suggested to reduce complications.[4,141] Early gastrostomy for enteral feedings has been considered as a strategy to reduce VAP in patients with head injury and stroke.[142]

Intensive Insulin Therapy

Hyperglycemia, relative insulin deficiency, or both may directly or indirectly increase the risk of complications and poor outcomes in critically ill patients. Van den Berghe et al. randomized patients in surgical ICUs to receive either intensive insulin therapy to maintain blood glucose levels between 80 and 110 mg/dl or to receive conventional treatment.[143] The group receiving intensive insulin therapy had reduced mortality (4.6% vs. 8%, $p<0.04$), and the difference was greater in patients who remained in the ICU for more than 5 days (10.6% vs. 20.2%, $p=0.005$). When compared to the control group, those treated with intensive insulin therapy had a 46% reduction of bloodstream infections, decreased frequency of acute renal failure requiring dialysis by 41%, fewer days with antibiotic treatment, and significantly shorter length of mechanical ventilation and ICU stay. While the same degree of benefit may not be seen in VAP as in other populations, aggressive treatment of hyperglycemia has both theoretical and clinical support for SICU patients.

A recent study of intensive insulin therapy in 1,200 medical ICU patients did not significantly reduce overall hospital mortality and actually increased mortality in patients with ICU stays less than 3 days.[144] However, the intensive insulin therapy group had reduced acquired renal failure, duration of mechanical ventilation, and length of ICU and hospital stay. Unfortunately, predicting the length of stay is difficult, and coupled with concerns about the risks of hypoglycemia and with increased resource implications, the benefit of intensive insulin therapy for specific hospital or MICU patients will require further evaluation.

Stress Bleeding Prophylaxis

Histamine-type 2 (H_2) antagonists and antacids have been identified as independent risk factors for ICU-acquired HAP. Sucralfate has been used for stress bleeding prophylaxis, as it does not increase intragastric acidity or gastric volume, but is less effective in preventing gastrointestinal bleeding.[1,2]

Numerous randomized trials, using different doses and various study populations, have provided controversial results on the benefits of specific stress bleeding prophylaxis agents in relation to the increased risk of VAP and bleeding.[25,145] One large randomized trial comparing antacids, H_2 blockers, and sucralfate reported no differences in rates of early onset VAP, but rates of late-onset VAP were lower in patients treated with sucralfate.[25] More recently, Bornstain et al. examined risk factors for early onset VAP (from 3 to 7 days) in 747 patients.[146] Several different variables were identified in the univariate analysis, but only sucralfate used in the first 48 h of ICU stay and unplanned extubation were predictors of VAP in the multivariate analysis, and antibiotics were protective. In an earlier multicenter study of VAP in patients with ARDS, sucralfate and duration of exposure to sucralfate were associated with an increased risk of VAP.[147]

A recent, large, double-blind, randomized trial comparing ranitidine to sucralfate demonstrated a trend toward lower rates of VAP with sucralfate, but clinically significant gastrointestinal bleeding was 4% higher in the sucralfate group.[145] Data indicate that H_2 blockers and protein pump inhibitors are associated with lower rates of gastrointestinal bleeding when compared to sucralfate, which may be doubly important, as transfusion also is a possible risk factor for VAP.

Concerns have been raised over reports of increased rates of *C. difficile* infections among persons receiving proton pump inhibitors.[148] A cohort study from a database of 1,187 inpatients at a Montreal teaching hospital showed that patients who had also received proton pump inhibitors other than antibiotics were at increased risk for *C. difficile* diarrhea.

Transfusion Risk

Multiple studies have identified exposure to allogeneic blood products as a risk factor for postoperative infection and postoperative pneumonia, and the length of time of blood storage as another factor modulating risk.[2] In one prospective randomized control trial, the use of leukocyte-depleted red blood cell transfusions resulted in a lower incidence of postoperative infections and, specifically, a reduced incidence of pneumonia in patients undergoing colorectal surgery.[149] Routine red blood cell transfusion should therefore be conducted with a restricted transfusion trigger policy.

Prevention Strategies at Discharge

The focus of prevention has been on ICU patients while in the ICU, but these patients are also at increased risk for relapse or re-infection during their rehabilitation. Therefore, efforts should be directed at risk reduction at discharge, such as routine vaccinations and patient education aimed at reducing lifestyle risks, such as smoking cessation, exercise, and weight control.

Conclusion

In spite of the progress in the diagnosis, prevention, and management of HAP/VAP, these diseases still have a significant effect on outcome. Immediate administration of adequate antimicrobials is now considered a critical element in the effort to improve survival in HAP/VAP. The choice of the initial antibiotic regimen should be patient-oriented and guided by directed staining of respiratory samples. Prior hospitalization, presence of comorbidities, and the pressure of index cases are helpful indicators in order to anticipate the presence of MRSA, *A. baumanii* and *P. aeruginosa.* Local surveillance data and prior exposure to specific antibiotics (which should be avoided in the initial regimen) help in the choice of the initial antibiotic treatment. Antimicrobial therapy should be adjusted 48–72 h after the onset of pneumonia, based on a combination of quantitative respiratory cultures and resolution assessment. The duration of treatment should also be individualized; however, courses longer than 1 week are rarely justified.

Investing in prevention can pay great dividends in improved quality of life and reduced morbidity and mortality.[1,2] In addition, prevention can have a huge impact in reducing length of hospital stay and healthcare costs during acute care. Spreading the seeds of prevention into chronic care and rehabilitation facilities also is vitally needed in the increasing diversity of our healthcare settings.

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30
Intra-abdominal Sepsis

Marc E. Brozovich and Peter W. Marcello

Postoperative infection has surpassed hemorrhage as the leading cause of mortality among surgical patients. Despite advances in diagnostic modalities, antibiotic therapy, and critical care medicine, mortality remains high. Intra-abdominal infection is defined as an inflammatory response of the peritoneum to microorganisms and their toxins, which results in purulent exudate in the abdominal cavity.[1] The transition from intra-abdominal infection to intra-abdominal sepsis occurs when the domain of the local inflammatory process breaches the abdominal cavity and the patient develops the systemic, physiologic ,and immunologic manifestations of inflammation. This chapter reviews the systemic response to inflammation, the causes of intra-abdominal sepsis, its diagnosis, and management.

Systemic Inflammatory Response Syndrome

For decades it has been acknowledged that patients with severe intra-abdominal infection may develop systemic manifestations of infection such as fever, diaphoresis, chills, and hemodynamic instability, and were given the diagnosis of "sepsis."[2] The transition from a local to a systemic event has been a subject of debate, but most surgeons can easily recognize a patient with severe sepsis. In the past two decades, a number of inflammatory mediators or cytokines have been identified and are known to play a role in the development of a "sepsis syndrome." The microorganisms and their products (endotoxins) stimulate the host's cellular defenses, activating a variety of inflammatory mediators (Table 30.1). Because of their activation, the resulting metabolic and physiologic response to severe intra-abdominal infection has been well documented (Table 30.2). However, it has also been recognized that activation of these cytokines may occur without infection. There is considerable evidence that a sepsis-like syndrome can emerge from severe noninfectious initiators of inflammation, such as severe burn injury, chemical aspiration, or severe pancreatitis.[2] In a consensus conference in 1992, the term "systemic inflammatory response syndrome" (SIRS) was created to describe this systemic response of the host due to the activation of the human inflammatory response.[2,3] "Sepsis" is defined as the SIRS that is secondary to an invasive infection. The degree of SIRS exhibited by an intra-abdominal source depends not only on the nature and degree of infection but also on the intensity of the host's immune response.

Classification of Peritonitis

Peritonitis may result from inflammation of the peritoneal cavity by any cause. Peritonitis is not synonymous with intra-abdominal infection, since other causes may result in peritoneal inflammation. A simplified classification of peritonitis is presented in Table 30.3. Primary peritonitis is typically a monomicrobial, aerobic infection that occurs in patients who have ascites secondary to cirrhosis, congestive heart failure, or from peritoneal dialysis. Patients with primary peritonitis usually respond to antibiotics and rarely develop a severe systemic inflammatory response. Patients with an infected peritoneal dialysis catheter may not respond to antibiotic therapy alone, necessitating catheter removal and temporary hemodialysis.

Secondary peritonitis remains the most common source of peritonitis and may result from a primary intra-abdominal

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Table 30.1. Mediators released after intra-abdominal infection.

Mediator	Response
Complement	Bacterial destruction Bacterial opsonization PMN chemotaxis
Histamine	PMN activation Increased vascular permeability
Interleukin 1 (IL-1)	Amplified inflammatory response Increased release of IL-2 PMN adherence
Interleukin 8 (IL-8)	PMN chemotaxis
Platelet activating factor (PAF)	Activates PMNs/macrophages PMN adherence Vasoconstriction
Tumor necrosis factor (TNF)	Amplifies inflammatory response Increased vascular permeability PMN adherence and phagocytosis
Protein C (activated (APC)) Drotrecogin alfa (iDAA)	Fibrinolysis

Anti-inflammatory inhibition of thrombosis, inhibits factors Va and VIIIa inhibits PMN adherence, inhibition of TNF, IL-1, Il-6.
PMN polymorphonuclear leukocyte.

Table 30.2. Physiologic and metabolic consequences of intra-abdominal sepsis.

Reduced systemic vascular resistance
Increased cardiac output
Lactic acidosis with reduced arteriovenous oxygen content difference
Exaggerated gluconeogenesis and increased insulin resistance
Hypermetabolism with increased urinary nitrogen excretion
Multiorgan dysfunction

Table 30.3. Classification of peritonitis.

Type	Examples
I. Primary peritonitis	
Diffuse bacterial infection without abdominal viscus injury peritonitis	Spontaneous peritonitis in children Spontaneous peritonitis in adults Peritonitis in patients on peritoneal dialysis Tuberculosis or other granulomatous peritonitis
II. Secondary peritonitis	
Localized or diffuse peritonitis from an abdominal visceral injury	Intraperitoneal inflammation Gastrointestinal perforation Intestinal ischemia Gynecologic Retroperitoneal inflammation Postoperative peritonitis Anastomotic leak Accidental perforation Post-traumatic peritonitis Blunt abdominal trauma Penetrating trauma
III. Tertiary peritonitis	
Abnormal host immune response producing a peritonitis-like syndrome	Peritonitis without evidence of pathogens Peritonitis with fungi Peritonitis with low-grade bacterial

infection (such as a perforated ulcer, diverticulitis, or pancreatitis) or a secondary injury from prior abdominal surgery or trauma. The infection is generally polymicrobial with a combination of aerobic and anaerobic bacteria. The inoculum of bacteria is dependent on the site of visceral injury. The number and types of bacteria increase progressively as the distal bowel is reached. The outcome of secondary peritonitis depends on the struggle of two main forces: the response of the peritoneal and systemic defenses versus the nature, volume, and duration of the abdominal contamination that initiated the inflammation.[1]

In tertiary peritonitis, the systemic inflammatory response persists despite the clearance within the abdomen of the usual invasive bacteria. This typically develops late in the postoperative phase and is associated with a sterile peritoneal cavity or peculiar microorganisms such as yeast or low virulence organisms. This late form of peritonitis is usually fatal and represents the current limitations in the management of intra-abdominal sepsis, where the infective insult has been treated but the systemic response persists without the possibility of recovery. Further development of immune modulators may alter the outcome of these patients.

Diagnosis

The classic systemic manifestations of sepsis have included fever, diaphoresis, tachycardia, hypotension, and oliguria. The degree of symptoms depends partly on the nature and duration of the inflammation and the status of the host's immune response. Patients with intra-abdominal infection usually exhibit abdominal tenderness and evidence of peritoneal inflammation (rigidity or rebound). In the elderly population, those patients on corticosteroids, or those who are immunocompromised, there may be a lack of physical findings. In the postsurgical patient, the development of an abscess following intra-abdominal surgery may be masked by incisional tenderness.

Patients with intra-abdominal sepsis will exhibit varying signs of fluid sequestration resulting in tachycardia, hypotension, and oliguria. Transfer to an ICU (intensive care unit) setting is usually required where invasive monitoring is routinely employed. Once monitoring lines are placed, further evidence to support the diagnosis of sepsis can be gained as reported in Table 30.2.

In the ICU patient who develops intra-abdominal sepsis – such as the cardiac surgical patient who develops intestinal ischemia or acalculous cholecystitis – a shift in the hemodynamic parameters from cardiogenic shock to septic shock may be the prevailing sign that an intra-abdominal infection is in development.

Plain radiographs of the abdomen may be helpful in the diagnosis of intra-abdominal infection if free air is demonstrated or an abnormal collection of gas or fluid is seen. Computed tomographic (CT) scanning, however, remains

the most reliable radiologic study for the evaluation of intra-abdominal sepsis, especially in the postsurgical patient who does not exhibit the obvious physical findings of peritonitis. In a study of 85 critically injured trauma patients, abdominal CT scans were obtained for sepsis of unknown origin.[4] Forty-nine patients had an intra-abdominal focus of infection identified on CT scan. The overall sensitivity was 97.5% with a specificity of 61.5%. In selected cases, other radiologic procedures may be of more value. In patients with intestinal leakage early after surgery, luminal contrast studies such as a Gastrografin enema or small bowel series may better elucidate the site and degree of leakage than CT scanning.

Management

The management of intra-abdominal sepsis includes both operative repair to reduce the initiator of the infection and support measures to combat the host's response to sepsis. Prior to operative repair and drainage of infection, the patient with severe sepsis will require transfer to the ICU for invasive monitoring and fluid resuscitation. The goals of supportive measures are (1) to combat hypovolemia and maintain adequate tissue perfusion, (2) to destroy bacteria not eliminated by drainage with antibiotics, (3) to provide support for failing organs, and (4) to maintain adequate nutrition.[1] Maintenance of adequate tissue perfusion and organ function are necessary while the patient awaits the recovery brought about by drainage and antibiotics.

Advances in microbiology and antimicrobial therapies have significantly impacted our understanding of the bacteria involved in intra-abdominal sepsis. Numerous experimental studies of seconfdary peritonitis have refocused our attention on the treatment of *Escherichia coli* (*E. coli*) and *Bacteroides fragilis (B. fragrilis)*, which are the primary target organisms in intra-abdominal infections.[5,6]

The use of antimicrobial therapy in intra-abdominal sepsis is an area of ongoing investigation. Patient selection, antibiotic regimen selection, and duration of treatment are all prominent areas of interest. In 2002, the Surgical Infection Society published guidelines on antibiotic selection and usage for intra-abdominal infections.[7,8] For low-risk patients, according to the authors, level 1 evidence suggested that no antibiotic regimen was superior to another. Single agents such as ampicillin/sulbactam, cefotetan, cefoxitin, ertapenem, imipenem/cilastatin, meropenem, piperacillin/tazobactam, or ticarcillin/clavulanic acid may be used. With equal efficacy, combination regimens may be used such as an antianaerobe (metronidazole or clindamycin) combined with an aminoglycoside, aztreonam, cefuroxime, ciprofloxacin, or third/fourth-generation cephalosporin. Recommendations also include the acceptable conversion to oral ciprofloxacin and metronidazole or amoxicillin/clavulanic acid when possible. For community-acquired infection, the routine coverage of enterococcus and candida is unnecessary. The guidelines also suggest that the routine culture of peritoneal contaminants is controversial and that altering antibiotics based on intraoperative culture results does not change outcomes in this group of patients.

The Surgical Infection Society made separate guidelines for higher risk patients.[7,8] For those patients with advanced age, multiple medical problems, elevated Acute Physiology And Chronic Health Evaluation II (APACHE II) scores, or poor nutritional status, the risk of treatment failure is higher. Additionally, there is a greater risk of nosocomial or multidrug-resistant infection. This prompts guidelines as to the use of extended-coverage antibiotic regimens. Single agent coverage is recommended, such as imipenem/cilastatin, meropenem, or piperacillin/tazobactam. Combination therapy may still include metronidazole or Flagyl in addition to an aminoglycoside, aztreonam, ciprofloxacin, or a third/fourth-generation cephalosporin. Regimens to cover candida or enterococcus may be warranted in this population.

The guidelines also address length of treatment.[7,8] The duration of antibiotics should not continue for >24 h postoperatively for removable sources of sepsis, such as nonperforated viscera. For most intra-abdominal infections, antibiotics should be stopped in 5–7 days when fever and leukocytosis subside. Beyond that time, continued signs of sepsis should initiate additional investigation and further source control; however, longer antibiotic therapy may be warranted.

Providing nutritional support to the patient recovering from intra-abdominal sepsis is the final and maybe the most critical supportive measure. Experimental evidence has suggested that the gut itself is a source of persistent bacterial translocation and infection in the ICU patient.[9] It is speculated that sepsis may increase the permeability of the gastrointestinal mucosa with resulting translocation of endotoxins and bacteria. Maintenance of gut substrates, such as glutamine, may prevent bacterial translocation. In the patient with persistent sepsis that cannot be isolated, the potential for bacterial translocation across the gut membrane must be considered.

The *sine qua non* in the management of intra-abdominal sepsis is the timely operative or nonoperative intervention that stops the delivery of bacteria and its adjuvants into the peritoneal cavity.[1] All other measures pale by comparison to the successful removal of the infective source and reduction of the infective inoculum. The goals of operative intervention include (1) controlling the source of infection, (2) evacuating bacterial inoculum (peritoneal washout), (3) treating abdominal compartment syndrome, and (4) preventing or treating recurrent or persistent infection.

Operative intervention may be successfully completed by percutaneous drainage in selected cases. CT- or ultrasound-guided drainage has been highly successful when the abscess is well localized and unilocular. In a series of 71 abscesses in 67 patients, percutaneous drainage was achieved in 86%.[10] Complications occurred in 11 patients (15%), and six deaths were attributed to persistent sepsis. Further studies have

verified the role of percutaneous drainage in the treatment of abdominal sepsis.

Unfortunately, despite our best efforts, the outcome of patients with severe intra-abdominal sepsis remains tenuous, mainly due to multisystem organ failure. Mortality approaches 30% for generalized peritonitis and may rise to 80% when multiorgan failure develops. Known prognostic factors include age, preexisting disease, severity of physiologic derangement at the time of diagnosis, and peritonitis occurring in the postoperative period.[11] Following appropriate management of intra-abdominal sepsis, persistent peritoneal contamination is an unusual cause of mortality. Studies have confirmed that mortality relates to the factors described above and not recurrent peritoneal infection. In a series of 105 consecutive patients with peritonitis, 77 patients had pulmonary failure or multiorgan failure, and death occurred in 38 patients (36%).[12] Recurrent intra-abdominal infection occurred in 15 patients; however, only one patient developed organ failure and two (13%) other patients died.

In the majority of cases, after the initial operation for intra-abdominal sepsis, where the primary source of infection has been removed, there is little role for reoperative surgery except where a new focus of infection has been identified. Blinded reoperation to exclude persistent infection should be discouraged. In rare cases, a staged approach to effectively treat the source of infection may be implemented. Indications for planned reoperation include hemodynamic instability that precludes definitive repair, excessive peritoneal edema that limits closure of the abdomen, massive abdominal wall loss, incomplete debridement of infected or necrotic tissue, concerns about the viability of remaining bowel, and excessive hemorrhage that requires packing.[1]

Special Considerations

Acalculous Cholecystitis

Occurring in 0.5–1.5% of long-term (>1 week) ICU patients,[13,14] acute acalculous cholecystitis is a "treacherous and potentially lethal disease."[15] The cause of this disease remains unclear and the diagnosis can be elusive. Whether it is a primary or secondary event, the cystic duct becomes edematous and occludes. The gallbladder wall becomes thickened and inflamed with enteric organisms. The critically ill patients may not manifest the classic right upper quadrant tenderness. Liver function tests and radionucleotide scanning are generally not helpful. Ultrasound or CT scan usually confirms the diagnosis when pericholecystic fluid, intramural gas, or wall thickening (less reliable) is identified. If the clinical suspicion is sufficiently high, then cholecystectomy (either conventional or laparoscopic) is recommended. Alternatively, in poor-risk candidates, a percutaneous cholecystostomy tube can be placed with minimal risk. In the critically ill patient in whom a source of sepsis cannot be identified, acalculous cholecystitis should be strongly considered.

Role of Laparoscopy in Intra-abdominal Sepsis

With the advent of minimally invasive surgery, the role of laparoscopy in the evaluation and management in intra-abdominal sepsis has slowly risen. Concerns about hemodynamic compromise during laparoscopy have limited its application in the critically injured patient. Utilizing a porcine shock and sepsis model, the hemodynamic effects of pneumoperitoneum during sepsis have been reported.[16,17] In comparison to laparotomy, animals exposed to laparoscopy had significant hypercarbia and diminished cardiac index. Further studies utilizing aggressive fluid resuscitation and other experimental agents demonstrated that these effects could in part be ameliorated.[17]

The possible adverse hemodynamics of laparoscopy may be offset by the potential preservation of immune function. Creation of a large midline laparotomy is associated with exacerbation of the systemic immune response to sepsis and may be blunted by the employment of laparoscopic techniques. In several animal studies of sepsis, laparoscopy lessened the inflammatory response to sepsis in comparison to laparotomy and allowed better clearance of a bacterial inoculum.[18,19]

Several clinical reports have demonstrated the feasibility and efficacy of diagnostic or therapeutic laparoscopy in the critically injured patient.[20,21] A series of 26 surgical ICU patients with possible abdominal sepsis underwent diagnostic laparoscopy (eight at the bedside).[21] Ten of 15 patients with suspected cholecystitis had the diagnosis confirmed laparoscopically; four underwent conventional cholecystectomy, four had laparoscopic cholecystectomy, and two had tube cholecystostomy. Of nine patients with suspect mesenteric ischemia, laparoscopy was positive in five. There were no adverse hemodynamic events in any of the cases. Further laboratory and clinical investigation will be necessary to clarify the role of laparoscopy in the patient with intra-abdominal sepsis.

Modulation of Immune Response

A series of prospective randomized control trials have been undertaken to modify the human inflammatory response in patients with intra-abdominal sepsis, most with disappointing results. The theoretical possibility of blocking the immune response to infection has not proved efficacious in most clinical studies. Monoclonal antibodies to neutralize endotoxin,[22] tumor necrosis factor,[23] and receptor antagonist to interleukin 1[24] and bradykinin[25] have failed in randomized clinical studies. In all reports, the investigational drug is given after sepsis has begun and, therefore, modulation of the systemic inflammatory response is difficult. Using animal models of sepsis, a variety of other therapies have undergone investigation including nitric oxide inhibitors,[26] endotoxin inhibitors,[27] granulocyte colony-stimulating factor (G-CSF),[28,29] and polysaccharide immunomodulators,[30] but they have not been tried in large-scale randomized clinical trials.

The current interest in anti-inflammatory and anticoagulant therapy in the treatment of sepsis has led to more recent evaluation of drotrecogin alfa (activated) (DAA), which is a recombinant human activated protein C (APC). In a prospective, randomized, double-blinded, phase 3 trial of 1,690 patients, the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group revealed a significantly lower all-cause mortality in septic patients treated with DAA (24.7%) compared to placebo (30.8%) at 28 days.[31] This represents a statistically significant 6.1% absolute risk reduction and a 19.4% relative risk reduction in death from all causes at 28 days.

A subgroup analysis further revealed a mortality benefit in surgical patients.[32] The clinical evaluation committee identified 474 patients (28%) from the initial PROWESS trial, who were classified as surgical patients. Of the surgical patients, 315 (66.5%) had intra-abdominal surgery. Absolute risk reduction from mortality at 28 days was 3.2% among all surgical patients and 9.1% for intra-abdominal surgical patients. Further studies of DAA have demonstrated 10.7% all-cause mortality benefit in high-risk surgical patients with an APACHE II) score ≥25, but no statistically significant survival benefit in low-risk surgical patients (APACHE II <25).[33] Based upon the results of these studies, the use of DAA should be considered in surgical patients with severe intra-abdominal sepsis, especially those with an APACHE II score ≥25.

With its anticoagulant properties, one of the potentially serious side effects of DAA is bleeding, especially if given in the early postoperative period. This concern for bleeding in surgical patients led to further subset analysis of the PROWESS study group. The risk of serious bleeding in surgical patients was 3.7% for the DAA group compared to 1.9% in the placebo group. The results were similar for the nonsurgical group (3.5% vs. 2.1%), suggesting that the use of DAA in the surgical group does not lead to a higher incidence of severe postoperative bleeding.[34] The incidence of fatal or life-threatening hemorrhage, including intracranial bleed, was similar for both surgical (1.8%) and nonsurgical (1.4%) patients treated with DAA, but was significantly higher than the placebo groups (0.2% surgical, 0.9% nonsurgical).[33] DAA, therefore, can be utilized in the surgical population. In our experience, postoperative intra-abdominal bleeding from DAA can be managed with transfusion and has not led to either the need for reoperation or significant morbidity.

Conclusions

Intra-abdominal sepsis remains one of the leading causes of mortality among surgical patients. The transformation from a local inflammatory response to a systemic response may result in devastating consequences to organ function and patient outcome. Secondary peritonitis remains the most common form of intra-abdominal sepsis from intestinal perforation, postsurgical leakage or injury, or as a consequence of trauma. Rapid diagnosis and intervention is paramount to patient survival. CT remains the leading radiologic investigation, which may also allow therapeutic drainage of an intra-abdominal infection. Management of peritoneal contamination requires rapid fluid resuscitation with invasive monitoring to maximize tissue perfusion, broad-spectrum antibiotics, and percutaneous or operative drainage of infection. Recent trials of DAA have demonstrated a modest advantage to the use of immune modulators. Hopefully, additional future trials with other therapies will allow repression of the systemic response to sepsis, which currently results in significant organ dysfunction and mortality.

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Evaluation of the Febrile Patient in the ICU

Alexis Tabah, François Philippart, and Jean Carlet

Introduction

Normal body temperature is generally considered to be 36.8°C (98.2°F), with 37.7°C (99.9°F) as an upper limit in healthy adults.[1] A wide range of biologic processes, some infectious and many noninfectious, can cause temperature elevation. Some of the noninfectious conditions can be as life-threatening as infectious ones.[2]

In the clinical setting, fever is defined as a pyrogen-mediated rise in body temperature above the normal range.[3] O'Grady et al. believe it to be reasonable to consider everyone with temperature ≥ 38.3°C (101°F) to be febrile and warrant special attention to determine if infection is present.[2]

Although noninfectious disorders are very common causes of fever in intensive care unit (ICU) patients, diagnosis for infection should never be missed, as delay in antimicrobial therapy and source control is potentially harmful. Delayed antimicrobial therapy has been proven to be a critical determinant of survival in human septic shock.[4] Moreover, inadequate empirical antimicrobial therapy is a predictor of in-hospital mortality,[5,6] with an increasing impact on survival in the most severely ill patients.[7]

The six most commonly identified types of infections in the ICU are pneumonia, blood-stream infection (including infective endocarditis), intravascular catheter-related sepsis, intra-abdominal infections, urosepsis, and surgical-wound infections.[8] Source control – defined as drainage of abscesses, debridement of devitalized infected tissue, and removal of colonized foreign bodies[9] – is always recommended when possible.

Consequently, evaluation and treatment of febrile patients for infection are urgent, but the clinician should be aware that if the diagnosis for infection is made too frequently, it can lead to overuse of antimicrobial agents and an increase in bacterial resistance and costs.[10]

Conversely, a substantial proportion of infected patients are not febrile; such patients may be euthermic or hypothermic. These patients include elderly patients, patients with open abdominal wounds or large burns, patients on extracorporeal membrane oxygenation or renal-replacement therapy, and patients taking anti-inflammatory or antipyretic drugs.

Because a patient who is hypothermic or euthermic may have a life-threatening infection, other symptoms and signs – such as otherwise unexplained hypotension, tachycardia, tachypnea, confusion, rigors, skin lesions, respiratory manifestations, oliguria, lactic acidosis, leukocytosis, leukopenia, or thrombocytopenia – might appropriately mandate a comprehensive search for infection, and aggressive, immediate empiric antibiotic therapy.[2] It is important to draw the adequate bacteriological samples before initiating any new antimicrobial therapy and withhold additional antibiotics when there is no microbiological confirmation of infection, because prolonged empiric therapy may be associated with adverse consequences.[11]

In this chapter, we will focus on the pathophysiology and mechanisms of fever, and ICU-related infectious and noninfectious causes of fever. We will not discuss hyperthermia, the other life-threatening cause of temperature elevation, where body temperature rises because of an inability to eliminate heat or overproduction by hypermetabolic response to drugs.

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Hyperthermia can be associated with external conditions, such as heat stroke,[12] drug-adverse effects, neuroleptic malignant syndrome, and anesthetic-related malignant hyperthermia.[13] It is also common in patients who chronically consume benzodiazepines, amphetamines, narcotics, or alcohol – substances that are commonly withdrawn without precautions in hospitalized patients.

Pathophysiology of Fever

Human body temperature is regulated around a physiologically determined set point. The elevation of body temperature may improve the efficiency of macrophages in killing bacteria and impair the replication of many microorganisms. Conversely, the elevation of body temperature may induce systemic changes such as tachycardia and increased energy and oxygen demands, which might be harmful especially to critically ill patients.

Fever is defined as the elevation of the body core temperature, which occurs as a response to pathogens or activation of the immune system.[14] In infections, the elevation of body temperature is usually between 1 and 4°C.[15] Most infections produce fevers at an average temperature of 38.5 and 39.5°C.[16]

Fever is the result of a three-phase integrated signaling between cells and soluble mediators. First, peripheral immune cells are activated by the inflammation created by pathogens or other sources, such as thromboembolic diseases, autoimmunity, and allergy. These cells produce a pyrogenic message, which is transmitted to the central nervous system (CNS). Second, specialized areas of the CNS integrate this first message and modulate the thermoregulatory mechanisms to cause fever. This acute-phase reaction is extensive, causing neuroendocrine, metabolic, behavioral, and other changes. Last, in order to limit the increase in core body temperature, an antipyretic process takes place as a negative-feedback process.

The Pyrogenic Signaling

The CNS controls thermoregulation through an integrated system composed of numerous areas from the hypothalamus and the limbic system through the lower brain stem and the reticular formation to the spinal cord and the sympathetic ganglia. The hypothalamus plays an important role in controlling body temperature, by coordinating thermal information from the whole body and organizing the efferent responses in terms of signaling to the heat-production areas and heat conservation regions.

Thermosensitive neurons, which are located in the preoptic anterior hypothalamic area (POA) and particularly the ventromedial preoptic nucleus, modulate the thermoregulatory mechanisms that affect the development of fever. The organum vasculosum laminae terminalis (OVLT), a circumventricular organ in the medial POA that lacks a blood-brain barrier, is a key site for the production of fever.[17]

Exogenous pyrogens as microbial products are able to trigger the inflammatory response to induce fever. Many endogenous pyrogens can induce the pyrogen response, such as immune complexes, particularly in the presence of complement proteins,[18,19] complement system activation of any origin,[19] or immune-cell activation in autoimmune diseases, coagulation abnormalities (thromboembolic disease), or allergic processes.

The pyrogenic message begins with the production of proinflammatory cytokines and prostaglandin E_2 by immune cells in the periphery; production possibly associated with the activation of the complement system and the formation of anaphylatoxins C3a and C5a. Pyrogenic cytokines include IL-1, IL-6, TNFα, and interferon γ.[20–23] Cytokines released in the blood stream by immune cells, have to pass through a region without a blood-brain barrier, such as the OVLT,[24,25] and act in the ventromedial preoptic nucleus[26] of the POA. Cytokines may also be actively transported through the blood-brain barrier,[27] or they may stimulate local production of secondary mediators by endothelial cells or by perivascular microglia and meningeal macrophages.

However, fever may precede cytokine appearance in the blood[28]; clinical fever frequently occurs without increase in cytokine levels in plasma,[29,30] and tumor necrosis factor (TNF) seems to have a role in maintaining fever more than inducing it.[31] Some neurons that have been identified as immunoreactive to IL-1β in the hypothalamus innervate key portions of the brain involved in elaborating the febrile response.[32]

Simultaneously, activated macrophages produce prostaglandin E_2 (PGE_2), which is known to cause a rise in the thermal set point. The PGE_2 receptors are widely distributed, notably on sensory neurons, including hepatic and abdominal vagal afferent ones.[14,33] However, PGE_2 detected in the brain is thought to be produced locally and not transported from the circulation.[17] C5a induces immediate release of PGE_2 and cytokines by Kupffer cells,[34] which in turn presumptively activate local vagal afferences to the POA.

Hypothalamic thermoregulation is mediated by neurotransmitters and catecholamines.[35] The peripheral pyrogenic message is probably conveyed very rapidly via vagal afferents[36–39] to the nucleus *tractus solitarius*, where it is passed to the A1/A2 noradrenergic cell groups, which transmit it to the anteroventral third ventricle region. Noradrenergic release in this site[40] stimulates the local release of prostaglandin E_2,[28,41] thus presumably triggering the febrile response. Cytokines also lead to prostaglandin E_2 production in the preoptic region through activation of phospholipase A_2; allowing liberation of arachidonic acid from the plasma membrane.

The Antipyretic Process

Numerous negative-feedback processes regulate this temperature-increase mechanism. Cytokines, such as IL-18 and IL-10, by inhibiting IL-1β production in the brain stem and hypothalamus, limit the elevation of the thermal set point.[42] Numerous endocrine pathways participate in limiting the increase in heat production, including cortisol, alpha-melanocyte-stimulating hormone (α-MSH),[3] and arginine vasopressin.[43] Lipocortin 1

has been shown to inhibit the pyrogenic action of IL-1 and interferon.[44] Nitric oxide (NO) could play an antipyretic role in the anteroventral preoptic region.[14,45] Noteworthy as a feedback-control mechanism, temperature elevation seems to be able to modulate production of pyrogenic cytokines.[46–50]

Thermal Measurements

The ideal system for measuring temperature should provide reliable, reproducible values safely and conveniently. Temperature has traditionally been measured orally, rectally, and centrally (by intravascular thermistor), as well as in the axilla.[2] The thermistor of a pulmonary artery catheter is considered to be the standard for measuring core temperature.

Axillary (or inguinal) measurements by measuring skin temperature have always failed to correlate with central temperature,[51–54] and should be discouraged.[2] Rectal temperature is accurate but creates risk for perforation or trauma to the rectum and represents a risk for pathogen transmission. Oral-temperature accuracy is inconsistent in different studies and might be influenced by thermometer placement, tachypnea, drinking, or the presence of invasive respiratory devices.[52,53,55] Tympanic temperature is considered a good index of core temperature but needs a direct-contact measurement on the tympanic membrane,[56] in contrast with an "ear-based" temperature, which is a convenient, noncontact way to measure body temperature that gives an estimate of core temperature extrapolated from an infrared reading of radiant energy from the tympanic membrane.[2,55] Although infrared thermometers have been shown to correlate with core temperature in a controlled setting, they can be inaccurate because of local inflammation or obstruction. Urinary temperature measured with a thermistor Foley catheter gives an accurate reading of core temperature,[53–55,57,58] in a continuous way, allowing for accurate and timely detection of body-temperature shifts. In patients who do not need a urinary catheter, esophageal temperature can be considered as an accurate option.[54]

Evaluating the Febrile Patient for Infection

Evaluating a new fever in a patient in the ICU should begin with a thorough history and physical examination. Important aspects of the history include identifying underlying comorbidities. History of alcohol abuse, organ transplantation, chronic obstructive pulmonary disease, chronic renal and hepatic disease, and use of a cytotoxic agent place patients at an increased risk for infection. A review of transfusions and current and recent medications is important. A history of recent antibiotic or chemotherapy administration can precipitate *Clostridium difficile* diarrhea or colitis. Steroids may mask or exacerbate infection. Previous antibiotic use contributes to the development of resistant nosocomial pathogens and culture-negative infections. The history should also include a review of recent surgical procedures, the class of the wound (clean, contaminated, dirty), and the date and conditions under which indwelling devices were inserted.

The patient's history helps clinicians focus on specific aspects of the physical examination. Central and peripheral access sites should be examined. If patients have a nasotracheal or nasogastric tube in place, the nose must be inspected for purulent discharge. If patients have undergone recent surgery, the physical examination should include inspection of the wound. Patients who underwent a recent cardiovascular procedure or those with an intravascular access device should be assessed for a new heart murmur or pericardial rub. Lung fields should be evaluated for signs of consolidation and collapse. An abdominal examination of a patient who has recently undergone a laparotomy may elicit pain secondary to an acute intra-abdominal process. The lower extremities should be examined for erythema or edema even in patients who are receiving deep venous thrombosis prophylaxis. The skin should be inspected for lesions suggestive of a drug-induced adverse event. Examination of the genitalia and rectum may demonstrate unsuspected epididymitis, prostatitis, prostatic abscess, perirectal abscess, or occult blood. Patients who have undergone neurosurgical procedures require assessment for changes in mental status and focal neurologic signs.

Laboratory studies and radiographic examinations are best directed by the results of the physical examination. A complete blood count with differential is a standard test, but it is nonspecific because both infectious and noninfectious etiologies can cause leukocytosis and a left shift with immature forms. Diagnostic evaluation also includes serum chemistries with liver-function tests, urinalysis, and blood and urine cultures. C-reactive protein is an acute-phase protein produced in the liver that increases during systemic inflammation and can be monitored to follow the progress of the disease.

Bacteremia has been identified in 7 to 10% of ICU patients and is associated with a threefold increase of ICU mortality.[59] Blood cultures are considered essential for evaluating fever in the ICU patient. It is recommended to obtain at least two blood cultures from separate sites by venipuncture 10 min apart. Cultures of abnormal fluid collections, sputum, cerebrospinal fluid, and stool should be sent if clinically indicated.[59–61]

Initial evaluation should also include a chest roentgenogram. Additional diagnostic methods are recommended according to the clinical suspicion. If the patient has clinical findings of sinusitis, a computerized tomography (CT) scan of the sinus should be performed. A CT scan has also been shown to be the first and best test for diagnosing intra-abdominal abscess in patients who have recently had abdominal surgery; bedside ultrasound is the diagnostic method of choice to help confirm a clinical suspicion of acalculous cholecystitis. A CT venous-duplex scan should be performed on patients with symptoms and signs of venous thromboembolism; and lumbar puncture has been recommended as a diagnostic tool in patients who have undergone a neurosurgical procedure and present with fever and change in mental status.

Patients Admitted for a Febrile Process

Febrile patients admitted to the ICU should be promptly evaluated, and if infection is entertained, appropriate bacteriologic samples should be obtained and the patient started on empiric antibiotic therapy. Community-acquired infections often present with clear signs and symptoms that will facilitate diagnosis. Medical history and clinical examination are the keys to prompt diagnosis leading to appropriate treatment.

The rest of the chapter will focus on the causes of hospital-acquired fever, providing the information needed to determine the etiology of fever in the ICU-treated patient in order to provide for rapid source control.

Fever in ICU Patients

Patients hospitalized in ICUs are more likely to acquire nosocomial infections than are other hospital patients. The frequency of infections at different anatomic sites and the risk of infection vary by the type of ICU. The frequency of specific pathogens varies by infection site.

This increased risk of nosocomial infection results from two major factors: (1) intrinsic risk factors related to the need for intensive care, such as severe underlying disease, multiple illnesses, malnutrition, extremes of age, and immunosuppression; and (2) invasive medical devices, such as endotracheal tubes for mechanical ventilation, intravascular catheters, and urinary tract catheters.

ICU-Related Sources of Infection

Catheters

Intravascular catheters (which may be central, peripheral, arterial, or long-term implanted) are the primary sources for secondary blood-stream infections in ICU patients.[60] When evaluating the patient for new fever, the clinician should focus on evaluating intravascular devices as possible sources of infection. Clinical findings are unreliable for establishing the diagnosis of intravascular device-related infection because of their poor specificity and sensitivity. When a catheter-related blood-stream infection is suspected, a common practice is to remove the catheter and to replace it at a new site. After catheter removal, the tip is aseptically cut and sent for semiquantitative culture. Findings from the semiquantitative roll-plate method are significant when there are greater than 15 colony-forming units (CFU)/ml. Patients with suspected intravenous-catheter-related infection should have two sets of blood cultures drawn, with at least one set drawn percutaneously. If the patient is critically ill or has signs of sepsis, broad-spectrum, empiric antibiotic therapy is recommended. If the patient is also immunosuppressed or at risk for opportunistic fungi infection, antifungal therapy should be added as well. Once the peripheral blood or pull-back blood-culture pathogen and antibiotic-sensitivity data are available, antibiotic therapy can be de-escalated and the duration of therapy determined. The best method to treat catheter-related infection is prevention. Adherence to practices that have been proven to reduce the risk of infection should be actively encouraged in every ICU. See Chap. 28 on catheter-related infections.

Ventilator-Associated Pneumonia

The diagnosis of ventilator-associated pneumonia (VAP) represents a difficult dilemma for the clinician. A presumptive clinical diagnosis of pneumonia is often made when a patient develops a new radiographic infiltrate associated with fever, leukocytosis, and purulent tracheal secretions. It might be helpful to use the clinical pulmonary infection score (CPIS).[62] Clinical scoring, however, is not specific and should trigger the collection of bacterial samples.[63] Such isolates can be obtained noninvasively by endotracheal aspiration or by following an invasive management strategy based on direct examination of bronchoscopic-protected specimen brush samples or bronchoalveolar lavage samples and their quantitative cultures.[64] The topic remains controversial and the invasive strategy was recently challenged.[65] American Thoracic Society guidelines recommend that a patient with suspected VAP should have a lower respiratory-tract sample sent for culture, and extrapulmonary infection should be excluded as part of the evaluation before administration of antibiotic therapy.[66] See Chap. 29 on pneumonia.

Urinary Tract Infection

Screening for catheter-associated urinary tract infection (CAUTI) is a frequent dilemma when searching for the cause of fever in the ICU patient. Urinary catheters can be colonized intraluminally when there is a failure of the closed drainage system or, more commonly, extraluminally by the colonic flora of the patient (when the catheter is inserted or later by microorganisms ascending the mucus film between the catheter and the urethra).[67] Of the patients with a urinary catheter, 9 to 15% acquire significant bacteriuria or CAUTI.[68,69] The most important and constant risk factor for CAUTI is the duration of catheterization.[68–71] The relationships among bacteriuria, CAUTI, and ICU outcome are not well known. In a recent study performed in 12 ICUs in France, 3.8% of the nosocomial blood-stream infections (BSIs) had a urinary source.[60]

In non-catheterized patients, UTI is defined as clinical symptoms associated with significant bacteriuria (>10^5 CFU/ml, usually with a single microorganism) associated with pyuria. In catheterized patients, we could use the same 10^5 CFU/ml cutoff to define bacteriuria or consider a 10^3 concentration sufficient because it is known that, once colonized,

the level of bacteria in the catheterized urinary tract rapidly increases in the absence of antimicrobial therapy.[67,72]

Most patients with CAUTI are asymptomatic and do not have associated fever. Pyuria should not be used as the sole criterion to obtain a urine culture in a patient with a catheter.[69] In patients with short-term indwelling urinary catheters, pyuria is less strongly correlated with CAUTI than in non-catheterized patients with UTI. The strongest association is with CAUTI caused by gram-negative bacilli; the association is far weaker for infections caused by gram-positive cocci or yeasts.

Urine dipstick results (presence of nitrites and leukocyte esterase) can be used to screen for a urinary source. They have a very good specificity (95–100%), but their sensitivity is poor (20–24%).[71,73] They remain a rapid-result tool to screen for UTI; keeping in mind that some frequent microorganisms (*Pseudomonas* sp., *Acinetobacter* sp., *Enterococcus* sp., and *Candida* sp.) do not produce nitrites and might give false-negative results.

Because CAUTI occurs frequently in catheterized patients and is not associated with an increased mortality,[74] if the clinician decides to treat all episodes of uncomplicated and asymptomatic bacteriuria, it would result in antibiotic selection pressure on the ward microbial ecology and the emergence of resistant microorganisms without affecting outcome or reducing the risk of urosepsis.[75,76] Moreover, the presence of a CAUTI does not exclude another source of infection. When possible, the removal of the catheter might be sufficient to treat an uncomplicated CAUTI. If complicated with sepsis or bacteremia, the CAUTI should be treated with antibiotics and the catheter changed after the antibiotics are administered. Fragile, immunodepressed patients and patients with cardiac or orthopedic devices and prostheses may benefit from antibiotic treatment of an uncomplicated bacteriuria.

Clostridium Difficile Colitis

Clostridium difficile is a gram-positive spore-forming anaerobic bacillus capable of producing two toxins, A and B, directed to the colonocyte. Colonization by *C. difficile* is facilitated by a disruption in the colonic flora, antibiotic use being its most important risk factor.[77]

Transmission of *C. difficile* is mostly hand-ported.[78] It is excreted in the feces of infected or asymptomatic carriers, and the spores can reside in the environment for months and are resistant to many commonly used cleaning agents.[79,80] None of the agents used in antiseptic handwash or hand-rub solutions are reliably sporicidal against *C. difficile*[81]; causing a risk of outbreaks in health-care facilities.[82,83]

Clinical features of *Clostridium difficile*-associated diarrhea (CDAD) usually include abdominal symptoms (pain, cramps, diarrhea, nausea, colitis, and pseudomembranous colitis), fever, and malaise.[84,85] Some cases localized in the cecum and the right colon present with leukocytosis, fever, and pain, but little or no diarrhea.

Some patients – mainly postoperative or immunosuppressed patients – develop fulminant colitis with life-threatening systemic toxicity, despite adequate medical treatment.[86,87] Those cases of toxic megacolon present with sepsis symptoms and sepsis-like shock but usually not diarrhea because of severe colonic dysmotility. Dallal et al. found that in impeding fulminant CDAD a rapid elevation of white blood cells to extraordinary levels (30,000 to 50,000) almost always preceded hemodynamic instability and the development of organ "dysfunction."[87]

The standard test for diagnosis of CDAD is detection of the toxin in stool samples on cell cultures (assays for cytotoxicity), requiring up to 4 days for results. Enzyme immunoassays to detect toxins in stool samples give almost immediate results, but are only 75% sensitive compared with cultures. If clinical suspicion is high, however, repeated tests and empirical treatment may be required.[88,89]

In severely ill patients, CT scan will show colitis with colonic wall thickening or massive colonic dilatation and ascites.[87] Intravenous or oral contrast is not necessary for diagnosis in those cases. Endoscopic examination of the colon can reveal characteristic yellowish pseudomembranes[90]; mucosal biopsies show characteristic histological changes of pseudomembranous colitis or simple colonic inflammation.[91] In those severely ill patients without diarrhea, stool samples might remain negative or take too long to be processed; in which case CT scan or endoscopy or both will provide timely diagnosis and the means to start antibiotic treatment and discuss emergency total colectomy.[86,92]

Sinusitis

Sinusitis occurs in 18 to 32% of endotracheally intubated patients. However, sinusitis alone is responsible for fever in only a minority of intubated patients. Nosocomial sinusitis is usually caused by gram-negative bacilli or is polymicrobial. Critically ill patients with suspected sinusitis should undergo CT scan of all paranasal sinuses. If the scan shows opacification, mucosal thickening, or air-fluid level, aspiration is performed. Infection is confirmed if a pathogen is identified along with neutrophils.

Intra-Abdominal Infections

Intra-abdominal infections are a leading cause of mortality among surgical patients. In the critically ill, intra-abdominal infections usually result from a ruptured hollow viscus or occur as a complication of a previous surgical intervention. The diagnosis of an intra-abdominal source of infection can be difficult. Fever and leukocytosis are classically associated with infection, but both have only moderate sensitivity and specificity. Abdominal pain and peritoneal signs are commonly associated with intra-abdominal infection; however, in the critically ill patient who is obtunded or sedated and on a ventilator, these symptoms may not be readily apparent. The procedures performed for the diagnosis of intra-abdominal infection include a radiograph of the abdomen, a CT scan, and an ultrasound. The presence of free air in the radiograph

of the abdomen usually represents a perforated viscus. Other findings that may lead to a diagnosis of intra-abdominal infection are calcified gallstones, renal stones, or appendicoliths. A CT scan of the abdomen and pelvis has excellent sensitivity and is the preferred test for the diagnosis of an intra-abdominal source of sepsis. In addition to being diagnostic, it may provide an opportunity for therapeutic intervention. Ultrasound may also be used as a diagnostic test. It is safe, does not require moving the patient out of the ICU, and may allow for therapeutic intervention as well. However, it is less sensitive than a CT scan.

Systemic Fungal Infections

The concern with *Candida* and fungal infections has been increasing in recent years, probably because of a higher number of immunodepressed, neutropenic, and high-risk patients being admitted to the ICUs.

The reported incidence of *Candida* infections varies, depending on the case mix and considered infection site. Invasive candidiasis is defined as isolation of *Candida* from blood or other sterile sites, excluding the urinary tract.[93] In a large multicenter study in ICUs in Europe, invasive candidiasis accounted for 17% of hospital-acquired infections.[94] Candidemias are reported to occur in 6.7 to 46 per 1,000 ICU admissions,[60,95–97] representing the fourth pathogen found in BSIs.[98,99]

Although crude mortality of invasive candidiasis is very high,[100] fungal infections occur in the most severely ill patients, and, after adjustment on severity and confounding factors, attributable mortality does not appear to be significantly elevated.[101,102]

Clinical presentation of invasive candidiasis is nonspecific and difficult to distinguish from other causes of sepsis and inflammation. A review of 15 years of autopsies in a German hospital showed that only 22% of the invasive fungal infections were suspected or documented before death.[103]

Known risk factors for invasive candidiasis include *Candida* colonization, antibiotic exposure, vascular access, neutropenia, steroids, surgical procedures, higher severity scores, or longer ICU stays.[104]

When an invasive candidiasis is suspected, it is not always possible to obtain deep-tissue samples. Furthermore, microbiological culture techniques are associated with a low sensitivity. Empirical antifungal therapy has been debated for patients with a suspected infection who have not responded to antibacterial therapy.

Because *Candida* is a normal inhabitant of the skin, gastrointestinal, genitourinary, and sometimes respiratory tracts,[104,107] fungal sampling of these sites will often be positive.

Pittet et al.'s "*Candida* colonization index" was designed on a small group of very high risk surgical patients of which 38% (11 of 29) developed severe *Candida* infections.[108] The *Candida* colonization index is defined as the ratio of sites screened positive by the number of distinct body sites tested for *Candida* colonization. In this subgroup of patients, heavy *Candida* colonization was highly predictive of the risk to develop *Candida* infection; and a colonization index higher than 0.5 was suggested as the threshold to start antifungal therapy. When adjusted for the density of growth, the corrected *Candida* colonization index reached higher specificity and positive predictive values. By using data from a large cohort of non-neutropenic ICU patients from the EPCAN surveillance study, taking into account other risk factors – such as total parenteral nutrition, surgery, and severe sepsis – Leon et al. propose a "*Candida* Score" as a better predictor of the risk for *Candida* infection.[109]

Such scores are very appealing, but in lower-risk patients true *Candida* infection remains uncommon.[110] If routinely used, such scores might lead to overuse of antifungal therapy as most of the patients will be colonized without developing infection. The use of amphotericin B was limited by its renal toxicity. New antifungal agents have fewer side effects and are usually well tolerated, but their use can be extremely costly,[97] and might favor the emergence of fluconazole-resistant strains.[111]

Noninfectious Causes of Fever

Circiumaru et al. detected the presence of fevers in 70% of ICU patients that were caused by infective and noninfective processes in approximately equal numbers.[112] In their study, Circiumaru et al. found the most common cause of noninfectious fever was "postoperative fever." Other common causes of noninfectious fever in ICU patients are myocardial infarction, venous thromboembolism, acute acalculous cholecystitis, mesenteric ischemia, blood-product transfusion, drug allergy, pulmonary atelectasis, vasculitis, acute pancreatitis, cerebral hemorrhage, and neoplasms.

Postoperative Fever

Benign postoperative fever is a frequent entity characterized by early onset, short duration, and good outcome.[112] In a retrospective analysis of cases of major gynecologic surgeries, Fanning et al. found that 39% of the patients were febrile in the days following the procedure, of which 92% did not develop an infectious process.[113] In another series, after knee and hip arthroplasty, Shaw and Chung found the presence of fever in 90% of the patients without any evidence of infection.[114] Similar findings were achieved in major oral and maxillofacial surgery.[115] In a study on vascular-surgery patients, Frank et al. found a maximum temperature greater than 38.5°C in one-fourth of the patients. There was an association between high temperature and increased IL-6 blood levels but not with leukocytosis. They concluded that a regulated elevation in body temperature occurs normally after surgery. The association among temperature elevation, extent and duration of surgery, and the cytokine response suggests that early postoperative fever is a manifestation of perioperative stress.[116]

Cardiac- and vascular-surgery patients often develop a febrile systemic response with a sepsis-like shock, often requiring vasopressors for several days, without any evidence of infection or surgical complication such as ischemic cholecystitis or colitis. The challenge in those patients will be to exclude any cause of infection and have the patience not to treat with antibiotics a noninfectious response to surgical stress.

Usually noninfectious postoperative fever begins on the first day following surgery and does not last more than 3 or 4 days. If the duration of fever is more than 3 or 4 days or is accompanied by other signs or symptoms of infection, deep surgical-site infections, wound infections, or other causes of infectious or noninfectious fever should then be ruled out.

Myocardial Infarction

Fever in acute myocardial infarction (AMI) is a common finding[117] and is associated with the severity and size of the infarction.[118,119] Most often it is a low-grade fever, which begins to rise 4–8 h after the onset of myocardial infarction, peaks in the first 24 h, and usually resolves by the fourth or fifth day. Increased body temperature in AMI is a predictor of in-hospital cardiac events, and patients with higher temperature have a worse clinical outcome.[118]

A significant number of critically ill patients with AMI do not present with the classic symptoms of chest pain or pressure. In fact, any change in the hemodynamic status in an at-risk patient – even in the absence of chest pain or electrocardiogram changes – should alert the clinician to the possibility of AMI. Troponin is the preferred biomarker for diagnosis, but it can also be elevated in myocarditis, pericarditis, heart failure, and pulmonary embolism.[120] Cardiac troponin may also rise in septic shock, most probably a result of direct cell injury, and is correlated with cardiac dysfunction in the absence of myocardial infarction.[121–123]

Venous Thromboembolism

Low-grade fever appears to be present in 18 to 24% of the cases of acute pulmonary embolism,[124,125] and in only 9% of patients presenting with deep vein thrombosis. Therefore, the presence or absence of fever does not appear to be a sensitive or specific factor for the diagnosis of venous thromboembolism.[126]

Acute Acalculous Cholecystitis

Acute acalculous cholecystitis has been reported to occur in critically ill patients, particularly in those suffering from major trauma, hemorrhagic shock, sepsis, and multiple organ failure, as well as after cardiovascular surgery.[127–129] Identified risk factors are a higher Acute Physiology and Chronic Health Evaluation (APACHE) II score, the severity of hemorrhagic shock, and massive transfusion.[129] Additional risk factors are total parenteral nutrition, use of opiates, and gallbladder dysmotility, which are thought to increase the formation of biliary sludge and thus the risk for cholecystitis.[130]

Unexplained fever, rise in white blood cell (WBC) count, and hemodynamic instability are all nonspecific signs of acalculous cholecystitis. Usual clinical features of cholecystitis might be absent, but the presence of right upper-quadrant abdominal pain, tenderness and guarding, palpable mass, abdominal distention, ileus or vomiting, or progressive jaundice should alert the clinician.[131] No single clinical finding or laboratory test carries sufficient weight to establish or exclude cholecystitis without further testing.[132]

Imaging studies for acalculous cholecystitis are ultrasound, CT scan, and hepatobiliary cholescintigraphy.[127] Ultrasound will show distention of the gallbladder, wall thickness ≥4 mm, intraluminal biliary sludge, pericholecystic fluid collection, and intramural gas.[131]

Management decisions should take into account the underlying comorbid conditions. For many patients, percutaneous cholecystostomy may be the best management option.

Mesenteric Ischemia

Mesenteric ischemia is a relatively common disorder in the elderly. If not treated promptly, it still carries a high morbidity and mortality rate. A high degree of clinical suspicion is of paramount importance in diagnosis because there is no specific laboratory test available and physical-examination findings may be subtle. Once the diagnosis is made, management relies on early resuscitation, identification, and treatment of the predisposing conditions, along with careful planning of the therapeutic invasive interventions, which altogether may help reduce the mortality and morbidity associated with this condition.

Mechanical ventilation with positive end-expiratory pressure (PEEP) and vascular surgery, especially aortic repairs, put patients at risk for mesenteric ischemia.[133–136] Moreover, patients undergoing cardiovascular surgery often suffer from micro- and macrovascular disorders with a higher risk of developing nonocclusive mesenteric ischemia if they develop hypotension.[137–139]

Mesenteric ischemia can manifest itself in a variety of ways, depending on etiology and degree of intestinal ischemia. Patients present during the ischemic episode with abdominal pain, but signs and symptoms may be subtle and nonspecific. Unexplained fever, rise in WBC count, sepsis-like symptoms, hemodynamic instability, and organ dysfunction are all nonspecific signs of mesenteric ischemia.[131]

Conventional angiography is considered the gold standard, but ultrasound, CT scan, and magnetic resonance angiography are gaining popularity when investigating for intestinal ischemia.

Effective management and treatment of mesenteric ischemia relies on prompt and accurate diagnosis before bowel infarction develops.

Blood Products

There is a great deal of literature addressing the indication for blood products in the critically ill patient.[140–142] Between 44 and 85% of ICU patients receive blood products.[143–145] When

fever develops after transfusion, the patient should be carefully evaluated for microorganism transmission, hemolytic reactions, and transfusion-related acute lung injury (TRALI). Febrile nonhemolytic transfusion reactions are the most frequent complications associated with transfusion of blood products.[146,147] Depending on local regulations, if a patient develops fever after transfusion, mandatory procedures are available to screen the patient and transfused bags.[148–150]

Actual risks for human immunodeficiency virus (HIV) or hepatitis transmission are very low, but other viruses, such as parvovirus B19, have a higher risk for transmission. Bacterial contamination or packed red cells is rare – with an estimated risk of 1 in 500,000 units – and highly dependent on the length and quality of storage.[151,152] The risk of platelet-related sepsis is estimated to be 1 in 12,000.[153]

Fatal acute ABO incompatibility hemolytic reactions are becoming very rare as a result of increased vigilance regarding transfusion procedures.[150,154] In addition, approximately 1 in 1,000 patients has clinical manifestations of a delayed reaction to transfusion[155] and 1 in 260,000 patients has an overt hemolytic reaction[156] because he or she has antibodies to minor red-cell antigens that were not detected by a routine antibody assay before transfusion.

TRALI is an uncommon complication of blood-products transfusion that is characterized by abrupt onset of dyspnea, hypoxemia, hypotension, bilateral pulmonary edema, and fever within the first 6 h of a transfusion. TRALI has been associated with the presence of antibodies in donor plasma-containing blood components, including red blood cells, platelets, fresh frozen plasma, cryoprecipitate, intravenous gamma globulin, stem cells, and granulocytes, that are directed against recipient white-cell antigen. Unlike the allergic or anaphylactic reactions sometimes seen in transfusion recipients, the antibodies implicated in TRALI come from the blood donor, not the recipient.

Drug Allergy

Fever is one possible manifestation of drug allergy, but it is often not considered in the differential diagnosis.[157] Clinical manifestations of hypersensitivity are heterogeneous and sometimes limited to fever.[158] The clinician should search for skin rashes, which are the most common drug-induced reactions. They usually appear between 4 and 14 days after starting a new drug. The eruption consists of erythematous macules or papules, often symmetric. They begin on the trunk and upper extremities and become confluent. The eruption is often polymorphic, morbilliform or urticarial on the limbs, confluent on the thorax, or purpuric on the feet. Drugs frequently implicated in drug reactions are beta-lactam antibiotics, sulfonamides, allopurinol, and antiepileptic agents.[158,159]

A drug rash associated with hypereosinophilia, severe eruption, and visceral involvement is referred to as drug rash with eosinophilia and systemic symptoms (DRESS) syndrome.[160] DRESS is most commonly caused by anticonvulsants: phenobarbital, phenytoin, and carbamazepine. In contrast to other drug reactions, DRESS may develop as late as 4–6 weeks after the offending medication has been introduced. The clinical manifestations include a diffuse maculopapular rash, exfoliative dermatitis, facial edema, lymphadenopathy, fever, multivisceral involvement, eosinophilia, and lymphocytosis.

More severe drug-induced disease presentations are Stevens-Johnson syndrome and toxic epidermal necrolysis, characterized by high fever, severe erosions of mucous membranes, and widespread skin blisters accompanied by mild hepatitis and intestinal and pulmonary manifestations.

The clinician should search for eosinophilia, which is present in only 20–40% of cases,[158] and serum-specific immunoglobulin E (IgE), both of which are helpful as an aid for the diagnosis.[161]

Clinical history will be the most helpful to make the right diagnosis, which is often a difficult clinical dilemma where the choice is whether the worsening of the patient's condition is caused by persistent infection or by its treatment. Withdrawal of the causative drug is the most appropriate initial approach.

Conclusions

The main objective in the management of a febrile patient is to identify the cause and eliminate it. In about half of the cases, fever is secondary to a developing infection, in which case, bacteriologic samples are obtained and empiric antimicrobial therapy initiated. The antimicrobial treatment must be continuously assessed, even when treatment appears successful. Medications should be reevaluated when the laboratory results become available.

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32
Antimicrobial Use in Surgical Intensive Care

Robert A. Duncan

Intensive care has evolved over its 50-year history to yield previously unimaginable recovery from major trauma, multiorgan system failure, and extensive surgery, including organ transplantation. Antimicrobial therapy plays an essential role in combating invasive infections in the intensive care population that are often the ultimate causes of death. However, a parallel evolution of antimicrobial compensation has occurred, engendering resistance and virulence mechanisms to circumvent each new antimicrobial agent. The surgical intensive care unit provides the ultimate microcosm of antimicrobial resistance selection, combining complex and severe underlying illness with invasive devices, bypassed defenses, compromised tissues, and proximity to other high-risk patients, all in one intimate environment. New resistance mechanisms may be introduced from referring institutions or can emerge in response to treatments, and then may spread to others within or outside the ICU. Multidrug-resistant organisms have become a dominant issue in modern health care; a strategic response is essential to short- and long-term success.

The best defense against infection in the surgical ICU is prevention, encompassing meticulous surgical technique that preserves tissue integrity, careful infection control, and care process improvement, accompanied by aggressive and timely diagnostics and judicious use of antimicrobial agents. This chapter will address the latter two strategies, providing general guidance and reference to more in-depth discussions.

General Principles

Infection and Diagnosis

Fever is a common occurrence in the postoperative patient.[1] This can reflect developing infection but may also stem from a myriad of noninfectious sources, most frequently when arising within 48 h of surgery. Differentiating these causes is essential to optimal care and serves to minimize excessive antibiotic use and its after effects. It must also be acknowledged that fever is a natural defense mechanism and is itself only rarely harmful.[2]

In addition to the common causes of postoperative infection – surgical site infection, central venous catheter infection, ventilator-associated pneumonia, urinary tract infection, *Clostridium difficile*-associated disease, and occasional cholecystitis, sinusitis, meningitis, or epidural catheter infection – fever may be associated with atelectasis, allergic drug reactions (frequently to beta-lactam antibiotics or phenytoin), infusion of blood products, pancreatitis, alcohol withdrawal, malignant hyperthermia, or neuroleptic malignant syndrome.[3] Interaction of linezolid with monoamine oxidase inhibitors, serotonin re-uptake inhibitors (SSRIs), tramadol, and meperidine can cause the serotonin syndrome, a potentially life-threatening combination of fever, agitation, and autonomic instability.[4,5]

Similarly, abnormal chest X-rays may reflect pneumonia or can result from numerous noninfectious causes, such as pleural

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effusions, congestive heart failure, aspiration pneumonitis, pulmonary hemorrhage, or acute respiratory distress syndrome (ARDS) (see Chap. 22). A diagnosis of pneumonia is the single largest reason for antibiotic use in the ICU, yet clinical diagnosis is only correct about half the time, driving unnecessary antibiotic consumption while risking adverse effects. Careful consideration of the diagnosis is thus imperative.

An early and aggressive diagnostic search for sources of infection helps to optimize anti-infective therapy.[3,6] Knowing the site of infection is one of the most important determinants of drug choice and administration. Identifying a specific etiologic agent then allows honing initial empiric therapy to the most effective, narrowest spectrum agent with the fewest side effects. The alternative strategy of rapidly initiating an aggressive, broad-spectrum regimen that "covers everything" often results in ballooning empiricism, treating symptoms without addressing the source and facilitating the development of resistance.

Cultures should be obtained immediately when suspecting sepsis or significant infection, before initiating antibiotics. These should include peripheral blood cultures; a blood culture from an intravascular catheter in place >48 h or suspected of contamination (total not to exceed three blood cultures in 24 h); urine with urinalysis; tracheal secretions if pneumonia is suspected (quantitative bronchoalveolar lavage is preferable); deep wound cultures; percutaneous drainage cultures if a collection is found; and stool detection of *Clostridium difficile* if there is diarrhea. Preexisting drainage catheters are often contaminated; cultures from these sources should be approached with great caution.

Diagnostic imaging should be obtained expeditiously. A computed tomography (CT) scan often helps to differentiate pneumonia from pleural effusion or scar, and may identify infarctions, occult abscesses, anastomotic leaks, fistulas, or fluid collections. Some of these may be amenable to percutaneous drainage and culture. Appropriate accompanying chemistry tests should not be omitted, as they may provide (or exclude) a diagnosis more rapidly than cultures.

Several guidelines exist for the diagnosis and treatment of common ICU-associated infections, including new fever,[3] catheter-related bloodstream infections,[7] urinary tract infection (guidelines to be published in *Clinical Infectious Diseases*), sepsis,[6] and ventilator-associated pneumonia[8] (see Chaps. 27, 28, 29, and 31).

Antibiotics and Resistance

Bacteria have been present on Earth for 3.5 billion years; antibiotics have been available for less than 70 years. Given their enormous biomass and rapid dividing time, bacteria have evolved nearly unlimited mechanisms of resistance against the antimicrobial armamentarium.[9,10] These include changes that exclude an antimicrobial agent from the cell (e.g., cell wall thickening in methicillin-resistant *Staphylococcus aureus* [MRSA] or porin changes in carbapenem-resistant *Pseudomonas aeruginosa*), alter antimicrobial targets (e.g., changes in cell surface penicillin binding protein sites or in ribosomal protein synthesis enzymes), attack the antimicrobial agent itself (e.g., beta-lactamases that inactivate penicillins and cephalosporins), or actively push an agent out of the cell via efflux pumps. These are only a few of the numerous evasion strategies available to microorganisms. The current crisis of resistance is a result of unfettered use of antibiotics in agriculture and medicine; controlling the rise in resistance will require increased attention to appropriate use of these agents.[11]

Table 32.1. Common multidrug-resistant organisms.

Methicillin-resistant *Staphylococcus aureus* (MRSA)
Vancomycin-resistant Enterococci (VRE)
Linezolid-resistant Enterococci
Penicillin-resistant *Streptococcus pneumoniae*
Pseudomonas aeruginosa
Fluoroquinolone-resistant *Escherichia coli*
Extended Spectrum Beta-Lactamase (ESBL)-Producing Enterobacteriaceae
Acinetobacter baumannii
Stenotrophomonas (Xanthomonas) maltophilia
Clostridium difficile
Candida species

Table 32.1 lists some of the common multidrug-resistant organisms encountered in the modern ICU. Prevalence of these problem organisms has been rising steadily, providing growing challenges.[12–14]

Antimicrobial resistance can come from three sources – emergence, influx, and spread. Resistance to an agent emerges under the influence of numerous selective factors, none more influential than the antimicrobial agent itself. Once resistance has developed, it may then spread to other bacteria within the host (e.g., transfer of an extended-spectrum beta-lactamase [ESBL] from *Klebsiella pneumoniae* to neighboring *Escherichia coli* in the gut) or may be transported to other patients, usually via the hands of healthcare workers. Similarly, there may be an influx of undetected antimicrobial-resistant organisms into the ICU via newly admitted or transferred patients or colonized staff members. The ICU thus represents a microcosm of the evolutionary pressures favoring resistance: severe underlying illness, numerous invasive procedures, proximity to other compromised patients under emergent conditions, and frequent use of antibiotics and other defense-altering drugs.

Several drugs are worth noting for their abilities to engender or select for resistance. Second- and third-generation cephalosporins, because of extensive gram-negative and antistreptococcal activity, favor growth of vancomycin-resistant enterococci (VRE). VRE has also been associated with use of both oral and intravenous vancomycin. Numerous agents, most notably clindamycin, fluoroquinolones, and possibly proton pump inhibitors, favor growth of *C. difficile*. Fluoroquinolones (e.g., ciprofloxacin and levofloxacin) and proton pump inhibitors have also been implicated in nosocomial acquisition of MRSA.[15] Resistance to carbapenems or fluoroquinolones may rapidly emerge during therapy of *Pseudomonas* infections.[16,17]

Researchers in New York documented a cascade of events that illustrates the roles of emergence, influx, spread, and the complexity of antimicrobial resistance. In response to an outbreak of ESBL-producing *K. pneumoniae* infections, they curtailed use of ceftazidime, successfully reducing these infections. However, imipenem use blossomed, leading to outbreaks of imipenem-resistant *P. aeruginosa* and *Acinetobacter baumannii* infection. This same clone of *A. baumannii*, resistant to almost all drugs available, was later found in each of the 15 hospitals throughout Brooklyn, apparently transferred between hospitals along with patient and/or medical staff traffic.[18–20]

Impact of Hospital-Acquired Infections and Antimicrobial Resistance

Infections acquired in the hospital are among the most significant safety hazards for patients. In a study of medical injuries to patients in 7.45 million hospital discharges, Zhan et al.[21] found an excess attributable length of stay of 10.89 days, added cost of $57,727, and excess mortality of 21.96% for patients experiencing postoperative sepsis. Postoperative complications constituted the most serious injuries identified in the study. In a study at Duke, patients with surgical site infections were five times more likely to be readmitted, 60% more likely to spend time in the ICU, spent twice as long in the hospital after surgery, and had twice the mortality rate of uninfected patients.[22] In an analysis of this study and others, surgical site infection added an average of $15,646 to the cost of care.[22,23]

Similarly, antimicrobial resistance typically compounds the already significant clinical and economic impact of infection, causing increases in morbidity and mortality, length of stay, and cost.[24] Costs of antimicrobial-resistant infections are often $6,000 to $30,000 greater than with an equivalent infection caused by a susceptible strain.[24] In another systematic review, MRSA infection had an attributable cost of $35,367.[23]

Antimicrobial Therapy

Pharmacodynamics

The effectiveness of certain antimicrobial drugs may depend on the manner of dosing. Fluoroquinolones and the aminoglycosides are concentration dependent and thus are most effective when they achieve high concentrations, surpassing the minimum inhibitory concentration (MIC) of a target organism manyfold. Once-daily dosing of aminoglycosides achieves both high concentrations of drug and very low trough levels, reducing potential toxicity.[25] In contrast, penicillins, cephalosporins, macrolides (such as azithromycin), and clindamycin are most effective when they achieve levels above the MIC of the infecting organism for a prolonged period of time. Using shorter administration intervals (or in some circumstances, continuous infusions) may serve to prolong the "time above MIC" and enhance clinical efficacy.

Monitoring Drug Levels

Drug level testing is most commonly used with aminoglycosides because of a relatively narrow toxic-therapeutic window. A trough level is usually adequate in once-daily administration, whereas both the peak and trough should be monitored for synergistic treatment, as in endocarditis. Monitoring vancomycin levels has gained momentum, largely in response to slowly rising vancomycin MICs in staphylococci and the concern for underdosing. Because of very predictable kinetics, efficient monitoring of vancomycin therapy can be accomplished with periodic (e.g., once or twice weekly) trough levels, rather than daily testing.

Dosing Considerations

Most antimicrobial agents are cleared via renal or hepatic metabolism. In patients with compromised renal function, dosing of several antibiotics must be adjusted to avoid accumulation and toxicity. Vancomycin and the aminoglycosides are commonly recognized as requiring dose-adjustment, but the carbapenems and penicillins can also accumulate, causing agitation or lower seizure thresholds. Appropriate dose adjustments are available from several resources, including the *Sanford Guide to Antimicrobial Therapy*[26] (updated yearly) and on the Internet (http://www.hopkins-abxguide.org). Dose adjustment is best initiated after administering a normal first dose. This achieves a rapidly effective drug concentration but avoids subsequent toxic accumulation.

Patients with cirrhosis or severe liver disease are at increased risk for toxicity from certain antimicrobial agents. Chloramphenicol is more likely to cause bone marrow suppression in patients with compromised liver function; dose reduction can avoid this. Other agents – including azithromycin, clarithromycin, and clindamycin – may require reduced doses. Rifampin accumulates in hepatic failure (due to a prolonged half-life), potentially augmenting its already notorious effect on hepatic metabolism of numerous other drugs (most notably anticoagulants) via cytochrome P450.

With the ongoing epidemic of obesity, treatment with "average" doses of antibiotics may be inadequate. Although few data exist to guide dosing in the obese patient, the principles of providing peak tissue and serum levels dictate that many agents should be used in higher doses in this setting.[27,28] Many clinicians increase cephalosporin doses from 1 to 2 grams for patients weighing more than 80 kg; similarly, vancomycin may be given at 15 mg/kg per dose.

Parenteral to Oral Conversion

Many antimicrobial agents achieve excellent oral absorption and are amenable to conversion from intravenous to oral forms, once other oral medications are tolerated.[11,29,30]

This can reduce the need for intravenous access and its resultant complications, shorten hospitalization, and reduce costs. Fluoroquinolones, metronidazole, linezolid, clindamycin, trimethoprim-sulfamethoxazole, fluconazole, voriconazole, valacyclovir, and valganciclovir all achieve excellent absorption. It should be noted that orally administered vancomycin is not systemically absorbed and should be used only for treatment of *C. difficile* infection.

Allergy and Other Adverse Effects

Penicillin allergy is perhaps the most frequently encountered, yet least well understood, allergy in health care. Many patients who report histories of allergy to penicillins do not react when re-challenged. In the past, crossover allergy to cephalosporins was estimated to occur in 7–14% of patients with penicillin allergy, yet in a recent review Pichichero estimates that this occurs only rarely, in about 0.5% of those receiving first-generation cephalosporins and almost never with the upper generation cephalosporins.[31,32] Therefore, cephalosporins can be safely used in most patients reporting penicillin allergy, unless there is history of an immunoglobulin E-mediated reaction, such as anaphylaxis or angioedema. Cross-reactivity between penicillins and carbapenems is controversial and of uncertain significance in clinical practice.

Although true allergy to vancomycin can occur, the "red man syndrome" is more frequently encountered. This is a nonallergic, infusion-related release of histamine, causing transient flushing of the face, neck, and shoulders, sometimes accompanied by itching and transient hypotension. It can usually be avoided by slowing the rate of administration.

Linezolid is used for treatment of MRSA, VRE, and other multidrug-resistant gram-positive infections. In addition to the serotonin-related effects noted previously, prolonged linezolid use has been associated with depletion of platelets and, less commonly, with marrow suppression of white and red blood cells. These effects appear to resolve quickly upon discontinuation.

Aminoglycosides (e.g., gentamicin, tobramycin, and amikacin) are associated with often irreversible toxicity to the kidney, ear, and vestibular system, and can also cause neuromuscular blockade. Once-daily administration, while maintaining low trough levels, tends to maximize effect but minimize toxicity.[25]

Allergy to sulfa drugs, such as trimethoprim-sulfamethoxazole, may commonly cause rash or, more rarely, aseptic meningitis or myelosuppression. This agent can also interfere with laboratory assays for creatinine, falsely raising concern for declining renal function.

Prolonged exposure to fluoroquinolones has been associated with Achilles tendonitis and rupture, especially in patients with renal insufficiency or transplantation. Fluoroquinolones may also facilitate acquisition of MRSA,[15] presumably by depleting susceptible normal skin flora.

Therapeutic Interactions

Interaction between drugs is a complex topic and will not be dealt with in detail here. The *Sanford Guide to Antimicrobial Therapy* provides comprehensive tables of interactions.[26] Some of the more notable ones include combined use of aminoglycosides with other nephrotoxic agents; altered cytochrome P450 metabolism induced by rifampin; interaction between azoles (e.g., fluconazole or voriconazole) with tacrolimus, cyclosporine, anticoagulants, and phenytoin; and decreased oral absorption of fluoroquinolones by divalent cations, including vitamins with iron, antacids, calcium, and sucralfate.

Special Patient Populations

Expert consultation should be considered for certain patients, including children, women who are pregnant, and patients with cystic fibrosis, human immunodeficiency virus infection, or organ transplantation. Indeed, optimal critical care may require routine incorporation of a pharmacist into the team. Similarly, expert antimicrobial stewardship is vital to optimizing use of these agents, delaying development of resistance, and providing the most cost-effective care.[11,29]

Pregnant patients have altered volume of distribution and clearance of some drugs (notably ampicillin), as well as concerns about potential effects on the fetus. Metronidazole is a teratogen in animals and should be avoided in pregnancy. Tetracyclines may deposit in bone and tooth enamel, whereas fluoroquinolones can interact with growth plates in bone and should be used only with caution. Penicillins and cephalosporins are generally considered to be safe in pregnancy.

Improving the Quality of Critical Care

Writing in *The New Yorker*, Gawande has argued eloquently that modern intensive care medicine is now so complex that a systems approach is necessary to providing optimal care and eliminating preventable errors.[33] He cites a collaborative project among most of the ICUs in Michigan to reduce catheter-related bloodstream infections (CRBSI).[34] Participants instituted protocols incorporating evidence-based best practices for central venous catheter insertion and care, including daily checklists. Within a few months, CRBSI had been reduced by two-thirds statewide.[34] Similar "bundled" care protocols, applied to ventilator care, urinary catheters, and sepsis offer promise and await further validation.

Prevention

Surgical Prophylaxis

William Halsted, operating in the pre-antibiotic era of the late nineteenth century, identified the principles of asepsis and

hemostasis as elements of surgical technique that would minimize infection. He advocated use of sharp dissection and fine sutures, gentle handling of tissues, and complete wound closure.[35] More than a century later, perioperative antimicrobial prophylaxis is an adjunctive measure to these mainstays of infection prevention. Although some of the details of prophylaxis for elective surgery are altered in previously hospitalized ICU patients, the principles remain. The purpose of prophylaxis is to prevent intrinsic and extrinsic bacterial contamination of the surgical site that occurs during an operation from developing into a postoperative infection. The ideal prophylactic agent would be active against the major potential infecting agents; not induce resistance; effectively penetrate relevant tissues; have a long enough half-life to maintain effective levels throughout the procedure (re-dosing as necessary); have low toxicity and potential for allergy; have few interactions with anesthetic agents and muscle relaxants; and be cost-effective.[36–38] It should be administered within an hour before the procedure (within 2 h for vancomycin and fluoroquinolones).[39] Postoperative doses provide no added benefit. In a review of 28 studies there was no clear advantage to either multiple- or single-dose prophylaxis (odds ratio 1.06, 95% CI, 0.89–1.25).[40] Furthermore, unnecessary postoperative doses may cause harm, including allergy or anaphylaxis, prolonged bleeding times, *C. difficile* colitis, and selection of resistant organisms. This is particularly important in surgical ICU patients, who may require prolonged care and risk progressive acquisition of multidrug-resistant organisms.[41] Similarly, "prophylaxis" of drains, tubes, and catheters is both ineffective and hazardous, as is an attempt to "maintain sterility of the wound."[38,42,43]

Prophylaxis for Infective Endocarditis

New guidelines from the American Heart Association have drastically reduced the indications for antibiotic prophylaxis of bacterial endocarditis.[44] Appropriate recipients are now limited to those patients with a prior history of endocarditis, a prosthetic valve, cardiac transplantation, or with certain major congenital heart defects. Procedures in these recipients that require prophylaxis are also restricted, including procedures breaching respiratory mucosa, infected skin, or infected musculoskeletal structures. Prophylaxis solely to prevent infective endocarditis is no longer recommended for genitourinary or gastrointestinal tract procedures.

Therapy

Treatment of established infection in the surgical ICU relies on the principles of good medical–surgical care to minimize the infective burden and maximize host responses; antimicrobial therapy is largely an adjunct. The source of infection should be identified, as detailed previously. Foreign bodies, including prosthetic devices and catheters, frequently require removal when infected. Abscesses and collections must be drained and nonviable tissue debrided in order to facilitate delivery of oxygen, leukocytes, nutrients, and antibiotics to the infected tissue. Optimal nutrition serves not only to improve the immune response but also fluid balance – serum albumin is thus a significant independent prognostic indicator in numerous studies of ICU outcome. In addition, treatment should alter normal flora as little as possible, as these organisms provide a natural defense against replacement by more resistant invading species.

Empiric Therapy

Early empiric therapy must reflect the urgency of the situation. For example, a new fever, elevated white blood cell count, and a new infiltrate on chest radiograph may not require more than a careful examination, diagnostic evaluation, and chest physiotherapy, whereas hemodynamic instability may force rapid initiation of broad-spectrum coverage. Choices of agents should also reflect a patient's history of exposures, as a newly admitted trauma patient usually bears little risk of carrying resistant organisms, compared to a patient transferred from an oncology floor or a chronic care facility. Antibiotic choices should thus reflect local resistance patterns where the infection originated. An antibiogram specific to the surgical ICU will more accurately direct most antibiotic choices than an institution-wide survey.

Gram-positive coverage is needed for suspected infections involving a breach of the skin (including surgical wounds and intravascular catheters) and for ventilator-associated pneumonia. Vancomycin has been the workhorse empiric choice for decades, as it has activity against streptococci, enterococci, and staphylococci, including MRSA. However, if isolated organisms prove sensitive, penicillin and oxacillin are the drugs of choice for streptococcal and staphylococcal infections, respectively, because of superior activity and narrower spectrum.

With the advent of vancomycin-resistant enterococci (VRE) and rising tolerance among staphylococci to vancomycin, use of linezolid or daptomycin may be needed. VRE is often encountered in biliary surgery, especially surrounding liver transplantation. Daptomycin does not penetrate well into the lung and should not be used for pneumonia.

Gram-negative organisms often contribute to ventilator-associated pneumonia and to surgical wound infections involving the abdomen or genitourinary tract. Vascular catheter infection by gram-negative organisms is less common, unless there is gross contamination of the catheter site. Postoperative meningitis and neutropenia require immediate and aggressive gram-negative coverage, to include *Pseudomonas*; cefepime or ceftazidime provide this and moderate additional gram-positive coverage while achieving adequate central nervous system penetration. Aminoglycosides have broad activity against gram-negative organisms, but are now less frequently used because of concerns about toxicity and

the need for monitoring drug levels. For these reasons, however, they now have regained activity against some of the more resistant pathogens and provide a potent alternative under select circumstances. Conversely, the fluoroquinolones (e.g., ciprofloxacin or levofloxacin) provide broad gram-negative activity and are easy to use, but their popularity has resulted in rapidly declining levels of activity against many major pathogens, moderating their utility. Aztreonam offers an alternative in the settings of beta-lactam allergy or intolerance of aminoglycosides.

Mixed infections of the gastrointestinal tract, including head and neck infections, and invasive infection in diabetics often require an anaerobic spectrum of activity. Clindamycin provides broad anaerobic (and gram-positive) activity and is particularly useful in head and neck infection or for aspiration pneumonia, whereas metronidazole is more often used for abdominal infection. These drugs are used in combination with agents with gram-negative and -positive activity, such as cephalosporins or fluoroquinolones. Alternatively, piperacillin-tazobactam or a carbapenem (imipenem or meropenem) can provide both aerobic and anaerobic coverage. These are appropriate choices in mixed abdominal infections, particularly when more resistant gram-negative organisms are suspected.

Antifungal Therapy

Antifungal therapy options have evolved from amphotericin B and its lipid preparations to the azoles (mostly fluconazole and voriconazole) and echinocandins (e.g., caspofungin and micafungin). Fluconazole has provided reliable activity against *Candida albicans* and more variable action against some other *Candida* species, but emergence of fluconazole-resistant *C. albicans* and the more intrinsically resistant species (e.g., *C. krusei* and *Torulopsis glabrata*) have raised caution in some locations. Voriconazole has activity against some of these more resistant species, as well as potent activity against *Aspergillus* species. Both agents have significant drug interactions related to hepatic metabolism. The echinocandins boast essentially none of the renal toxicity of amphotericin and few drug interactions while having activity against numerous other fungi. Newly released posaconazole provides potent antifungal activity that is broader yet, including mucormycosis. Each of these agents (other than now-generic fluconazole) generates significant expense, commonly resulting in restricted access. Most antifungal agents, other than fluconazole, do not provide reliable therapy within the bladder.

Indications for empiric antifungal therapy are usually limited and include yeast urinary tract infection[45] and either candidemia or contamination of an intravenous catheter. Secondary peritonitis may frequently involve significant yeast, as can organ transplantation. The behavior of invasive *Candida* infection is somewhat unpredictable, leading to controversy regarding the role of empiric therapy in high-risk patients.[46]

Table 32.2. Risk factors for multidrug resistance.[41]

Age
Male sex
Length of stay
Diabetes mellitus
Renal failure
Injection drug use
Use of invasive devices
Surgery involving the gastrointestinal tract
Solid organ transplantation
Prior antimicrobial use (particularly cephalosporins and fluoroquinolones)
Exposure to healthcare facilities
Transfer from a long-term care facility

Multidrug-Resistant Organisms

Multidrug-resistant organisms (Table 32.2) should be suspected in patients: hospitalized within the past year; admitted to the hospital for more than 2–3 days; exposed to recent antimicrobial use; or in contact with healthcare settings, such as nursing homes, rehabilitation facilities, or dialysis units.[41] Prior MRSA colonization or infection commonly persists, often for months or years, leading many institutions to identify such patients on readmission so that appropriate isolation and treatment can be instituted.

De-Escalation

Initial empiric therapy should be altered as microbiologic data become available. The Gram stain may provide rapid information – pneumonia due to *S. aureus* or *P. aeruginosa* is usually not subtle, so a negative Gram stain suggests an alternative etiology. Once a pathogen is identified, an optimal, high potency agent should be chosen, with a narrow spectrum of activity and minimal side effects. One should avoid the temptation to continue a "big gun" because of initial success, when a honed regimen has been identified.

Monitoring response to therapy relies primarily on clinical assessment, including hemodynamics, as well as white blood cell and platelet counts and renal and acid–base function. Duration of therapy will often depend on these measures, as controlled studies of optimal courses of therapy are often lacking. Therapy should be continued just long enough to maximize response, while minimizing subsequent development of resistance or toxicity. The Surviving Sepsis Campaign guidelines[6] suggest 7–10 days of antibiotic therapy is usually appropriate, guided by clinical response.

An important exception is bacteremia, which should usually be treated for a minimum of 2 weeks for uncomplicated infection. For bacteremia due to *S. aureus,* treatment should be extended to 4 or more weeks when there is evidence of deep infection, such as endocarditis. Osteomyelitis, prosthetic infection, or involvement of a non-removable focus require extended treatment. A longer course of therapy is also often warranted in patients with neutropenia, diabetes

mellitus, severe malnutrition, or cirrhosis. Correcting these underlying conditions contributes significantly to improved recovery.

The results of Chastre et al. are instructive.[47] In a multicenter trial treating ventilator-associated pneumonia, the authors found that most patients responded as well to 8 days of therapy as to 15, yet were exposed to fewer antibiotics and were thus less likely to develop subsequent resistance. This seminal study changed a long-standing practice of treating pneumonia for 3 weeks or more and provides a model for future investigation.

Conclusions

Antimicrobial agents offer a high probability of success against formerly devastating infections, accompanied by little complicating toxicity. Tempering this optimism is the observation that subsequent overuse has stimulated a modern crisis of resistance, exacerbated by a dearth of newly developed antibiotics. For the practitioner of intensive care medicine, growing antimicrobial resistance adds complexity to care of the individual patient but also to other patients in the ICU, as antibiotics exert their ecologic effect in the surrounding microbiologic environment. The solution to this "perfect storm" is careful diagnosis, thoughtful treatment, and judicious restraint, allied with systematic preventive measures to optimize safe care and remove the hazards that promote infection.

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Part VI
Hematology

33
Coagulation Abnormalities in the Critically Ill

Marcel Levi and Steven M. Opal

Bleeding is one of the major complications of surgery. Serious intraoperative and postoperative bleeding may be caused not only by a local problem in surgical hemostasis, such as a failed ligature, but can also be caused by a defect in the hemostatic system. Surgical hemostasis and an adequate function of the coagulation system are complementary; in some cases, a patient with a (minor) hemostatic defect may be operated upon without any specific perioperative intervention in the coagulation system, whereas in other instances improvement of blood coagulation may *be* necessary before surgery.[1]

Critically ill patients often present with abnormal coagulation tests. A myriad of abnormalities may be detectable, such as thrombocytopenia, prolonged global coagulation times, reduced levels of coagulation inhibitors, or high levels of fibrin split products. Each of these derangements in clotting may derive from a variety of different pathophysiological mechanisms.[2] Proper identification of the underlying causes of these coagulation abnormalities is required, as various coagulation disorders may necessitate different diagnostic and therapeutic management strategies. This chapter reviews the most frequently occurring coagulation abnormalities in patients in the intensive care unit, with emphasis on the differential diagnosis, the underlying molecular and pathogenetic pathways, and the appropriate diagnostic and therapeutic interventions.

Incidence and Relevance

A prolonged global coagulation time – such as the prothrombin time (PT) or the activated partial thromboplastin time (aPTT) – occurs in 14 to 28% of intensive care patients.[3,4] In particular, trauma patients seem to have a high incidence of coagulation time prolongation. A PT or aPTT ratio >1.5 was found to predict excessive bleeding.[3] In a prospective study of trauma patients, a prolonged PT and/or aPTT have been strong and independent predictors of mortality.[4]

In surgical and trauma patients, the incidence of *thrombocytopenia* (defined by a platelet count $<100\times10^9$/l) is 35–41%.[5,6]Typically, the platelet count decreases during the first 4 days in the intensive care unit.[7] This is higher than the incidence of thrombocytopenia (when defined by a platelet count $<150\times10^9$/l) in critically ill medical patients, which is 35–44%.[8–10] Overall, a platelet count of $<100\times10^9$/l is seen in 20–25% of patients, whereas 12–15% of patients have a platelet count $<50\times10^9$/l. The primary clinical relevance of thrombocytopenia in critically ill patients is related to an increased risk of bleeding. Indeed, severely thrombocytopenic patients with platelet counts of $<50\times10^9$/l have a four- to five-fold higher risk for bleeding compared to patients with higher platelet counts.[8,10] The risk of intracerebral bleeding in critically ill patients during intensive care admission is relatively low (0.3–0.5%), but in 88% of patients with this complication the platelet count is less than 100×10^9/l.[11] Moreover, a decrease in platelet count may indicate ongoing coagulation activation, which contributes to microvascular failure and organ dysfunction. Regardless of the cause, thrombocytopenia is an independent predictor of ICU mortality in multivariate analyses with a relative risk of 1.9 to 4.2 in various studies.[5,8,10] Figure 33.1 shows that the number of platelets in critically ill patients is inversely related to survival. In particular, sustained thrombocytopenia over more than 4 days after ICU admission or a drop in platelet count of >50% during ICU stay is related

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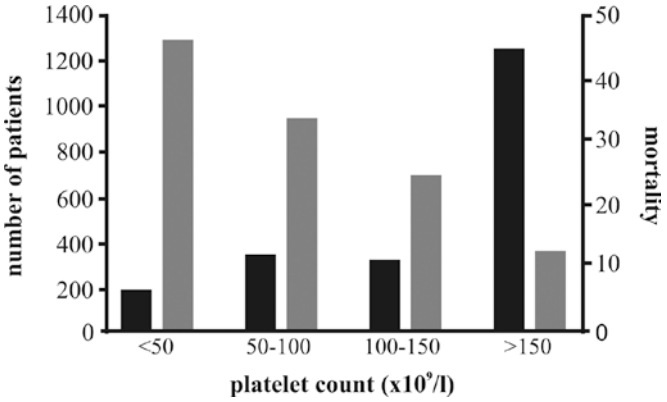

FIG. 33.1. Distribution of nadir platelet count (*black bars*) and survival (*gray bars*) in a pooled analysis of four clinical studies of consecutive groups of patients admitted to the ICU.[1,3,4,6]

to a four- to sixfold increase in mortality.[7,8] The platelet count was shown to be a stronger independent predictor for ICU mortality than composite scoring systems, such as the Acute Physiology and Chronic Evaluation (APACHE) II score or the Multiple Organ Dysfunction Score (MODS). A platelet count of $<100 \times 10^9$/l is also related to a longer ICU stay, but not the total duration of hospital admission.[10]

Other coagulation test abnormalities frequently observed in ICU patients include elevated fibrin split products and reduced levels of coagulation inhibitors. Fibrin split products are detectable in 42% of a consecutive series of intensive care patients, in 80% of trauma patients, and in 99% of patients with sepsis.[12–14] Low levels of coagulation inhibitors, such as antithrombin and protein C, are found in 40–60% of trauma patients and 90% of sepsis patients.[14,15]

Causes of Prolonged Global Coagulation Times

It is important to emphasize that global coagulation tests, such as the prothrombin time (PT) and the activated partial thromboplastin time (aPTT), poorly reflect in vivo hemostasis. However, these tests are a convenient method to quickly estimate the concentration of one or, at times, multiple coagulation factors for which each test is sensitive (Table 33.1).[16] In general, coagulation tests will be prolonged if the levels of coagulation factors are below 50%. This is relevant since the levels of coagulation factors, which are needed for adequate hemostasis, are somewhere between 25 and 50%.[17] The normal values and the sensitivity of these tests for deficiencies of coagulation factors may vary markedly between tests, dependent on the reagents used. Therefore, an increasing number of laboratories use the International Normalized Ratio (INR) instead of the prothrombin time. While this may carry the advantage of increased standardization between centers, it should be mentioned that the INR has only been validated for control of the intensity of vitamin K antagonist therapy and has never been developed for use as a screening test for coagulation abnormalities.[18]

TABLE 33.1 Global Coaqulation Tests.

Test result	Cause
PT prolonged, aPTT normal	Factor VII deficiency Mild vitamin K deficiency Mild liver insufficiency Low doses of vitamin K antagonists
PT normal, aPTT prolonged	Factor VIII, IX, or XI deficiency Use of unfractionated heparin Inhibiting antibody and/or anti-phospholipid antibody Factor XII or prekallikrein deficiency (no relevance for in vivo coagulation)
Both PT and aPTT prolonged	Factor X, V, II or fibrinogen deficiency Severe vitamin K deficiency Use of vitamin K antagonists Global clotting factor deficiency Synthesis: liver failure Loss: massive bleeding Consumption: DIC

A prolongation of global coagulation tests may be due to a deficiency of one or more coagulation factors. In addition, the presence of an inhibiting antibody, which can have major in vivo relevance (such as in acquired hemophilia) but can also be a clinically insignificant laboratory phenomenon, should be considered. The presence of such inhibiting antibody can be confirmed by a simple mixing experiment. As a general rule, if a prolongation of a global coagulation test cannot be corrected by mixing 50% of patient plasma with 50% of normal plasma, then an inhibiting antibody is likely to be present.

In the vast majority of critically ill patients, deficiencies of coagulation factors are acquired and we will not discuss the various congenital coagulation defects here. In general, deficiencies in coagulation factors may be due to impaired synthesis, massive loss, or increased turnover (consumption). Impaired synthesis is often due to liver insufficiency or vitamin K deficiency. The prothrombin time is most sensitive to both conditions, since this test is highly dependent on the plasma levels of factor VII (a vitamin K-dependent coagulation factor with a shortest half-life of the clotting factors). Liver failure may be differentiated from vitamin K deficiency by measuring factor V, which is not vitamin K dependent. In fact, factor V plays an important role in various scoring systems for severe acute liver failure.[19] Uncompensated loss of coagulation factors may occur after massive bleeding, for example in trauma patients or patients undergoing major surgical procedures. This is particularly common in patients with major blood loss where intravascular volume is rapidly replaced with crystalloids, colloids, and red cells without simultaneous administration of coagulation factors. This resulting depletional form of coagulopathy may persist and exacerbate the bleeding. In hypothermic patients (e.g., trauma patients) measurement of the global coagulation tests may underestimate coagulation in vivo, since in the laboratory test-tube assays are standardized

and performed at 37°C to mimic normal body temperature. Consumption of coagulation factors may occur in the framework of disseminated intravascular coagulation (discussed later in this chapter). In complicated cases, various causes for a prolongation of global coagulation times may be present simultaneously, and the cause may also change over time. For example, multi-trauma patients will often present with a loss of coagulation factors due to severe bleeding, but can later develop a consumption coagulopathy due to DIC as a consequence of a systemic inflammatory response. Coagulopathy may subsequently ensue from trauma-induced liver injury and acute hepatic failure with resultant impaired coagulation factor synthesis.

Some anticoagulant agents will also prolong global coagulation times. Unfractionated heparin prolongs the aPTT, but confusingly low molecular weight heparins do not (or only very modestly) have such an effect. Warfarin, or other vitamin K antagonists, causes a reduction in vitamin K dependent coagulation factors, resulting in an initial prolongation the PT followed by elevations of both the PT and aPTT.

Causes of Thrombocytopenia

There are many causes for thrombocytopenia in critically ill patients. Table 33.2 summarizes the most frequently occurring diagnoses recognized in intensive care patients with thrombocytopenia. The relative incidence of each of these disorders in ICU patients is provided along with the differential diagnostic approach to distinguish each of these entities.

Sepsis is a clear risk factor for thrombocytopenia in critically ill patients, and the severity of sepsis correlates with the decrease in platelet count.[20] The principal factors that contribute to thrombocytopenia in patients with sepsis are impaired platelet production, increased consumption or destruction, or sequestration platelets in the spleen or along the endothelial surface. Impaired production of platelets from within the bone marrow may seem contradictory to the high levels of platelet production-stimulating pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, and high concentration of circulating thrombopoietin in patients with sepsis. These cytokines and growth factors should theoretically stimulate megakaryopoiesis in the bone marrow.[21] However, in a substantial number of patients with sepsis, marked hemophagocytosis may occur (Fig. 33.2a, b). This pathologic process consists of active phagocytosis of megakaryocytes and other hematopoietic cells by monocytes and macrophages, hypothetically due to stimulation with high levels of macrophage colony stimulating factor (M-CSF) in sepsis.[22] Platelet consumption probably also plays an important role in patients with sepsis, due to ongoing generation of thrombin (which is the most potent activator of platelets in vivo), in its most fulminant form known as disseminated intravascular coagulation. Platelet activation, consumption, and destruction may also occur at the endothelial site as a result of the extensive endothelial cell-platelet interaction in sepsis, which may vary between different vascular beds in various organs.[23]

Table 33.2. Differential diagnosis of thrombocytopenia in the ICU.

Differential diagnosis	Relative incidence	Additional diagnostic clues
Sepsis	52.4%	Positive blood cultures, positive sepsis criteria, hematophagocytosis in bone marrow aspirate
DIC	25.3%	Prolonged aPTT and PT, increased fibrin split products, low levels of physiological anticoagulant factors (antithrombin, protein C)
Massive blood loss	7.5%	Major bleeding, low hemoglobin, prolonged aPTT and PT
Thrombotic microangiopathy	0.7%	Schistocytes in blood smear, Coombs-negative hemolysis, fever, neurologic symptoms, renal insufficiency
Heparin-induced thrombocytopenia	1.2%	Use of heparin, venous or arterial thrombosis, positive HIT test (usually ELISA for heparin-platelet factor IV antibodies), rebound of platelets after cessation of heparin
Immune thrombocytopenia	3.4%	Anti-platelet antibodies, normal or increased number of megakaryocytes in bone marrow aspirate, thrombopoietin (TPO) decreased
Drug-induced thrombocytopenia	9.5%	Decreased number of megakaryocytes in bone marrow aspirate or detection of drug-induced anti-platelet antibodies, rebound of platelet count after cessation of drug

Seven major causes of thrombocytopenia (platelet count $<150\times10^9$/l) are listed. Relative incidences are based on two studies in consecutive ICU patients.[1,6] Patients with hematological malignancies were excluded.
[a] Patients with sepsis and DIC are classified as DIC.

In patients with disseminated intravascular coagulation (DIC), the platelet count is invariably low or rapidly decreasing.[24] DIC is the most extreme form of systemic coagulation activation, which may complicate a variety of underlying disease processes – including sepsis; trauma; cancer; or obstetrical calamities, such as placental abruption – and will be discussed in a separate paragraph.

Heparin-induced thrombocytopenia (HIT) is caused by a heparin-induced antibody that binds to the heparin-platelet factor IV complex on the platelet surface.[23] This may result in massive platelet activation and, as a consequence, a consumptive thrombocytopenia and arterial and venous thrombosis occurs. The incidence of HIT may be as high as 5% of patients receiving heparin, and is dependent on the type and dose of heparin and the duration of its administration (especially when given for more than 4 days). A consecutive series of critically ill ICU patients who received heparin revealed an incidence of 1% in this setting.[25] Unfractionated heparin carries a higher risk of HIT than low molecular weight (LMW)

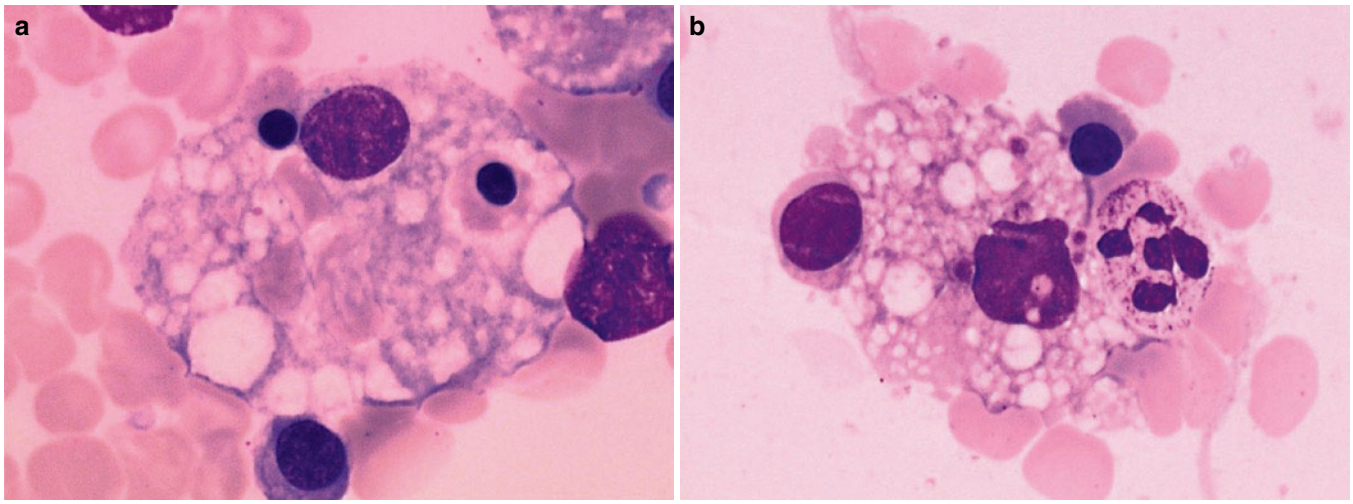

FIG. 33.2. (**a**) Typical example of hematophagocytosis (**b**) of bone marrow cells by a macrophage. The bone marrow was obtained from a patient with severe sepsis (May-Grunwald-Giemsa staining, ×1,000).

heparin.[26] Thrombosis may occur in 25–50% of patients with HIT (with fatal thrombosis in 4–5%) and may also become manifest after discontinuation of heparin.[27] The diagnosis of HIT is based on the detection of HIT antibodies in combination with the occurrence of thrombocytopenia in a patient receiving heparin, with or without concomitant arterial or venous thrombosis. It should be mentioned that the commonly used ELISA for HIT antibodies has a high negative predictive value (100%) but a very low positive predictive value (10%).[25] A more precise diagnosis may be made with a 14C-serotonin release assay, but this test is not routinely available in most settings.[28] Normalization in the number of platelets in 1–3 days after discontinuation of heparin may further support the diagnosis of HIT.

The group of thrombotic microangiopathies encompasses syndromes such as thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, severe malignant hypertension, chemotherapy-induced microangiopathic hemolytic anemia, and the HELLP syndrome.[29] A common pathogenetic feature of these clinical entities appears to be endothelial damage, causing platelet adhesion and aggregation, thrombin formation, and an impaired fibrinolysis. The multiple clinical consequences of this extensive endothelial dysfunction include thrombocytopenia, mechanical fragmentation of red cells with hemolytic anemia, and obstruction of the microvasculature of various organs, such as kidney and brain (leading to renal failure and neurologic dysfunction, respectively). Despite this common final pathway, the various thrombotic microangiopathies have different underlying etiologies. Thrombotic thrombocytopenic purpura is caused by deficiency of von Willebrand factor cleaving protease (ADAMTS-13), resulting in endothelial cell-attached ultra-large von Willebrand multimers that readily bind to platelet surface glycoprotein Ib and cause platelet adhesion and aggregation.[30] In hemolytic uremic syndrome, a cytotoxin released upon infection with a specific serogroup of gram-negative microorganisms (usually *E. coli* serotype O157:H7) is responsible for endothelial cell and platelet activation. In case of malignant hypertension or chemotherapy-induced thrombotic microangiopathy, presumably direct mechanical or chemical damage to the endothelium is responsible for the enhanced endothelial cell-platelet interaction, respectively. A diagnosis of thrombotic microangiopathy relies upon the combination of thrombocytopenia, Coombs-negative hemolytic anemia, and the presence of schistocytes in the blood smear. Additional information can be achieved by measurement of ADAMTS-13 and autoantibodies toward this metalloprotease and culture (usually from the stool or urine) of microorganisms capable of cytotoxin production.

Drug-induced thrombocytopenia is another frequent cause of thrombocytopenia in the intensive care unit setting.[5] Thrombocytopenia may be caused by drug-induced myelosuppression, such as the one caused by cytostatic agents, or by immune-mediated mechanisms. A large number of agents may cause thrombocytopenia by similar mechanisms, including medications that are frequently used in critically ill patients such as antibiotics (including cephalosporins or trimethoprim-sulfamethoxazole), benzodiazepines, or nonsteroidal anti-inflammatory agents (NSAIDs). Novel inhibitors of platelet aggregation, such as glycoprotein IIb/IIIa antagonists (e.g., abciximab) or thienopyridine derivatives (clopidogrel) are increasingly used in the management of patients with acute coronary syndromes and may also cause severe thrombocytopenia.[31] Drug-induced thrombocytopenia is a difficult diagnosis in the ICU setting, as these patients are often exposed to multiple agents and have numerous other potential reasons for platelet depletion. Drug-induced thrombocytopenia is often diagnosed based upon the timing of initiation of a new agent in relationship to the development of thrombocytopenia, after exclusion of other causes of thrombocytopenia.

The observation of rapid restoration of the platelet count after discontinuation of the suspected agent is highly suggestive of drug-induced thrombocytopenia. In some cases, specific drug-dependent anti-platelet antibodies can be detected.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) occurs in a substantial proportion of consecutive intensive care patients. DIC is a syndrome caused by systemic intravascular activation of coagulation, which may be secondary to various underlying conditions.[24] Formation of microvascular thrombi, in concert with inflammatory activation, may cause failure of the microvasculature and thereby contribute to organ dysfunction.[32] Ongoing and insufficiently compensated consumption of platelets and coagulation factors may pose a risk factor for bleeding, especially in perioperative patients or patients who need to undergo invasive procedures. The trigger for the activation of the coagulation system is nearly always mediated by several of the pro-inflammatory cytokines, expressed and released by mononuclear cells and endothelial cells. Thrombin generation proceeds via the (extrinsic) tissue factor/factor VIIa route concomitant with depression of inhibitory mechanisms of thrombin generation, such as antithrombin III and the protein C and S system. Impaired fibrin degradation, due to high circulating levels of PAI-1, further enhances intravascular fibrin deposition.

Patients with DIC have a low or rapidly decreasing platelet count, prolonged global coagulation tests, low plasma levels of coagulation factors and inhibitors, and increased markers of fibrin formation and/or degradation, such as D-dimer or fibrin degradation products (FDPs).[33] Coagulation proteins with a marked acute phase behavior, such as factor VIII or fibrinogen, are usually not decreased or may even increase. One of the often advocated laboratory tests for the diagnosis of DIC, fibrinogen, is therefore not a very good marker for DIC, except in very severe cases, although sequential measurements can give some insight.[34] There is no single laboratory test with sufficient accuracy for the diagnosis of DIC. However, a diagnosis of DIC may be made using a simple scoring system based on a combination of routinely available coagulation tests (Table 33.3).[35] In a prospective validation study, the sensitivity and specificity of this DIC score was found to be 93 and 98%, respectively. Furthermore, this DIC score was found to be a strong and independent predictor of mortality in a large series of patients with severe sepsis.[36]

TABLE 33.3. Diagnostic scoring system for the diagnosis of overt disseminated intravascular coagulation (DIC).

Score global coagulation test results:	
Platelet count (>100 × 10⁹/l = 0, <100 × 10⁹/l = 1, <50 × 10⁹/l = 2)	
Elevated fibrin-related marker (e.g., fibrin degradation products or D-dimer) (no increase: 0, moderate increase: 2, strong increase: 3)	
Prolonged prothrombin time (<3 s = 0, >3 but <6 s = 1, >6 s = 2)	
Fibrinogen level (>1.0 g/L = 0, <1.0 g/L = 1)	
Calculate score	

The scoring system can only be used if an underlying disorder, known to be associated with DIC, has been diagnosed. The cut-off values for the fibrin-related marker are dependent on the test used. In the prospective validation studies a moderate increase was defined as >0.4 mg/L and a strong increase as >4.0 mg/L. A score of ≥5 is compatible with DIC.

Coagulation Defects with Normal Routine Coagulation Tests

It is critically important to recognize that the routine coagulation tests, such as platelet count, global-clotting assays (like PT and aPTT), and measurement of coagulation factors, might miss clinically significant coagulation defects that can contribute to bleeding. The most important coagulation defects that may remain undetected with routine coagulation tests are platelet dysfunction and hyper-fibrinolysis.

Platelet dysfunction is a frequent occurrence in critically ill patients, for example as a result of uremia or severe liver failure. Another frequent cause for a defective platelet function is the use of anti-platelet agents, such as aspirin or other NSAIDs or potent thrombin inhibitors, such as hirudin. Extracorporeal circuits, including cardiopulmonary bypass, continuous venovenous hemofiltration, or extracorporeal membrane oxygenators may also cause a serious platelet function defect, presumably due to platelet activation within these circuits.[37,38] The use of these devices in clinical medicine often poses major problems for the clinician, as anticoagulation is required to prevent clotting in the extracorporeal circulation. The necessity for medical device-related anticoagulation, in combination with the coagulation defects induced upon the hemostatic system from the extracorporeal circulation itself, may cause significant bleeding. There is currently *no* accurate, routinely available test for platelet function in critically ill patients. The bleeding time is highly inaccurate in this situation, and also the recently developed platelet function analyzers have proved to be disappointing in clinical practice.[39,40]

Hyper-fibrinolysis is a relatively rare condition that may occur in patients with specific types of cancer, such as acute promyelocytic leukemia or prostatic carcinoma.[41] Patients on extracorporeal circuits may also experience a marked activation of fibrinolysis due to release of plasminogen activators from endothelial cells. Critically ill patients that have been treated with thrombolytic agents have an intentionally induced hyper-fibrinolytic state.[42] Hyper-fibrinolysis may be suspected if levels of fibrin degradation products (that often also detect fibrinogen degradation products) are inordinately

high and fibrinogen levels are low. The diagnosis can be confirmed by detection of very low levels of plasminogen and α2-antiplasmin.

Management of Coagulation Abnormalities in Critically Ill Patients

It is evident that the primary focus of attention in the treatment of a clinically relevant coagulopathy should be directed toward the adequate management of the underlying condition. This emphasizes the critical importance of making a correct diagnosis that underlies the acquired coagulopathy. Despite proper treatment for the underlying disorder, nevertheless, further supportive measures for the coagulation defects are often required.

Most guidelines advocate a platelet transfusion in patients with a platelet count of <30–50 × 10^9/l accompanied with bleeding or at high risk for bleeding, and in patients with a platelet count <10 × 10^9/l, regardless of the presence or absence of bleeding. Platelet concentrates usually contain a mixture of the platelets from a blood donation from 5 to 6 donors (equals 5–6 units). After platelet transfusion, the platelet count should rise with at least 5 × 10^9/l per unit of platelets transfused. A lesser response may be present in patients with high fever, DIC, or splenomegaly, or may indicate allo-immunization of the patient after repeated transfusion. Platelet transfusion is particularly effective in patients with thrombocytopenia due to impaired platelet production or increased consumption, whereas disorders of enhanced platelet destruction (e.g., immune thrombocytopenia) may necessitate alternative therapies, such as steroids or human immunoglobulin. Some causes of thrombocytopenia may require specific measures. Thrombocytopenia due to HIT requires immediate cessation of heparin and, if needed, institution of alternative anticoagulant treatment, e.g., with danaparoid or hirudin.[43] Vitamin K antagonists should be avoided in the initial treatment of HIT, since these agents may cause skin necrosis. In patients with a classic thrombotic microangiopathy due to low levels of von Willebrand cleaving protease (ADAMTS-13), plasmapheresis and immunosuppressive treatment should be initiated.[29]

Fresh frozen plasma contains all coagulation factors and may be used to replenish congenital or acquired deficiencies of these clotting factors. Current practice guidelines in most centers use solvent or detergent-treated plasma (SDP or ESDP), which may provide better protection against transmission of blood-borne infections but may also have a lower recovery of coagulation factors [44]. Most consensus guidelines indicate that plasma should only be transfused in case of bleeding or in a situation with a high-risk of bleeding, and not based on laboratory abnormalities alone. For more specific therapy or if the transfusion of large volumes of plasma is not desirable, fractionated plasma of purified coagulation factor concentrate is available. Prothrombin complex concentrates (PCCs) contain the vitamin K-dependent coagulation factors II, VII, IX, and X. Hence, these concentrates may be used if immediate reversal of vitamin K antagonist treatment is required. Also, PCCs may be used if global replenishment of coagulation factors is necessary and large volumes of plasma may not be tolerated. One should realize, however, that only selected elements of coagulation factors are administered in such cases, and that important clotting factor deficiencies may remain (i.e., factor V or fibrinogen). In some cases, administration of purified coagulation factor concentrates, such as fibrinogen concentrate or cryoprecipitate, may be helpful.

Pro-hemostatic treatment can be used as adjunctive treatment in patients with major blood loss.[45] De-amino D-arginine vasopressin (DDAVP, desmopressin) is a vasopressin analog that induces release of the contents of the endothelial cell associated Weibel Palade bodies, including von Willebrand factor. Hence, the administration of DDAVP results in a marked increase in the plasma concentration of von Willebrand factor (and associated coagulation factor VIII) and, by as yet unexplained additional mechanisms, a potentiation of primary hemostasis. DDAVP has proven to be effective in the management of patients with von Willebrand's disease and mild hemophilia A, but also in patients with uremic thrombocytopathy and other defects in primary hemostasis.[46] Relatively rare but notable adverse effects of desmopressin are the occurrence of acute myocardial infarction (particularly in patients with unstable coronary artery disease) and water intoxication with hyponatremia due to its antidiuretic effect, mostly in patients who receive large amounts of intravenous hypotonic fluids.

Anti-fibrinolytic agents, such as aprotinin and lysine analogs (ε-aminocaproic acid or tranexamic acid) may also be helpful in the prevention or management of bleeding, in particular if hyper-fibrinolysis is thought to be the major contributor to the hemostatic defect. Anti-fibrinolysis therapies may also compensate for other coagulation defects.[45]

Anti-fibrinolytic agents have been found effective in the prevention of blood loss and transfusion in patients undergoing major surgical procedures and are relatively safe.[47,48] Aprotinin may cause anaphylactic responses and lysine analogs should not be used in patients with hematuria since obstructive clots in the urinary tract may be formed. Recombinant factor VIIa is a relatively new pro-hemostatic agent that has been licensed for the treatment of patients with hemophilia and inhibiting antibodies toward factor VIII or IX. Initial clinical studies in patients with other types of coagulation defects or patients with major bleeding due to surgery or trauma are promising, and controlled clinical trials are still in progress.[49,50] The initial clinical use of recombinant factor VIIa results in a surprisingly low incidence of thrombotic complications.[51] Until ongoing clinical trials and further safety data in critically ill patients become available, however, off-label use of recombinant factor VIIa can only be justified in the case of life-threatening bleeding, when all other conventional treatments have failed.[45]

Supportive treatment of the coagulopathy associated with DIC is a complicated issue.[24] Administration of anticoagulants may theoretically be beneficial, but their efficacy has never been

proven in clinical trials. Restoration of dysfunctional physiological anticoagulant pathways by administration of antithrombin concentrate or (activated) protein C has beneficial effects on laboratory parameters, but the efficacy of this approach for clinically relevant outcome parameters remains unclear. In patients with severe sepsis, recombinant human activated protein C (drotrecogin alpha-activated) is effective.[14] Interestingly, the relative efficacy of activated protein C in the subgroup of patients with DIC was higher than in those without DIC; and patients treated with activated protein C had a more rapid resolution of DIC than placebo-treated patients.[36] A recent trial suggested that heparin might be a useful adjunctive treatment in patients with sepsis – in particular to prevent thrombotic complications – and also indicated that heparin prophylaxis should *not* be discontinued when activated protein C is initiated.[52]

Conclusions

Coagulation abnormalities occur frequently in critically ill patients and may have a major impact on the outcome. An adequate explanation for the cause of the coagulation abnormality is important, since many underlying disorders may require specific treatment. Treatment of coagulation abnormalities in critically ill patients should be directed at the underlying condition, but supportive therapy may be required. Deficiencies in platelets and coagulation factors in bleeding patients or patients at risk for bleeding can be set right by transfusion of platelet concentrate or plasma products, respectively. In addition, pro-hemostatic treatment may be beneficial in case of severe bleeding, whereas restoring physiological anticoagulant pathways may be helpful in patients with sepsis and DIC.

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34
Blood Products

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Blood components, commonly transfused in the intensive care unit (ICU), include packed red blood cells, platelets, plasma, and cryoprecipitate. The indications, dosing, and expectations for each will be discussed, in turn. Components occasionally transfused include albumin and factor concentrates. Although some indications of the latter are controversial and extensive discussions are beyond the scope of this chapter, a brief mention of their use is warranted.

Red Blood Cells

Red blood cells (RBCs) are administered to increase red cell mass and oxygen-carrying capacity in patients with symptomatic anemia and major hemorrhage. The transfusion threshold is based on clinical status rather than the hemoglobin or hematocrit[1]; however, patients with hemoglobin levels of 6 g/dL or less have been considered likely to benefit from transfusion, while those with hemoglobin levels of 10 g/dL or more are less likely to do so.[2,3] For patients with hemoglobin between 6 and 10 g/dL, recommendations have been more controversial. One study concluded that transfusions, when hemoglobin levels are less than 7 g/dL, are at least as effective as, and possibly superior to, transfusions when hemoglobin levels are less than 10 g/dL in intensive care unit patients, except for patients with cardiac ischemia.[4] Recent reviews provide additional discussion on the debate over appropriate transfusion triggers in the intensive care unit.[5,6] Physiologic transfusion triggers should progressively replace arbitrary hemoglobin-based transfusion triggers. These physiologic triggers are based on markers of impaired global oxygenation (lactate serum concentrations and venous oxygen saturation) or regional tissue oxygenation (electrocardiographic ST-segment abnormalities and electroencephalographic P300 latency).[7] As for the dose, one unit of RBCs would be expected to increase the hemoglobin by 1 g/dL or the hematocrit by 3% in a patient with a stable blood volume.

Alternatives to red cell transfusions include autologous donation, acute normovolemic hemodilution, intraoperative salvage, and exogenous erythropoietin administration.[8] Hemoglobin-based blood substitutes (HBBS) remain in clinical trials and have *not* been approved for use in the United States.[9] A recent meta-analysis including 3,711 patients showed that the use of HBBS is associated with a significant, increased risk of death and myocardial infarction. Hemoglobin molecules used to manufacture HBBS are not contained by a red cell membrane, and hence rapidly scavenge nitric oxide when released into the vasculature, potentially causing systemic vasoconstriction, decreased blood flow, and vascular thrombosis of the heart or other organs.[10]

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Platelets

Platelet transfusion is indicated for the treatment of bleeding caused by thrombocytopenia or thrombocytopathy. Prophylactic transfusions may also be considered in some patients. For example, many institutions would consider giving platelets to patients who require invasive procedures when the platelet count is less than 50,000/μL,[11] although a recent review suggests a paucity of evidence to support this practice.[12] Additionally, stable patients with platelet counts less than 5,000–10,000/μL may be given platelets to lower the risk of spontaneous bleeding. Platelets may be available from whole blood or as an apheresis product. Typically, those from whole blood are pooled to yield a pack of five or more, and an apheresis product, from a single donor, may yield the equivalent of 5–7 or more units. The efficacy of each type has generally been found to be equivalent. Transfusion of one unit would be expected to increase the platelet count by 5,000/μL in a patient with a stable blood volume.

Transfusion of platelets is usually not effective during rapid platelet destruction (ITP, TTP, untreated disseminated intravascular coagulation [DIC]). Under these circumstances, platelets should be administered only if active bleeding is present. Patients who are septic or suffer from hypersplenism, also, do not experience much of an increment from platelet transfusion.

Plasma

Indications for plasma (fresh frozen plasma [FFP], thawed plasma) include bleeding or preoperative prophylaxis in a patient with multiple factor deficiencies, and congenital factor deficiencies for which no concentrate is available (e.g., V, XI). The transfusion threshold has generally been a prothrombin time international normalized ratio (INR) of >1.5 or activated partial thromboplastin time (PTT) >1.5 times the midpoint of the normal range for the institution[11,13]; however, it should be noted that an elevated INR prior to a procedure does not accurately predict the likelihood of bleeding during or after the procedure.[12,14] Typically, 2 to 4 units of plasma are ordered initially, and repeated every 6 h. A helpful rule of thumb suggests that 10–20 ml of plasma/kg will increase factor levels by about 20%. The lower the INR, the more difficult it will be to correct. Infusion of a single unit is usually not adequate. Plasma infusion should not be used for volume expansion, or as a source of protein for nutritional deficiency.

Cryoprecipitated Antihemophilic Factor (Cryoprecipitate)

Cryoprecipitate contains fibrinogen, factor VIII, factor XIII, von Willebrand factor, and fibronectin. Cryoprecipitate may be used to correct a fibrinogen deficiency or factor XIII deficiency, or as an alternative for factor VIII or von Willebrand factor concentrates if purified or recombinant concentrates are not available.[11] Occasionally, it has been used in an attempt to arrest microvascular bleeding despite an adequate fibrinogen level, but this remains controversial. In addition, cryoprecipitate is considered second-line therapy, following desmopressin (DDAVP), for uremic bleeding. Finally, it has been used in surgery as a component of "fibrin glue," though commercially available products commonly referred to as "tissue sealants" have largely replaced it. The transfusion threshold to replace fibrinogen is a level of less than 100 mg/dL. Typically, a pool of 10 units is infused, with the expectation that each unit would increase the fibrinogen level by 5 mg/dL. Cryoprecipitate should not be used for deficiencies of other factors, as they are not present in the product. Although selection of type-specific cryoprecipitate is not required, it should be noted that transfusion of large amounts of ABO-incompatible cryoprecipitate may cause hemolysis.

Albumin

Albumin is often used in various settings,[15–18] but clear indications remain controversial. Generally, it is administered when both hypovolemia and severe hypoproteinemia are present, but the evidence is limited. The transfusion threshold is based on clinical status rather than laboratory value, but some use albumin levels <2 g/dL as a rough guide. Some specific indications include thermal injury, nephrotic syndrome, dialysis, large volume paracentesis, hepatorenal syndrome, subarachnoid hemorrhage, and coronary artery bypass grafting. Albumin is commonly available in 5 and 25% concentrations. Continued therapy is guided by response. Infusion of albumin will not correct chronic hypoalbuminemia and should not be used in dehydrated patients unless supplemented by crystalloid. Caution should be taken with patients who are susceptible to fluid overload.

Factor Concentrates

Factor concentrates available for correction of specific factor deficiencies include factor VIII, factor IX, and von Willebrand factor, the latter in combination with a factor VIII product, Humate P (ZLB Behring).[19] Certain forms of mild von Willebrand factor deficiencies may respond to administration of desmopressin (DDAVP).[20] Consultation with a hematology or transfusion medicine specialist is highly recommended when using these products.

Additional Processing

Additional processing, such as leukoreduction, irradiation, and washing of cellular products may be required under certain circumstances. Leukoreduction of cellular products is

Table 34.1. Decrease in febrile reactions following implementation of universal leukoreduction at Lahey Clinic.

Year	Number febrile nonhemolytic reactions
2000	40
2001	28
2002	10
2003	8
2004	14
2005	10
2006	15
2007	12

indicated for patients who experience repeated febrile reactions and for prophylaxis against alloimmunization in patients destined to receive intensive or long-term hemotherapy.[21] Because cytomegalovirus (CMV) is present in the white cells, leukoreduction has been used to prevent transmission of CMV infection.[22] Leukoreduction should not be used to prevent graft-versus-host disease (GVHD), since a low level of viable lymphocytes remains in the product. Many institutions have employed "universal" leukoreduction, exclusively using leukoreduced products. Our institution has noted a marked decrease in febrile reactions since implementing universal leukoreduction (see Table 34.1).

Irradiation of cellular products is indicated for prevention of GVHD,[23] which is a greater threat to certain immunocompromised recipients. Such recipients include those with hematologic malignancies, especially when receiving chemotherapy, those with certain immune deficiency syndromes, and patients receiving blood products from first- or second-degree related donors. Irradiation is not indicated for prevention of febrile reactions or alloimmunization, since white blood cells are not actually removed by irradiation.

Washed components are indicated for prevention of severe or recurrent allergic reactions, which may be caused by compounds that normally reside in the plasma compartment.[24] Washing should not be used alone for leukoreduction, since the residual white cell load remains significant. Thus, GVHD and CMV infection are threats because viable leukocytes are still present. Current white blood cell filters are more efficient at removing white cells. One disadvantage of using washed products lies in the fact that a significant number of cells are lost. Therefore, transfusion of such a product results in a smaller increment in counts when compared to an unwashed component.

Blood Product Administration

A few words about blood administration are worth considering. These include safety, warming of blood, and recommended infusion times for various products. It cannot be overemphasized that proper identification of the patient, both at the time of sample collection and at the time of transfusion, is of paramount importance. Most transfusion errors are linked to misidentification of the patient or mislabeling of the specimen tubes.[25,26] It is important that the tube be labeled at the bedside. In addition, stringent procedures to prevent administering a blood product to the wrong patient should be in place.

Table 34.2. Suggested guidelines for blood product infusion rates in stable patients.

Red blood cells	1½ h, not to exceed 4 h
Plasma	1 h, not to exceed 2 h
Platelets or cryo	Usually 20–30 min

Warming of blood may be necessary for some patients. Obviously, patients requiring multiple rapid transfusions should receive blood through a warming device approved for this purpose.[27] In addition, patients with severe cold autoimmune hemolytic anemia should be transfused using a blood warmer.

Infusion times may vary depending upon the clinical situation, faster for patients with severe hemorrhage or anemia, slower for those susceptible to fluid overload; however, some general guidelines used for hemodynamically stable patients are shown in Table 34.2.

Blood products should only come into contact with normal saline. Other concomitant IV solutions should be avoided because they may cause hemolysis or clotting, or otherwise affect the potency of the product.[28]

Urgent Transfusion

Urgent transfusion involves the administration of RBCs prior to completion of standard pre-transfusion testing. This is also referred to as transfusion of "uncrossmatched" blood. Urgent transfusion requires the need to establish both oxygen-carrying capacity and intravascular volume. Crystalloid or colloid solutions should be used for immediate volume restoration in hypovolemic shock. If the patient becomes stable, transfusion should await completion of the crossmatch, since there remains a very low risk of incompatibility. Group O RBCs are used if blood is needed and typing has not been completed. Since O-negative cells are often in short supply, it is reasonable to administer O-positive cells; however, Rh-negative RBCs should be given to females of childbearing potential and to children to avoid sensitization. Usually, policies require the ordering physician to sign a statement indicating the nature of emergency and acknowledging the fact that a full crossmatch has not been performed.

Once a specimen has been typed, type-specific RBCs may be issued, usually within 10 min from the time the blood bank receives the specimen. Although this conserves type O units if the patient is not type O, patients who need blood urgently should not be denied O units. Completing the antibody screen takes about 45 min and adds a small, but measurable degree of safety to the compatibility of selected units.[29] If the antibody

screen is negative and the blood bank is capable of performing a "computer" or "electronic" crossmatch, blood will be ready almost immediately after the screen is completed. If electronic crossmatch is not available, performance of a serological crossmatch in the test tube will add several additional minutes to the process. If the antibody screen is positive, more time will be needed to identify the antibody(ies) responsible so properly matched units can be provided. If life-threatening anemia is present, the transfusing physician must then weigh the risk of not transfusing the patient against the risk of a hemolytic transfusion reaction.

It should be noted that, once again, safety depends upon *correct identification* of the patient and the blood bank sample. These steps cannot be ignored simply because blood is urgently needed. In fact, many preventable life-threatening errors are made under these circumstances.

Over the years, many artificial oxygen carriers, such as perfluorocarbons and bovine hemoglobin, have been developed in order to make available a more universally compatible product in urgent/emergent situations.[3,30] Some have made it to clinical trials, but none have been approved by the FDA for use in the United States. In addition, recent advancements regarding enzymatic conversion of all red cell types to type O have been reported.[31] Such efforts hold promise in making urgent transfusion safer, easier, and less dependent on fluctuating blood inventories.

Massive Transfusion

Massive transfusion involves the replacement of one or more blood volumes within 24 h (~5 L in an average adult), or a bleeding rate of more than 150 mL/min. Metabolic, coagulatory, respiratory, and other types of complications may occur. These often result from tissue damage or hypoperfusion related to trauma or hemorrhage.[32,33] Hypothermia, which may impair hemostasis, can be mitigated by warming the patient, as well as the crystalloid and blood products being infused.

The entire array of products available from the blood bank may be called into play for support of a massive transfusion episode. It is important to make proper use of blood products at appropriate times. Transfusion of RBCs may be determined by history, vital signs, clinical situation, and hematocrit. Together with crystalloid or colloid, efforts are made to restore volume and oxygen-carrying capacity.

Platelet transfusions should be based on platelet count, with the exception of patients known to have taken anti-platelet medication or who have other reasons for platelet dysfunction (e.g., patients who have been on cardiopulmonary bypass or those who have platelet function disorders), thereby rendering the count essentially meaningless. Also, if the platelet count is not available in a timely manner, it may be prudent to give platelets according to a predetermined protocol. Administering blood components using formulas may under- or overestimate the need, but a massive transfusion guideline may prompt the transfusing physician to order laboratory studies and blood products at intervals that will avoid dilutional coagulopathy. Table 34.3 illustrates an example of a guideline for blood product replacement therapy during massive transfusion.

The use of plasma during massive transfusion is based on the INR and PTT, if testing is available in a timely manner. Elevations of these values, to the levels described earlier, may predispose a patient to microvascular (as opposed to surgical) bleeding. It is helpful to have a protocol to guide the physician about the appropriate times to monitor these values. When plasma is required, it is important to remember that FFP requires thawing and may not be immediately available. Some larger institutions may be able to keep a readily available supply of thawed product, but infrequent use may lead to repeated wastage of a valuable resource. Recent data suggest that, once a massive transfusion episode begins, transfusion of red cells and plasma in a 1:1 ratio may provide a survival advantage.[34,35]

Cryoprecipitate may also be required for replacement of fibrinogen during a massive transfusion episode. Thawing and pooling may be required, but since smaller volumes than those for plasma are involved, delay is minimal.

Many patients develop a coagulopathy during massive transfusion, but not all have microvascular bleeding.[36] This may be caused by consumption of coagulation factors or hemodilution. Severe tissue injury and prolonged hypotension make microvascular bleeding more likely. As mentioned, formulas that guide component replacement may result in under- or over-transfusion. Mild-to-moderate prolongation of the INR or PTT does not predict subhemostatic factor levels, but marked prolongations may reflect factor levels below 30%, and should be treated with fresh frozen plasma.[37] If bleeding continues, the platelet count should be kept >50,000/μL.

Persistent bleeding in the face of adequate platelets and coagulation factors requires re-evaluation and possibly, surgical exploration. For patients who continue to bleed despite maximal appropriate component therapy, antifibrinolytics, such as epsilon aminocaproic acid (Amicar, Wyeth-Ayerst, Madison, NJ) may be considered. Alternatively, prothrombin complex concentrates (PCCs) or activated factor VII (FVIIa, NovoSeven, Novo Nordisk Pharmaceuticals, Inc., Princeton, NJ) have been employed under these circumstances. This off-label use of FVIIa is controversial, but there is a body of mostly anecdotal and small series evidence to suggest some value in this setting.[38–41] Table 34.4 highlights some situations during which FVIIa has been used.[39] Doses vary widely in the literature; many institutions administer 30–40 μg/kg. Lyophilized factor is supplied in vials of graded doses, so that the actual dose administered is generally rounded off to the nearest available vial size. For cases in which bleeding continues, a second dose is recommended. FVIIa should be used with extreme caution as there have been reports of thrombotic episodes following its use.[42]

Communication with the blood bank during a massive transfusion episode is critical. A transfusion medicine expert can

Table 34.3. Guideline for blood product replacement therapy during massive transfusion at Lahey Clinic.

Volume of blood transfused (units of RBCs)	Laboratory testing recommended[a]	Platelet count	Platelet therapy (single donor packs)	PT/INR PTT results	Thawed FFP therapy	Fibrinogen level	Cryoprecipitate therapy	Factor VIIa therapy
After 5 units	Platelet count	≤50K	1 pack	INR ≥ 1.5	2 units	Not tested	None	None
	PT/INR PTT	≤25K	2 packs	INR ≥ 2.0	4 units			
				PTT > 44 s	2 units			
After 10 units	Platelet count	≤50K	1 pack	INR ≥ 1.5	2 units	<100 mg/dL	10 units cryoprecipitate	None
	PT/INR PTT	≤25K	2 packs	INR ≥ 2.0	4 units			
	fibrinogen			PTT > 44 s	2 units			
After 15 units	Platelet count	≤50K	1 pack	INR ≥ 1.5	2 units	Not tested	None	None
	PT/INR PTT	≤25K	2 packs	INR ≥ 2.0	4 units			
				PTT > 44 s	2 units			
After 20 units	Platelet count	≤50K	1 pack	INR ≥ 1.5	2 units	<100 mg/dL	10 units cryoprecipitate	Consider factor VIIa therapy
	PT/INR PTT	≤25K	2 packs	INR ≥ 2.0	4 units			
	fibrinogen			PTT > 44 s	2 units			

[a]If microvascular bleeding is noted prior to availability of laboratory results, consider giving 2 units of FFP and 1 dose of platelets.

Table 34.4. Some off-label applications for activated factor VII (VIIa).

Massive transfusion with continued bleeding despite optimal blood component support and surgical intervention	Life-threatening bleeding with thrombocytopenia unresponsive to platelet transfusion
Patients with liver failure and refractory bleeding	Rapid warfarin reversal in bleeding or emergent pre-op patient

offer advice, and help to maintain an adequate flow of product support. Additional guidance regarding massive transfusion and related protocols is available from the American Association of Blood Banks.[43]

Risks of Transfusion

Transfusion of blood products has never been safer, but significant risks remain, including transfusion reactions and transmission of disease. Although these risks should not prevent transfusion under appropriate circumstances, it is prudent to consider them during the decision-making process. When possible, the patient should provide informed consent for transfusion.

Transfusion Reactions

Transfusion reactions can be divided into acute or delayed categories, and subdivided into immunologic or non-immunologic types. Acute immunologic reactions include febrile nonhemolytic, urticarial (allergic), anaphylactic, transfusion-related acute lung injury, and hemolytic. Acute non-immunologic reactions include sepsis due to contaminated blood products and volume overload. Delayed immunologic reactions include hemolytic, alloimmunization, graft-versus-host disease (GVHD), and transfusion-related immunosuppression (TRIM). Iron overload is a delayed non-immunologic process.

Febrile nonhemolytic reactions are common. Recipient antibodies may react with transfused white cells or platelets, donor antibodies may react with recipient cells, or cytokines present in donor blood may cause a response in the recipient.[44,45] Signs and symptoms include fever during or within 2 h of completing the transfusion, chills, headache, tachycardia, and myalgias. Transfusion should be discontinued immediately and a reaction workup initiated. Therapy is generally supportive, including administration of an antipyretic, such as acetaminophen, and meperidine if chills are severe. Febrile episodes associated with transfusion should be given the benefit of a doubt until hemolysis is ruled out by the laboratory. Prevention includes premedication with antipyretics prior to future transfusions and, for those patients who have repeated episodes, transfusion of leukoreduced (if not already filtered) cellular products.

Allergic (urticarial, dermal hypersensitivity) reactions are also common.[46] These reactions result when the recipient is sensitized to donor plasma proteins or antibodies in the donor plasma interact with recipient proteins. Signs and symptoms include urticaria, flushing, itching, and erythema. There may be facial and/or glottal edema and respiratory distress. Therapy consists of administration of an antihistamine. In patients who respond to therapy, transfusion of the same product may be restarted, but if symptoms recur, that unit should be discontinued. Prevention is by administration of antihistamines prior to future transfusions and, if severe and repetitive, by washing cellular products. Administration of steroids prior to transfusion may also be considered in particularly refractory cases.

Anaphylaxis is relatively rare. The classic description is that of an IgA-deficient patient with preformed antibodies to IgA who receives blood from a donor with a normal level of IgA,[47] but other similar interactions can also cause anaphylaxis. Signs and symptoms include anaphylactic shock after as little as 5 mL of product. Hypotension, flushing, rash, chills, coughing, respiratory distress, abdominal cramping, vomiting, diarrhea, and loss of consciousness may all be seen. Therapy is supportive and includes administration of epinephrine, oxygen, and volume resuscitation. Patients with IgA deficiency and antibodies to IgA should receive washed cellular products or those from known IgA deficient donors. Since plasma cannot be washed, IgA-deficient donors are the only source of plasma for such patients. Alternatively, if blood loss is anticipated, e.g., during an elective surgical procedure, pre-donation of autologous blood accompanied by separation and freezing of the plasma may be helpful.

Transfusion-related acute lung injury (TRALI) is also relatively unusual, but it has recently been reported that it is now the leading cause of transfusion-associated death. Thus, the FDA and a number of blood transfusion organizations and establishments have placed a priority upon reducing its incidence. The proposed mechanisms for TRALI are somewhat complex, but one basic common description involves the interaction of incoming donor human leukocyte antigen (HLA) or neutrophil antibodies with antigens on the recipient's white cells. Clumps of white cells then become trapped in pulmonary capillaries and their products cause vasodilation and capillary leak; pulmonary edema results. A "two-event" model has also been proposed.[48] In this model, the first event is activation of the pulmonary endothelium and sequestration of neutrophils. These are caused by the patient's underlying condition (e.g., surgery, infection, TTP). The second event is the infusion of lipids or antibodies that accompany transfusion of a blood product, resulting in activation of the adherent white cells. This is followed by endothelial damage and capillary leak. Signs and symptoms include acute respiratory insufficiency without heart failure, dyspnea, hypotension, fever, tachycardia, frothy sputum, and a characteristic chest radiograph. The diagnosis is clinical, as testing involves donor as well as recipient samples, and results are not immediately available. Therapy is again supportive, with fluid and oxygen supplementation. Steroids and diuretics tend to be of little help, but fortunately, most episodes resolve within 24–72 h. Since the reaction is donor specific, there is no strategy for the prevention of recurrence in a particular patient who has experienced TRALI; however, reporting is encouraged because the blood collection center can defer donors whose units have been associated with TRALI, thereby sparing future recipients from possible reactions.

Acute hemolytic reactions are also relatively rare. The vast majority are caused by human clerical error, e.g., the phlebotomist drawing the wrong sample by misidentifying the patient or mislabeling the tube, staff hanging blood on the wrong patient, the blood bank giving out the wrong unit of blood. As previously mentioned, such errors are typical in acute care areas (operating room, emergency room, ICU), but can happen in any setting. Hemolysis is usually caused by the transfusion of ABO incompatible blood; e.g., giving A blood to an O patient (with naturally occurring anti-A). Recipient antibodies to donor red cell antigens in other blood groups (Kell, Kidd) may also cause hemolysis. Signs and symptoms include, fever, chills, back pain, and dyspnea.[49] The patient may experience a burning sensation along the vein used for infusion. Headache, chest pain, hypotension, shock, oliguria, nausea, feeling of impending doom, generalized bleeding due to DIC, hemoglobinuria, hemoglobinemia, and cardiac arrest may also occur. Vigilance is necessary because fatalities have occurred after transfusions of as little as 30 mL. When a reaction is suspected, transfusions should always be disconnected at the needle hub, because even the 10–20 mL of blood in the tubing can make a major difference in outcome. Beyond the resuscitative efforts that may be required, particular attention is paid to diuresing the patient in order to prevent renal shutdown from precipitation of free hemoglobin in the kidney. Prevention lies in a rigorous quality program to avoid misidentification of patients, and mislabeling of blood specimen tubes and blood products.

Septic reactions are also rare, but are more common from platelets because platelets are stored at room temperature. These events are often the result of infusion of bacterially contaminated blood products, either from unsterile collection or improper storage. Signs and symptoms include fever, chills, hypotension, vomiting, shock, and DIC.[50,51] Treatment is supportive, with efforts centered on resuscitation, fever reduction, and appropriate antibiotic therapy. Some surveillance testing mechanisms are in place for some platelet products, and others have been proposed or are in development.

Volume overload, often termed transfusion-associated circulatory overload or TACO, is caused by administering fluid too quickly or in too great a quantity to susceptible patients, generally in the setting of heart or renal failure.[52] Signs and symptoms include cough, dyspnea, tachycardia, rales, pulmonary edema, distended neck veins, hypertension, and headache. Diuresis may be necessary to remove fluid. Prevention includes reducing rates of infusion and avoidance of overtransfusion. Splitting units in the blood bank and transfusing each half over a longer period may also be considered.

Thermal, mechanical, or oncotic hemolysis may rarely be caused by improper handling of blood; e.g., warming in an unapproved or malfunctioning device, storing in a non-certified refrigerator, passing blood through a malfunctioning pump, allowing hypotonic solutions like D5W instead of normal saline to come into contact with the blood. The point is twofold: (1) the blood product may be destroyed and (2) the result may simulate a hemolytic transfusion reaction. Again, it is important to handle and administer blood products properly to allow for safe and effective transfusion.

Alloimmunization is a delayed event seen in up to 20% of multiply transfused patients and is caused by exposure to foreign antigens. The recipient can form antibodies against

red cells, white cells, or platelets through transfusion or pregnancy. Delayed hemolytic reactions may initially go unrecognized because they are generally less dramatic than their acute counterparts. These reactions result from the late formation of antibodies against antigens on transfused red cells, causing destruction of transfused cells over a 6-week to 3-month period.[49,53,54] Signs and symptoms include fever, chills, falling hematocrit, and jaundice. Treatment is usually conservative, but a blood sample must be worked up by the blood bank to identify any new antibodies. Prevention is provided by giving future units that are negative for the antigens against which the patient's antibodies are directed, but this does *not* prohibit formation of antibodies against new antigens in subsequently transfused blood products.

Refractoriness to platelet transfusions may result when antibodies are directed against HLA or platelet antigens. Platelet refractoriness can, indeed, be a very difficult problem, especially if the antibody is against a common antigen in blood donors. One way to prevent this form of refractoriness in an already immunized patient is to transfuse platelets with a similar or identical HLA type,[55] or in the case of platelet antibodies, a similar platelet type. Crossmatching of platelets may also be helpful.[56] Despite these efforts, some patients continue to remain refractory, and may be at risk of developing life-threatening hemorrhage. If such patients are not bleeding, platelet transfusions should be avoided since they provide no benefit to the patient and may be used to help others. Transfusion of leukoreduced products may help to reduce the incidence of platelet refractoriness by lowering exposure to the immunizing stimulus.[57]

Transfusion-associated graft-versus-host disease (TA-GVHD) is extremely rare. It develops when donor lymphocytes engraft into the bone marrow of an immunosuppressed patient, setting up an immune response where the donor cells recognize the host as foreign, causing an immune "rejection."[58,59] This can manifest as a combination of rash, mucositis, diarrhea, and hepatosplenomegaly. Unfortunately, GVHD following transfusion is almost universally fatal. Prevention requires irradiation of all cellular products for patients at risk, as described previously.

Although the exact mechanisms underlying TRIM still remain to be elucidated, allogeneic blood transfusions have been shown to cause a decrease in the helper/suppressor T-lymphocyte ratio and a decrease in natural killer cell function as well. In addition, allogeneic blood transfusions have been associated with defective antigen presentation, the suppression of lymphocyte blastogenesis, and a reduction in delayed-type hypersensitivity and allograft tolerance.[60]

Transfusion-Transmitted Diseases

Transmission of disease by transfusion has, of course, been a great cause for concern for patients and healthcare providers alike. Thanks to many developments over the past two decades, transfusion has never been safer than it is today.[61] Pre-donation questionnaires help to screen out potentially risky donors, while technological advances in testing help to detect known diseases. For example, nucleic acid testing (NAT) for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) began in 1999. This is a PCR method that can detect the presence of the virus prior to the body mounting an immune response (seroconversion), i.e., during the "window period." This testing can detect the presence of HIV several days before seroconversion and HCV several weeks before seroconversion. NAT for West Nile Virus has been added more recently.[62]

Unfortunately, there remain window periods for many agents, and others have yet to be identified. Table 34.5 lists many of the agents currently known and their associated risks from blood transfusion.[63]

Table 34.5. Some transfusion-transmitted diseases and associated risks.

Agent	Risk
Viral	
Hepatitis A	1:1,000,000
Hepatitis B	1:220,000
Hepatitis C	1:1,800,000
HIV	1:2,300,000
HTLV-I and -II	1:2,993,000
Parvovirus B19	1:20,000 to 1:50,000
CMV	Rare
Epstein-Barr	Rare
West Nile	Rare
Bacterial	
Gram-positive	1:75,000 to 1:500,000 (platelets more likely)
Gram-negative	1:75,000 to 1:500,000 (platelets more likely)
Syphilis	Rare
Parasitic	
Chagas' disease	Several reports
Babesiosis	1:1,800 in endemic regions
Leishmaniasis	Described in endemic areas
Malaria	1:4,000,000
Prions	
Creutzfeldt-Jakob disease	Rare, but reported

Utilization Review

Utilization review and the establishment of safe transfusion practices are important parts of ensuring quality care.[64,65] Utilization review provides quality assurance, assessment, and improvement. It optimizes therapy while minimizing risk, and improving cost-effectiveness. It is also required for institutional accreditation by agencies such as the Joint Commission. These functions are often performed under the auspices of the institution's transfusion committee. This committee may be responsible for assisting medical staff in using blood products appropriately; evaluating performance of the blood

Table 34.6. Annual evaluation of blood component utilization review at Lahey Clinic.

Component	Products issued	Orders reviewed	Orders approved	Orders denied
Plasma	3,555	26	17	9
Platelets	1,162	32	18	14
Cryo	450	5	2	3
Total	5,167	63	37	26

bank; and formulating guidelines for ordering, distributing, handling, dispensing, and administering blood products. The membership generally consists of representatives from the blood bank, as well as users across all of the clinical services, including physicians and nurses.

Several methods may be used to perform utilization review.[64] Prospective review occurs when orders are reviewed *prior* to transfusion based on available laboratory and clinical data. Retrospective review occurs when orders are reviewed *after* the transfusion has occurred, usually by examining the medical record. Finally, concurrent review occurs when orders are reviewed within 24 h of transfusion, while the event is fresh in the clinician's mind. Any one or a combination of these may be used in the process. When established criteria are not met, the ordering physician is contacted to provide justification for the transfusion. This dialog provides the opportunity for education in both directions, for the reviewer regarding possible new practices that may be emerging, and for the ordering physician regarding the established practices of the institution. Thus, it should *not* be adversarial. On the other hand, if repeated events occur in the absence of evidence-based medicine, a mechanism is provided to forward the matter to a peer review setting.

An example of a recent annual review at our institution appears in Table 34.6. This resulted in the avoidance of 26 unnecessary component exposures, a direct cost savings of about $8,000 in products and some savings in administration costs, indirect savings by avoiding transfusion reactions, conservation of resources, and improved compliance with institutional guidelines.

Conversely, it is important to consider the possibility of under-transfusion. This is more difficult to monitor, but can be performed using prospective review. The volume of the order can be checked against the pre-transfusion counts or other laboratory values. For example, plasma or platelet orders can be reviewed to ascertain whether or not they can be expected to meet the intended target.

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Part VII
Metabolism and Nutrition

35
Hyperglycemia in the Surgical Intensive Care Unit

Gary W. Cushing

Introduction

Hyperglycemia is the most common metabolic disturbance seen in the postoperative, intensive care patient. It can occur in patients with previously diagnosed diabetes mellitus, with undiagnosed diabetes,[1] and in patients without diabetes under the acute stress of trauma, surgery, or myocardial infarction.[2] Critical illness induces insulin resistance at the cellular level, which coupled with relative insulin inadequacy and unabated hepatic glucose release, leads to persistent elevation in blood glucose. A number of factors released during acute illness and stress act as mediators for this response, including cytokines, growth hormone, glucagon, catecholamines, and cortisol.[3] Impairment of insulin action leads to lipolysis and protein catabolism that produce substrates for additional glucose production by the liver. Glycogenolysis is promoted by release or administration of catecholamines. Insulin-mediated glucose uptake by heart and skeletal muscle is impaired and further worsens glucose homeostasis. To some extent, the resultant increase in blood glucose can be adaptive to provide increased substrate to organs that do not require insulin for glucose uptake such as brain and blood cells. Not surprisingly, when pushed to the extreme by critical illness these accommodations can lead to untoward consequences requiring interventions in order to reverse this metabolic derangement.

Hyperglycemia and Adverse Clinical Outcomes

A large body of evidence has accrued showing a correlation between degree of stress-induced hyperglycemia and adverse clinical outcomes (Table 35.1). This relationship holds true with or without a prior diagnosis of diabetes. A report from the Mayo Clinic of more than 1,800 patients admitted to medical-surgical intensive care units documented a strong correlation between level of glucose and hospital mortality. With mean glucose values between 80 and 99 mg/dL, the hospital mortality was nearly 10% and it increased progressively as glucose values increased, exceeding 40% among patients with mean glucose levels above 300 mg/dL. The use of glucose values added predictive power above that achieved by Acute Physiology and Chronic Health Enquiry (APACHE) II scores alone.[4] Likewise, in patients with brain injury, hyperglycemia is associated with poorer neurologic outcomes, increased intracranial pressure, and longer hospital stays.[5] In children with burns, higher glucose levels are correlated to bacteremia and greater need for skin grafts.[6] Trauma patients suffer longer intensive care unit (ICU) stays, increased infection rates, and mortality when they present with elevated glucose.[7] Intraoperative hyperglycemia in cardiac surgery patients represents an independent risk factor for perioperative complications.[8] Similar deleterious effects of glucose have been seen in patients with myocardial infarction and the development of congestive heart failure and in stroke patients with resultant poor functional recovery.

These observations suggest an important connection between glucose metabolism and pathophysiologic processes. The establishment of a causal relationship requires evidence that glucose control can ameliorate the adverse consequences. Several lines of evidence now point strongly in that direction. Before examining those data, an overview of the diabetic condition is warranted.

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TABLE 35.1. Hyperglycemia and adverse outcomes.

Condition	Adverse outcome
SICU	↑Hospital mortality
	↑Complications
Brain injury	↑Intracranial pressure
	↑Neurologic dysfunction
	↑Hospital stay
Burns	↑Bacteremia
	↑Skin graft numbers
	↑Mortality
Trauma	↑ICU stay
	↑Infectious morbidity
	↑Mortality rates
Cardiac surgery	↑Perioperative complications
	↑Sternal wound infection

TABLE 35.2. Type 1 and Type 2 diabetes – distinguishing features.

Feature	Type 1	Type 2
Etiology	Autoimmune beta cell destruction	Insulin resistance relative insulin deficiency
Family history	3%	30–50%
Clinical onset	More rapid	Gradual
Age at onset	Younger	Older
Ketoacidosis prone	Yes	No
Therapies	Insulin from onset	Oral medications then insulin

Diabetes Mellitus

Prevalence and Nomenclature

Diabetes is present in the United States in approximately 7% of the entire population, 9% of the adult population, and nearly 20% of those 60 years or older, and the incidence is rising annually. Impaired glucose tolerance is present in an even higher percentage. In 2004, in the USA, there were 6.3 million hospitalizations for patients with diabetes. The large majority (>90%) of patients with diabetes have Type 2 diabetes. The remainder will have Type 1 diabetes with smaller fractions presenting with diabetes due to pancreatectomy, infiltrative diseases such as hemochromatosis, infections such as hepatitis C, or related to medication usage – especially acute corticosteroids. The major determination that is of critical importance in the postoperative and ICU setting is distinguishing between Type 1 and Type 2 patients (Table 35.2). Type 1 diabetes results from an autoimmune attack on the islet cells of the pancreas rendering the patient essentially completely insulin deficient. These patients are prone to developing diabetic ketoacidosis if insulin is withheld or given in even moderately insufficient amounts. Moreover, in the patient who is NPO (nothing by mouth) and may have depletion of hepatic glycogen stores, blood glucose may not rise to the typical high levels usually associated with ketoacidosis.[9,10] However, this condition can develop rapidly, even in the hospital setting, unless careful attention is paid to glucose, electrolyte, and acid-base monitoring. The proper identification of a patient as having Type 1 diabetes can alert the intensivist to the need for mandatory glucose monitoring and insulin administration. The most common mistake is made in the older patient on insulin by assuming that they have Type 2 diabetes and, hence, can be made NPO and maintained on a sliding scale insulin protocol without basal insulin administered. The features listed in Table 35.2 that should raise the suspicion for Type 1 diabetes include the patient's history of onset in youth, no history of oral anti-diabetic medications, prior history of ketoacidosis, coexistent autoimmune diseases, or prior positive islet cell antibodies.

Complications

Diabetic complications are traditionally grouped into microvascular and macrovascular complications. The microvascular complications include retinopathy resulting in vision loss, nephropathy with nephrotic syndrome, renal failure and dialysis, and neuropathy with foot ulcers. The macrovascular conditions encompass the usual atherosclerotic diseases, but are overrepresented in terms of frequency and severity in the patient with diabetes. These include coronary artery disease with angina and infarction; cerebrovascular disease with stroke; and peripheral vascular disease leading to claudication, extremity ischemia, and gangrene. These complications increase the adoption of surgical procedures such as coronary artery bypass grafting, vascular access and renal transplantation, lower extremity arterial bypass, and amputations. Evidence of these complications should be sought in the postsurgical or trauma patient as their presence can affect management of the acute illness for which they are being treated.

Special attention needs to be paid to the diabetic patient with regards to cardiac ischemia. The intubated or comatose patient who cannot express symptoms or the conscious patient who may have silent ischemia[11] and not manifest symptoms can develop postoperative ischemia or infarction without warning. In addition, autonomic neuropathy due to diabetes is a risk factor for cardiac arrhythmia and sudden death.

Renal function is often compromised in the patient with long-standing diabetes who exhibits proteinuria or microalbuminuria. Serum creatinine or estimated glomerular filtration rate should be carefully monitored. These patients are susceptible to all the usual renal insults that often accompany a stay in the ICU. Nephrotoxic agents such as aminoglycosides, amphotericin, cyclosporine, and NSAIDs must be used judiciously and with appropriate monitoring. Iodinated contrast agents often employed for imaging are another potential source of injury to the diabetic kidney.

Medical Therapy

The rapidly increasing incidence of diabetes has led to a number of new medical therapies to treat both Type 1 and more so, Type 2 diabetes. It is not uncommon for patients admitted to the intensive care area to be on multiple agents for their glucose control. In addition to several newer insulin analogs, numerous oral and parenteral agents are now available to treat this disease (Table 35.3). In general, most of these drugs will not be appropriate for the intensive care setting and will be temporarily discontinued in favor of insulin, but an awareness of their actions and particularly side effects is needed.

Specific concerns by class include hypoglycemia with longer acting sulfonylureas such as glyburide. This effect may persist long after the drug has been discontinued and is accentuated in the presence of renal insufficiency. Likewise, metformin can persist in the circulation when the glomerular filtration rate (GFR) is depressed and can precipitate a lactic acidosis – although the risk may be overstated, at least in cardiac surgery patients with normal renal function.[12] Thiazolidinediones, such as pioglitazone and rosiglitazone, which act as insulin sensitizers, have fairly long biologic half-lives effecting nuclear transcription. The most worrisome effect of these drugs in the acute ICU setting is the retention of salt and water and propensity to aggravate or induce congestive heart failure.[13] They should be avoided in the decompensated cardiac patient until hemodynamics are stabilized and the patient can be reassessed.

Two newer agents include the glucagon-like-peptide 1 (GLP-1) analog, exenatide, and the dipeptidyl-peptidase-4 inhibitor, sitagliptin. These drugs work respectively by acting as a GLP-1 agonist or by inhibiting the enzyme that breaks down endogenous GLP-1. The result is stimulation of insulin release by GLP-1 receptors on beta cells, glucagon suppression, and centrally mediated appetite suppression and reduced gastric emptying. The latter effects would be a concern in the case of acutely ill patient, especially with reduced gut function. Pramlintide, an injectable amylin analog used in conjunction with insulin in the outpatient venue, likewise contributes to these latter effects on glucagon secretion and stomach emptying and therefore, should be held in the ICU.

A variety of short- and long-acting insulin analogs are now commonplace in the management of diabetes (Table 35.4). They fall into short-, intermediate-, and longer acting categories. The short-acting agents are analogs of regular insulin and have similar kinetics with onset of action, when given subcutaneously, of 5–15 min, and duration of action of about 3–4 h. They are the insulins of choice for pre-prandial administration and can be used in sliding scale protocols. The neutral protamine Hagedorn (NPH) products represent intermediate-acting insulin. The peak and trough effects of NPH can present a problem in the patient who is NPO or who is on a fixed hourly calorie intake. The longer acting insulins glargine and detemir are relatively peakless in their pharmacodynamics and can serve as basal insulins in a subcutaneously administered program. They should not be mixed with short-acting analogs or regular insulin. These agents work well for patients on enteral tube feedings where the calorie intake is fixed and consistent.[14] When a longer acting insulin is on board, care must be taken to ensure that the source of enteral calories is discontinued. Instead, intravenous glucose should be supplemented to avoid hypoglycemia.

TABLE 35.3. Medical therapies for diabetes.

Drug class	Route	Action	Side effects
Sulfonylureas Glyburide Glipizide Glimepiride	Oral	Stimulates insulin secretion via SU receptor on beta cell	Hypoglycemia can be prolonged
Meglitinides Repaglinide Nateglinide	Oral	Stimulates meal-initiated insulin secretion	Hypoglycemia shorter duration
Biguanide Metformin	Oral	Insulin sensitization reduces hepatic glucose output	Rarely lactic acidosis avoid in hemodynamic or renal instability
Thiazolidinediones Rosiglitizone Pioglitazone	Oral	Peripheral insulin sensitizer Ppar gamma agonist	Fluid retention, edema avoid in CHF
Disaccharidase inhibitors Acarbose Miglitol	Oral	Inhibits carbohydrate breakdown	Intestinal gas
Exenatide	sq	GLP-1 analog stimulates insulin release suppresses appetite reduces glucagon secretion	Delayed gastric emptying hypoglycemia
Sitagliptin	po	DPP-4 inhibitor raises GLP-1 levels	Delayed gastric emptying hypoglycemia
Pramlintide	sq	Amylin analog suppresses glucagon increases satiety	Delayed gastric ehypoglycemia with insulin

TABLE 35.4. Insulins.

Insulin	Onset	Duration	Utility
Short acting			
Regular	30–45 m	5–8 h	IV infusion hyperglycemic coverage
Lispro (Humalog)	15 m	3–5 h	Pre-prandial meal coverage
Aspart (Novolog)			Coverage scales
Glulisine (Apidra)			sc infusion pumps
Intermediate acting			
NPH	1–3 h	12–15 h	Bid split dose regimens
Long acting			
Glargine (Lantus)	1–2 h	24 h	Basal insulin
Detemir (Levemir)	1–2 h	12–24 h	Peakless

Glycemic Control

Evidence for Benefit

Convincing evidence has accumulated for the benefit of tight control of blood glucose in preventing the chronic complications of diabetes. The now classic Diabetes Complication and Control Trial (DCCT)[15] and the subsequent follow-up Epidemiology of Diabetes Interventions and Complications (EDIC)[16] trial have demonstrated reduction in the risk of microvascular and macrovascular complications, respectively, in patients with Type 1 diabetes. Likewise, the United Kingdom Prospective Diabetes Study (UKPDS) showed similar findings in Type 2 patients.[17] These results spurred initiatives to translate this degree of glycemic control to hospitalized settings. As already reviewed, hyperglycemia presents an increased risk for a number of poorer outcomes in patients undergoing surgery. Several lines of evidence offer explanations for poorer outcomes with hyperglycemia including increased production of free radicals, oxidative stress, toxic effects on leukocyte function, and increased proinflammatory state with elevated cytokines.[18] Likewise, hyperglycemia is associated with elevations in free fatty acids, which are detrimental to cardiac function, decreased nitric oxide activity, and increased levels of plasminogen activator inhibitor-1.[19] These abnormalities could contribute to infection, reduced tissue healing, decreased cardiac function, and a hypercoagulable state. Evidence has mounted that these complications can be reduced with due attention to glucose control.

One of the earlier studies documenting benefit from intensive insulin therapy showed a 66% reduction in deep sternal wound infections after cardiac surgery.[20] Later, the Portland Project demonstrated reduction in mortality in these patients from 5.3 to 2.5%, with the lowest mortality in patients whose serum glucose levels were kept under 150 mg/dL.[21]

The landmark study from Leuvin, Belgium was a prospective trial of intensive insulin therapy in a surgical ICU setting. More than 1,500 mechanically ventilated patients were randomized to keep glucose levels between 80 and 110 mg/dL or treated only for glucoses >220 mg/dL. An insulin-infusion protocol was used to maintain control within the parameter range. In the prolonged critically ill group, mortality was reduced from 20.2 to 10.6%. Benefit was seen regardless of a preadmission diagnosis of diabetes. Additional improvements were seen including duration of ventilatory support, intensive-care stay, number of blood transfusions, incidence of bacteremia, critical illness related neuropathy, and acute renal failure.[22]

An observational study of 800 patients on a medical-surgical floor comparing outcomes before and after instituting intensive insulin protocols showed a 29% reduction in mortality, fewer transfusions, and shorter ICU stays.[4] Similar findings were found in hospitalized patients with strokes when their glucose levels were maintained between 110 and 126 mg/dL.[23]

In a medical critical care setting of post-myocardial infarction, similar benefits of near-normal glucose control have been demonstrated. In the Diabetes and Insulin-Glucose Infusion in Myocardial Infarction (DIGAMI) trial, patients with myocardial infarction and hyperglycemia were randomized to 34 h of glucose and insulin infusion followed by 3 months of multiple daily injections of insulin versus standard therapy. One-year mortality was reduced by 30% in the intensively treated group, which persisted to the 3-year mark.[24] Although a follow-up trail, DIGAMI 2,[25] did not reproduce those results, it should be noted that the standard of care in the control group at the time of the second trial had improved and the treatment arm did not achieve the tight glycemic goals desired. This may have negated the statistical significance of benefit.

Two additional studies employed glucose-insulin-potassium (GIK) infusion in vascular-event populations: the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiologicos Latin America (CREATE-ECLA)[26] and the Glucose Insulin in Stroke Trial (GIST).[27] Neither showed a reduced morbidity or mortality. Of note, the goal of these studies was not to try to improved glucose control but rather the infusion of insulin using glucose and potassium. In fact, in CREATE, the GIK-treated patients actually had higher blood glucose levels than the control group.

Finally, a meta-analysis of 35 studies in critically ill adult patients found a 15% short-term reduction in mortality with intensive insulin therapy over a range of clinical settings.[28] Taken together, the evidence showed better outcomes with nearer normal glucose levels in the intensive care setting. As a result, a more regimented glycemic control has now become the standard of care. This improvement in survival comes with an actual financial benefit. Costs were compared over a 12-month time frame in approximately 600 surgical ICU patients who were given either standard glucose control or intensive glucose monitoring and control. Total costs decreased from $4.1 to $2.9 million – an impressive 30% savings.[29]

Intraoperative Glycemic Control

Extrapolation of improvement in outcomes from the intensive care setting to the operating room would appear to be a logical process. An observational study indicated that poorer intraoperative glucose control was associated with an increase in hospital cardiovascular, neurologic, renal, and respiratory complications. Infectious morbidity, however, remained unchanged.[30] A retrospective review from the Mayo Clinic suggested that intraoperative hyperglycemia was a risk for adverse postoperative complications in patients undergoing cardiac surgery.[31] This same group, in a prospective study, failed to show a reduction in hospital stay, sternal infection, morbidity, or mortality in a randomized arm that received tight glycemic control (80–100 mg/dL) versus a control arm treated only for glucose levels above 200 mg/dL.[32] One has to ask,

however, in the setting of tight postoperative glucose control for 72 h, how much additional benefit could be expected from the relatively short intraoperative hours of improved glycemia? Until further information is available, tight control of glucose levels should be initiated in the post-op intensive care setting, at least in cardiac patients.

Insulin Therapy

Infusion Protocols

Intravenous insulin infusion is the appropriate treatment for diabetic ketoacidosis, non-ketotic hyperosmolar state, post-cardiac or non-cardiac surgical ICU glucose control, or any patient with critical illness who is kept NPO. In addition, intravenous insulin is the treatment of choice where total parenteral nutrition (TPN) is employed and hyperglycemia is threatening, either by separate insulin infusion or by insulin within the TPN solution. A number of published protocols have proliferated. Most share similar features:

- Glucose threshold to initiate infusion
- Predetermined target glucose range
- Frequent bedside glucose monitoring
- Constant infusion of glucose when necessary
- Algorithm for adjusting dose to reach glucose target
- Mechanisms to avoid hypoglycemia

Initiation of an insulin infusion should commence when acceptable thresholds for glycemia are exceeded or if patients exceed 140 mg/dL while already on subcutaneous basal and/or correction insulin therapy (Table 35.5). Based on current data, the target glucose for critically ill patients should be 80–110 mg/dL. For less severely ill surgical and non-surgical patients, a target of 90–140 mg/dL may be acceptable.[33] To assure that goals are reached and not exceeded, hourly to every 2 h bedside glucose monitoring is required. Glucose infusions are not required initially when hyperglycemia is marked or when there is a high degree of stress such as post-cardiac surgery. In addition, in order to maintain glucose levels, the prolonged use of insulin infusions will need to be accompanied by a constant source of glucose, either by enteral or parenteral nutrition or with intravenous glucose infusions.

TABLE 35.5. Thresholds for initiation of intravenous insulin.[33]

Status	Glucose threshold mg/dL
Perioperative care	>140
Surgical ICU	>110–140
Nonsurgical illness	>140–180
Pregnancy	>100

TABLE 35.6. Insulin infusion protocols.

Source	Author	Reference
Leuven, Belgium	Van den Berghe	22
University of NC	Braithwaite	33
Portland Protocol	Furnary	34
Yale	Goldberg	35
Atlanta	Bode	36

Numerous insulin algorithms have been devised to maintain target blood glucose (Table 35.6).[34–36] Several key elements of an effective protocol include:

- Consistent concentration of regular insulin in the solution
- Intravenous priming bolus of insulin if appropriate
- Initial infusion rate
- Frequency of monitoring
- Adjustment of infusion rate that takes into account both current glucose concentration and rate of change of glucose level
- Possible re-bolusing for persistent hyperglycemia
- Threshold glucose level that stops insulin infusion for hypoglycemia
- Resumption of infusion at readjusted rate after hypoglycemia is treated
- Parameters to notify physician for marked or prolonged hypo- or hyperglycemia not responding to protocol

The long-range goal over several hours is progressively smaller oscillations of glucose levels until the target glucose range is reached and maintained. Practical aspects of the protocol include: single-order entry to initiate, ease of implementation, appropriate training of nursing personnel, and 24-h review of orders. With these types of protocols, it is usually possible to achieve glucose levels in the target range within 6 h of start-up, and to maintain at target as long as necessary with a minimum of hypoglycemia.

Hypoglycemia Correction

Hypoglycemia (blood glucose <50 mg/dL) has been the major barrier to institution of insulin infusion protocols or any program of tight glycemic control. Valid concerns exist especially in the ICU where patients may not be able to express symptoms. Sudden tachycardia, rise in blood pressure, and diaphoresis are initial adrenergic signs that can be followed in the conscious patient by irritability, confusion, combativeness, seizure, or coma. Frequent glucose testing is the best defense. When hypoglycemia does occur in the patient who is NPO, correction with intravenous bolus of 50% dextrose solution (D50) is the best approach. Fifty milliliters provides 25 g of glucose and will raise blood glucose, on an average, by 125 mg/dL. To avoid overcorrection, the amount of D50 solution necessary to bring glucose levels back to 100 mg/dL can be calculated from the formula:

$$(100 - \text{current BG}) \times 0.4 = \text{mL of D50\% solution as IV}$$

Insulin adjustment and institution of maintenance caloric support are keys to preventing recurrence. For persistent hypoglycemia, consideration should be given to search for complicating conditions such as adrenal or pituitary insufficiency including prior prolonged corticosteroid use, sepsis, liver failure with decreased substrate release, and renal failure with prolongation of insulin effects. More common causes include undetected or unexpected interruption of calorie intake and prior administration of long-acting insulin secretagogues such as glyburide coupled with renal insufficiency. The latter can result in prolonged hypoglycemia that may take up to 72 h to correct. Current assessment and management of hypoglycemia can keep this complication to a minimum and should not dissuade the clinician from aiming at tight glucose control.

Transitioning to Subcutaneous Regimens

When the patient is hemodynamically stable, with good tissue perfusion and is ready to take oral calories, transition from intravenous insulin infusion to subcutaneous insulin can be instituted if hyperglycemia persists. The components of a subcutaneous regimen are calorie intake, glucose monitoring, and basal insulin and prandial insulin administration. These components are devised to proactively maintain near-normal glycemia in contrast to the former approach of sliding scale insulin coverage to treat undesirable hyperglycemia.

Basal Insulin

If the patient has been on an insulin infusion, the basal insulin can be given with an agent such as glargine that has 24-h duration of action. The initial dose can be calculated by determining the mean hourly insulin units given over the last 6 to 8 h of a stable insulin infusion, multiplying times 24 and giving 70–80% of this as subcutaneous glargine. As mentioned earlier, basal insulin is critical for Type 1 diabetic patients, especially those who are at the mercy of exogenous insulin administration, in order to avoid diabetic ketoacidosis (DKA). On certain occasions, basal insulin may also be necessary for the Type 2 diabetic and hyperglycemic patient. In order to maintain tight control, the glargine dose is readjusted upward or downward every 24 h based on response. Values below 80 mg/dL require glargine dose reduction of 10–20%, those within target range can be maintained on the same dose, whereas values >150 mg/dL can have the dose increased by 10–20%.

Pre-prandial Insulin

If continuous tube feeding is to be the only source of enteral calories initially, only a basal insulin program is required. A correction scale with regular or analog rapid-acting insulin can be superimposed on an every 6-h basis starting at glucose values of 150 mg/dL. For the patient who will begin liquid or solid meals, preprandial insulin should be given in anticipation of the calories. Any of the short-acting analogs can be used 5–15 min prior to the meal or, in cases of uncertain intake, immediately with or after the meal. The common error to be avoided is the so-called sliding scale that only gives short-acting insulin when the glucose exceeds 200 mg/dL. This is likely to result in unacceptable glucose control. In a known diabetic patient who has been on insulin, the dosing can be estimated by the home doses adjusted for anticipated intake, surgical or infectious stress, and previous 24-h requirements. In the patient previously on oral diabetic medications, a minimum of 3–5 units of rapid-acting analog is usually required if the patient will be taking meals. Correction scales from there can go up by 1–3 units/50 mg/dL, depending on the level of insulin resistance. Pre-printed or electronic algorithms have been devised for different intensities of correction. Daily reassessment is needed as long as the patient is in the intensive care setting.[37] In appropriate patients, transition back to oral diabetic medications can be initiated after the patient is transferred to the general surgical floor.

Special Circumstances

Diabetic Ketoacidosis

In Type 1 diabetic patient and rarely in Type 2 patient, severe or absolute insulin deficiency can lead to the development of DKA. Common precipitants can include surgical stress, infection, myocardial infarction, trauma, and failure to supply insulin. This metabolic derangement is characterized by a metabolic acidosis caused by the production of ketoacids. Ketoacids develop as the by-product of utilizing lipid for energy due to the effective unavailability of glucose to the cell that results from absence of insulin. The absence of insulin also promotes lipolysis that fuels ketoacid production. The hallmarks of this syndrome include metabolic acidosis with anion gap, hyperglycemia, hyperosmolality, glycosuria, and polyuria leading to marked hypovolemia, culminating in pre-renal azotemia. Clinical features include hyperventilation (Kussmaul's breathing), tachycardia, hypotension with postural features, nausea, vomiting, and abdominal pain that can mimic acute abdomen. Laboratory findings include pH < 7.2 (unless mixed acid-base disturbances are present); serum bicarbonate <15 mEq/L; calculated anion gap >12; and elevated concentrations of serum acetone, beta-hydroxybutyrate, as well as urine acetone. Glucose levels are generally >300 mg/dL but can be lower in the unfed, nutritionally deprived patient. The serum osmolality is usually >300 mOsm/L. Potassium, initially, can be high due to renal impairment and acidosis with shift in potassium to extra-cellular space, but total body stores of potassium are depleted. Blood urea nitrogen (BUN) and creatinine are usually elevated. Sodium may be low as a result of hyperglycemia but when corrected for glucose will be high indicating hyperosmolality. Phosphorous and magnesium concentrations may be low as well.

Table 35.7. Treatment of DKA/NKHS.

Hemodynamic monitoring and adequate IV access
Fluid resuscitation: 0.9% sodium chloride ~1L/h (0.45% saline can be used in patients with severe hypernatremia (>155 mEq/L)
Regular (short-acting insulin): Loading dose: 0.1–0.15 U/kg IV bolus;maintenance dose: 0.1 U/kg/h IV infusion, typically 5–7 U/h
Replace K+: 20–40 mEq/L of KCl to each liter of fluid once K+ is under 5.5 mEq/L
Frequent monitoring of glucose, electrolytes
Begin 5% dextrose when glucose reaches ~200 mg/dL
Reserve sodium bicarbonate for pH<7.0
Consider mannitol (0.25–1 g/kg), hyperventilation, and slowing the IV fluid replacement if neurologic deterioration occurs (cerebral edema)
Identify and treat the precipitating cause
Prevention of acute DKA recurrences

Treatment is outlined in Table 35.7. The mainstays are volume resuscitation, insulin administration to reverse ketoacidosis, and electrolyte correction.[38] Initially, isotonic fluid is given to correct volume deficits and restore blood pressure and perfusion of brain and kidneys. Once hemodynamically stable, more hypotonic solutions can be substituted to correct hyperosmolality. Insulin should be administered as a bolus, then with a continuous infusion using one of the protocols described previously. Dextrose needs to be supplied once the glucose level drops to below 200 mg/dL to allow for a continued supply of insulin. The main metabolic goal is the reversal of ketoacid production and correction of glucose levels in the blood. Potassium repletion should occur early once renal output has been established, beginning well before hypokalemia occurs. Except in cases of severe acidosis (pH<7), bicarbonate is not required and may be detrimental. Serum bicarbonate can be regenerated endogenously from ketone bodies once the ongoing acidosis is arrested.

Frequent monitoring of vital signs and laboratory parameters is mandatory. Glucose levels should be followed per the insulin infusion protocol, and chemistry profiles taken every 4–6 h initially. Although DKA can carry with it a significant mortality rate, with careful attention to prevention, early detection and appropriate aggressive therapy in the ICU, this can be kept to a minimum.

Non-ketotic Hyperosmolar State

More typical of patients with Type 2 diabetes is a non-ketotic hyperosmolar state (NKHS). This develops in the setting of relative insulin deficiency without an absolute absence of insulin. Patients are often older, with underlying impaired renal function. Because they are less able to excrete glucose through the kidneys, levels mount in the blood leading to progressive hyperosmolality. Fluid losses coupled with inadequate fluid intake aggravate the situation. Precipitating factors are similar to DKA including surgery, renal insults, myocardial infarction, stroke, and infection. Iatrogenic factors include drugs such as diuretics, corticosteroids, and therapies such as hyperalimentation. These patients are often profoundly volume depleted and dehydrated. Impaired mentation is the norm, and generalized or focal neurologic deficits can be seen. Glucose levels can exceed 600–800 g/dL. Fluid deficits may exceed 6–10 L and renal impairment with creatinine levels >3 mg/dL are common. Serum osmolality often exceeds 330 mOsm/L. A metabolic acidosis may be absent unless a lactic acidosis has supervened. Potassium deficits are not as severe as that seen in DKA.

Treatment[39] involves aggressive volume resuscitation with isotonic saline to correct the hemodynamic instability followed by 0.45% saline to replace free water losses and correct the hyperosmolality. Insulin is required to move glucose into the cells and assist in lowering the osmolality. An intravenous (IV) insulin protocol is useful, but lower dosing may be sufficient as patients are often more sensitive to insulin and fluids. Correction of the hyperosmolality should proceed in a gradual fashion over 12–24 h to avoid the risk of cerebral edema that can accompany overzealous fluid administration. Cerebral edema can occur in the treatment of DKA as well,[40] although it is most often seen in children.

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36
Adrenal Insufficiency

Bala Venkatesh and Jeremy Cohen

The contribution of adrenal insufficiency (AI) to the morbidity of critically ill patients is currently under renewed scrutiny. Activation of the hypothalamic–pituitary–adrenal (HPA) axis is an integral part of the organism's response to stress and so a thorough understanding of the normal functioning of the HPA axis and potential pathophysiological changes is essential. Yet despite over 50 years of research, the nature and significance of the changes that occur in the system and the response of the adrenal gland to critical illness is still the subject of debate. The definitions of the syndromes "relative adrenal insufficiency" (RAI) and "critical illness related corticosteroid insufficiency" (CIRCI) have been the subject of intense controversy. In this chapter, we review the adrenocortical physiology and the feedback loops, discuss the clinical features of and the optimal methods for diagnosing adrenal insufficiency, and discuss possible pathways of future research.

The important milestones leading to our understanding of adrenocortical physiology and pharmacology are outlined in Table 36.1. Plasma cortisol levels are reported in both µg/dl and nanomoles/l; 1 µg/dl = 27.6 nmol/l.

Adrenal Physiology

The primary endogenous glucocorticoid (GC) in humans is cortisol. It plays a pivotal role in normal physiology, and is necessary for the synthesis of adrenergic receptors, normal immune function, wound healing, and vascular tone.[1–3] In circumstances of decreased cortisol production, such as adrenalectomized animals or patients with Addison's disease, critical illness has an increased mortality.[4,5] It is worthwhile to note the pharmacological preparation of "hydrocortisone" is cortisol by another name.

Cortisol is synthesized and secreted by the fasciculata layer of the adrenal cortex. The majority of circulating hormone is bound to an alpha-globulin called transcortin (corticosteroid-binding globulin, CBG). At normal levels of total plasma cortisol, (e.g., 375 nmol/l or 13.5 µg/dl) less than 5% exists as free cortisol in the plasma; however, it is this free fraction that is biologically active. CBG levels have been documented to fall during critical illness,[6–8] thus leading to relative increase in circulating free levels; most available assays measure only total levels, and so this increase is not usually apparent.

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Table 36.1. The important milestones leading to our understanding of adrenocortical physiology and pharmacology.

1849	Description of Addisonian syndrome by Thomas Addison
1923	Role of adrenal gland in survival from bacterial sepsis determined
1935	Isolation of cortisone; also came to be known as Kendall compound
1936	Description of "stress syndrome" by Hans Selye
1948	First description of the corticotrophin test to determine adrenal reserve
1949	Introduction of cortisone into clinical practice by Philip Hench
1950	Kendall, Reichstein, and Hench awarded the Nobel Prize for Physiology and Medicine for characterization of adrenal hormones

Table 36.2. Important physiological parameters.

Total daily output of cortisol	5–30 mg/day (40–80 µmol/day)
Peak plasma concentration (8–9 am)	150–550 nmol/l (5–20 µg/dl)
Nadir plasma concentration (midnight)	110 nmol/l (4 µg/dl)
Plasma free cortisol concentrations	5.5–38 nmol/l (0.2–1.4µg/dl)
Plasma CBG concentrations	26.0 mg/l
% of cortisol bound to CBG	80%
% of cortisol bound to albumin	12–15%
% free cortisol	5–8%

Cortisol exerts its effects via binding to the glucocorticoid receptor (GR), a 777 amino acid cytoplasmic protein found in nearly all nucleated cells. Cortisol passes through cell membranes to bind with this receptor, following which the steroid-receptor complex migrates to the nucleus and influences gene transcription. It is estimated that approximately 20% of the expressed genome can respond to GR binding[9] (Table 36.2).

Control of Secretion

Regulation of cortisol secretion is via the central nervous system, and is controlled by secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, which is in turn under the control of corticotropin-releasing hormone (CRH). CRH is secreted from the paraventricular nucleus of the hypothalamus, in response to a normal hypothalamic circadian regulation and various forms of "stress," including pain, hypoglycemia, tissue damage, and cytokine release.

CRH acts upon the pituitary to favor ACTH release, which stimulates the synthesis and secretion of cortisol from the adrenal cortex. In addition, ACTH stimulates dehydroepiandrosterone (DHEA) and aldosterone secretion, although the renin–angiotensin system is primarily responsible for the control of mineralocorticoid release.

Vasopressin, oxytocin, angiotensin II, and beta-adrenergic agents also stimulate ACTH release, while somatostatin, beta-endorphin, and enkephalin reduce it. Cortisol has a negative feedback on the hypothalamus and pituitary, inhibiting hypothalamic CRH release induced by stress, and pituitary ACTH release induced by CRH. During periods of stress, trauma, or infection, there is an increase in CRH and ACTH secretion and a reduction in the negative feedback effect, resulting in increased cortisol levels, in amounts roughly proportional to the severity of the illness.[10,11]

HPA Axis Changes in Critical Illness

The HPA axis undergoes significant changes in critical illness. The most fundamental is an increase in total cortisol production, which may be up to sixfold from baseline, and although highly variable, is roughly proportional to the severity of the illness. This is thought to result from increased corticotropin production in response to endotoxin and the inflammatory cytokines tumor necrosis factor α (TNF-α), and interleukin (IL) 1 and IL-6.[12] Other factors, which may also stimulate ACTH production, include arginine vasopressin, macrophage migratory inhibitory factor, and atrial natriuretic factor.

The normal diurnal variation of cortisol production is lost, and an enhanced variability is seen, which can complicate interpretation of measured plasma levels. In addition, production of cortisol binding globulin is reduced and its cleavage at sites of inflammation (by neutrophil elastase) is increased.[13] This results in increased levels of free cortisol, especially at the tissue level. The increased production of cortisol in response to critical illness is likely to be adaptive and may reduce the severity of the inflammatory response, as well as increase vaso-motor responsiveness to endogenous and exogenous vasoconstrictors. Cortisol levels may also increase secondary to impaired cortisol clearance, particularly in patients with hepatic or renal impairment.

It is now recognized that during the acute phase of critical illness, the predominant driver for cortisol release is ACTH mediated, whilst during the subacute or chronic phase, non-ACTH dependant mechanisms (neurotransmitters, cytokines, growth factors, neural and non-neural peptides, and vascular and endothelial molecules) come into play.[12] Whilst initially elevated, ACTH levels fall during critical illness, despite total plasma cortisol concentrations remaining elevated indicating a biphasic response.[14] Thus non-ACTH regulation of the adrenal cortex appears to play an important part in the adaptation of the HPA axis to stress.

Tissue Activity of Glucocorticoids in Critical Illness

More recently there has been increasing attention drawn to tissue cortisol metabolism in critical illness. Data has suggested that GR translocation into the nucleus may be impaired, or that GR sensitivity may be reduced, thus leading to a situation of tissue cortisol resistance.[15,16] Conversely, evidence of increased peripheral formation of cortisol from inactive cortisone

in the tissues also exists, suggesting that GC tissue activity may be increased.[17] Glucocorticoids (GC) are regulated at the tissue level through the 11β-hydroxysteroid dehydrogenase (HSD1&2) enzyme system. Increased 11beta-HSD1 activity (which results in local regeneration of active cortisol from inactive cortisone) has been implicated in the pathogenesis of many common conditions including obesity and the metabolic syndrome.[18–21]

Emerging evidence suggests that in septic shock there is similar upregulation of HSD 1 activity, potentially increasing local tissue cortisol concentrations.[17] These findings are in marked contrast to the commonly held view that there is relative adrenal insufficiency (RAI) in septic shock (based *entirely* on plasma cortisol and the corticotropin response).[17,22]

Adrenal Insufficiency

Adrenal insufficiency (AI) may be classified as primary or secondary. In addition, a form of AI has been described in the setting of critical illness, which appears to have features of both.

Primary AI or Addison's disease is a rare disorder. In the western world its estimated prevalence is 90–140 per million.[5] In adulthood, the commonest cause is autoimmune, where it can arise on its own or as part of a spectrum of other autoimmune conditions, including hypothyroidism and diabetes. Additionally, it may arise as part of the syndrome of adrenoleukodystrophy where it is associated with neurological impairment secondary to demyelination. Other causes are rare, but include infection, hemorrhage, and infiltration. Tuberculosis is the commonest infective cause worldwide, but fungal infections such as histoplasmosis, coccidiomycosis, and cytomegalovirus (especially in immunocompromised patients) should also be considered. Adrenal hemorrhage as a cause of hypofunction is seen with septicemias, particularly meningococcal (Waterhouse–Friedrichsen syndrome). Asplenia and the antiphospholipid syndrome may also be associated with adrenal hemorrhage. Infiltrative processes, such as tumors, or amyloid, may lead to destruction of the gland and symptoms of adrenal insufficiency.

Drugs can cause adrenal insufficiency by either impairing adrenal synthetic function (etomidate and ketoconazole) or by inducing hepatic cortisol metabolism (rifampicin, phenytoin). High levels of circulating cytokines are also reported to have a suppressive effect upon ACTH release.[23]

Presentation

Symptoms include tiredness and fatigue, vomiting, weight loss, anorexia, and postural hypotension. Hyperpigmentation is seen in non-exposed areas (such as palmar skin creases) and is due to the hypersecretion of melatonin, a breakdown product from the ACTH precursor pro-opiomelanocortin (POMC). Due to the nonspecific nature of the symptomatology, the diagnosis is often delayed, and 50% of patients will have had signs of Addison's disease for over a year before the diagnosis is confirmed.[5]

Presentation to an intensive care physician is likely to be in the form of adrenal crisis. This may be precipitated by concurrent illness or surgery, or by failure to take replacement medication. Classically, adrenal crisis will present as refractory shock with poor response to inotropic or vasoactive agents. Abdominal or flank pain is often present and may lead to an erroneous diagnosis of an acute surgical abdomen.

Rapid recognition and early treatment is vital. This should consist of immediate supportive measures, fluid resuscitation, and high-dose intravenous glucocorticoid therapy. A standard dose would be 100 mg hydrocortisone 6-hourly, or as an infusion. At these doses separate mineralocorticoid replacement is not required.[24] It is important to recognize that the use of dexamethasone in an attempt to allow for subsequent ACTH stimulation testing (see below) is an inadequate treatment as it does not provide mineralocorticoid cover.[25]

Adrenal crisis should be suspected in cases of undifferentiated shock not responding to standard management. Suggestive features would include a history of symptomatology consistent with the diagnosis, hyperpigmentation on examination, and demonstration of hyponatremia, hyperkalemia, and peripheral blood eosinophilia. A random plasma total cortisol taken during a crisis will be low (below 3 μg/dl or 80 nmol/l) and in the acute phase, ACTH stimulation testing is not required.

Secondary Adrenal Insufficiency

The commonest cause of ACTH deficiency is sudden cessation of exogenous glucocorticoid treatment; however, rarer causes include pituitary infarction secondary to hypovolemic shock (Sheehan's syndrome), and pituitary tumors, irradiation, or trauma. Patients who have been taking more than 30 mg/day hydrocortisone or equivalent for more than 3 weeks are at risk of adrenal suppression,[2] if this treatment is abruptly ceased.

Presentation is similar to that of primary AI. The major distinguishing characteristics are lack of hyperpigmentation, and the absence of mineralocorticoid deficiency; hence, hyperkalemia is not a feature of secondary AI, although hyponatremia may still be present due to increased vasopressin levels.

Diagnosis

Adrenal insufficiency can be diagnosed by a combination of random plasma hormone estimations, dynamic tests, and radiological interventions. The choice of test will depend on the clinical presentation and status of the patient and the suspected etiology.

In the case of a patient with refractory shock in whom adrenal crisis is suspected, treatment must be started promptly.

Immediate screening tests consist of plasma electrolytes and total plasma cortisol. Cortisol concentrations below 3 mic/dl (83 nmol/l) are diagnostic, whilst levels above 19 mic/dl (525 nmol/l) rule out the disorder.[24] Intermediate values mandate further investigation. Local laboratory values should always be used for interpretation of test results.

Dynamic Testing

The mainstay of diagnosis is the ACTH stimulation test, or the Short Synacthen Test (SST).[26] This is performed by the intravenous or intramuscular injection of 250 µg of tetracosactin, which comprises the first 24 amino acids of normally secreted ACTH. Plasma total cortisol levels are measured at baseline prior to administration and at 30 min subsequently. A normal response is defined as a peak plasma cortisol of greater than 20 µg/dl (550 nmol/l); however, due to assay variability normal values should be defined by the local laboratory. The test cannot be performed whilst the patients are taking hydrocortisone, as these will cross-react with the cortisol assay; dexamethasone treatment, if of short duration, is acceptable. Note that dexamethasone is an inadequate sole treatment for adrenal crisis.

Differentiation of primary from secondary AI can usually be made by basal measurement of ACTH levels; in primary AI the ACTH level will be disproportionally elevated. However, in complex or unclear cases, additional dynamic tests may be employed. The prolonged ACTH test involves the depot administration of tetracosactin over a 24- to 48-h period. Patients with secondary AI manifest a delayed cortisol response.

The insulin tolerance test (ITT)[27] is considered the gold standard and is performed by inducing symptomatic hypoglycemia via an insulin infusion and measuring the cortisol response. It should be avoided in patients with ischemic heart disease, epilepsy, or cardiovascular instability. An alternative is the Glucagon Stimulation test.

Metyrapone inhibits cortisol synthesis, and in patients with an intact axis the response to an overnight dose is an increase in ACTH levels and in the cortisol precursor 11 deoxycortisol.[28]

The CRF stimulation test can be used to differentiate primary from secondary AI. In patients with primary AI, ACTH levels rise following CRF stimulation, whereas in secondary AI the ACTH levels do not respond to CRF stimulation.[29]

Low Dose Short Synacthen Test

The standard SST produces circulating ACTH levels that are significantly supraphysiological, which has led some workers to suggest that a "low dose" SST requiring only 1 mic of tetracosactin may be more sensitive.[30] This concept has not yet been generally accepted and the role of the low dose SST is still unclear.

Additional Testing

Additional tests utilized in investigating hypoadrenalism include autoantibody estimation, radiological imaging of the adrenals and pituitary, and adrenal biopsy (Table 36.3).

Adrenal Insufficency in Critical Illness

The existence of a syndrome of relative adrenal insufficiency (RAI) or Critical Illness Related Corticosteroid Insufficiency (CIRCI) continues to generate controversy. These terms describe a postulated subset of patients who do not have demonstrable structural damage to the HPA axis, but who have failed to mount an adequate GC response to their illness. Implicit in this concept is that supplementation with so-called "low dose" steroid in this group may improve outcome.[31] Support for this concept comes from the observation of GC responsive hypotension in septic shock, suggesting that transient adrenal gland failure may be a common feature of severe sepsis. However, determining whether this syndrome exists or how it can be recognized has proved difficult. Of note, steroid therapy based on the presence of RAI has not been consistently able to demonstrate any mortality benefit and there is even a suggestion of adverse effects.[32,33] The two tests used to define

Table 36.3. Investigations for hypoadrenalism.

	Principle	Advantages	Limitations
Corticotropin test	Cortisol response to synthetic ACTH	Simple safe and well validated. Can be used in low dose or in prolonged test	Does not distinguish primary from secondary. High dose may miss early secondary AI
Metyrapone test	Inhibition of cortisol synthesis	Assesses integrity of entire HPA axis	Cumbersome, gastric irritation, metyrapone difficult to obtain, risk of precipitating adrenal insufficiency
Insulin hypoglycemia test (IHT)	Response to induced hypoglycemia	Gold standard for HPA axis assessment	Unsuitable for patients with cardiac and neurological illnesses
CRH stimulation test	Response to CRH	Differentiates primary and secondary	Rarely used over basal ACTH levels
Glucagon stimulation test	Response to glucagon	Alternative to IHT	May be less sensitive than IHT

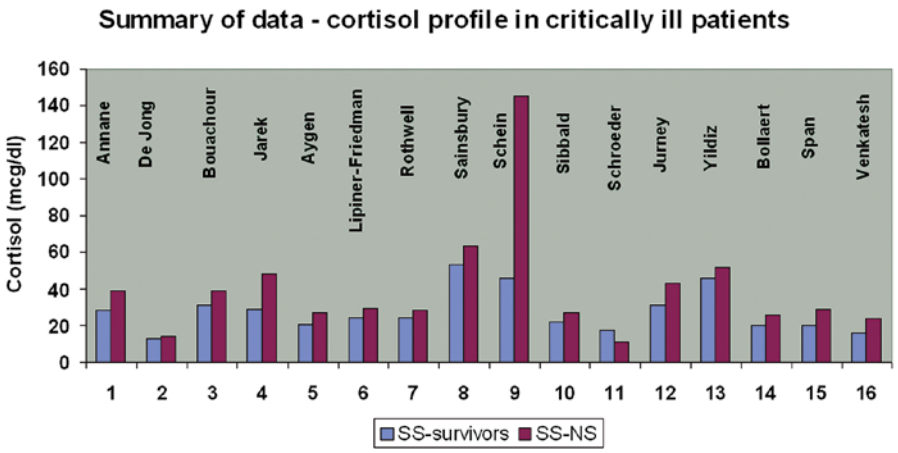

FIG. 36.1. Summary of cortisol profiles in critically ill patients.

TABLE 36.4. Limitations of total plasma cortisol.

1. A normal reference range for total plasma cortisol in the critically ill has been difficult to establish. Studies have demonstrated a wide range of elevated total plasma cortisol concentrations in stressed ICU patients
2. Marked variability of total plasma cortisol over a 24-h period in critically ill patients suggests that a diagnosis of adrenal insufficiency based on single point cortisol estimation may be inaccurate[51]
3. A clear relationship between serum cortisol and mortality in critical illness has not been demonstrable
4. What is measured routinely is total plasma cortisol; however, what is biologically active is the plasma free cortisol (PFC)

the presence of RAI/CIRCI are a total plasma cortisol and the cortisol response to corticotrophin. The controversy surrounding the interpretation of these tests and therefore the diagnoses of the syndromes are discussed as follows in more detail.

Total Plasma Cortisol

As noted, plasma cortisol levels are elevated in patients with critical illness, but the observed range is highly variable, particularly in patients with sepsis.[34–41] The hypothesis of RAI would suggest that a subgroup of patients with lower plasma cortisol concentrations would be expected to have a higher mortality; however, this cannot be demonstrated observationally, and, in fact, mortality appears to be associated with higher plasma cortisol values[34,36,37,40–52] (Fig. 36.1). The limitations of total plasma cortisol are outlined in Table 36.4.

The Corticotropin Test in Critical Illness

The primary observation supporting adrenal insufficiency of critical illness is a blunted plasma cortisol response to a standard corticotropin stimulation test (also known as the SST test), a pattern which was thought to be associated with an increase in mortality. Initially documented by Rothwell et al.,[47] the largest study examining the response to a standard high dose Synacthen test in septic patients was performed by Annane and coworkers.[42] They prospectively studied 189 patients with septic shock and detailed a 3-level classification system based upon the basal cortisol level and response to ACTH. Mortality was found to be highest in those patients with a basal cortisol level above 34 µg/dl (938 nmol/l) and response to ACTH of less than 9 µg/dl (248 nmol/l). Patients with a basal cortisol above 34 µg/dl, but a cortisol response greater than 9 µg/dl did better; whilst the best prognosis was seen in the group with a lower basal cortisol level and high response to ACTH. Subsequent studies have confirmed these findings but produced great variability in the diagnostic criteria, resulting in reported incidences from 20 to 75%. Similar patterns of reduced responsiveness to ACTH have been described in patients with trauma, head injury, burns, and liver failure.[53–56]

Opponents of the relative adrenal insufficiency hypothesis contend that dynamic stress testing in the setting of preexisting adrenal stimulation from critical illness is difficult to interpret and may represent limited adrenal reserve rather than true insufficiency.[57,58] Other limitations of the SST in this setting include poor reproducibility,[59] debate about the optimal dose of corticotropin,[60] its poor concordance with the gold standard metyrapone test,[61] and a high degree of variability between available cortisol assays such that the functional diagnosis of adrenal insufficiency may be entirely dependent on the local assay.[62]

A further complicating factor in the assessment of adrenal function in this patient group is the role of free cortisol. Free cortisol levels have been shown to increase in critical illness,[8] and some research has suggested that free cortisol may be more closely related to sickness severity than total cortisol levels.[63] However, free cortisol measurements are not routinely available, and their role in diagnosing AI in critical illness is currently uncertain.

It can be seen from the foregoing that both the existence of, and the recognition of, an RAI/CIRCSI syndrome in critically ill patients is controversial. Two recent consensus conferences have been held – one by the Society of Critical Care Medicine, USA,[64] and the other by the European Society of

Table 36.5. Suggested diagnostic criteria for RAI/CIRCI.

Random total cortisol	Short Synacthen test	Free cortisol	Clinical
<15 mic/dl[34,66]	Peak < 18 mic/dl[43]	Rise < 4 mic/dl following SST[63]	Failure to respond to fluid and inotrope treatment[65]
<18 mic/dl[67,68]	Peak < 20 mic/dl[69]		
<20 mic/dl[69]	Rise < 7 mic/dl[70]		
<25 mic/dl[71]	Rise < 9 mic/dl[42]		

Intensive Care Medicine (publication of consensus statement awaited) – to develop criteria for diagnosis and recommend therapy for adrenal insufficiency. Suggested diagnostic criteria have included random total cortisol measurements, high or low dose SST tests, free cortisol measurements, and empiric treatment on clinical parameters. This diagnostic uncertainty has resulted in numerous published criteria for the recognition of RAI/CIRCSI in critically ill patients (Table 36.5). Application of these different criteria to the same patient population results in estimated incidence of adrenal insufficiency of between 6.25 and 75%.[34] The most widely accepted diagnostic scheme indicates a cortisol response of less than 9 μg/dl (250 nmol/l) to a high dose SST should be taken as evidence of AI. However, recent guidelines for the management of sepsis do not recommend that ACTH testing be performed to identify patients who may benefit from hydrocortisone, and instead suggest that steroid supplementation be given only to patients with septic shock who are poorly responsive to fluids and inotrope therapy.[65] This recommendation comes primarily as a result a large multicenter trial in sepsis that failed to show a mortality benefit for steroid treatment. Steroid use was associated with a faster resolution of shock, but this was not predicted by the SST.[32]

Conclusions

A functioning HPA axis is a prerequisite for survival from severe stress. Failure to recognize a patient with primary or secondary AI and institute prompt and appropriate treatment can be catastrophic.

In critical illness, the HPA axis undergoes complex changes, and a proportion of patients may have relative deficiency of cortisol, or tissue cortisol resistance. However, the accurate identification of these patients remains a challenge. Whilst the role of steroids to improve vasopressor responsiveness in septic shock is widely accepted, their role in improving outcome in septic shock remains unproven. Further research into this area - in particular the role of free and tissue cortisol - is warranted.

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Nutrition Support in Intensive Care

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Nutritional support of the critically ill patient is an important aspect of medical care and universally applicable to all hospitalized patients. Malnutrition is prevalent in the surgical intensive care unit (SICU) and can impair vital organ function, depress immune status, prolong ventilator dependence, and increase infection and mortality rates.[1–4] In surgical patients, a preoperative weight loss of greater than 10% of usual body weight has been associated with increased postoperative complications such as pneumonia, wound infection, longer length of stay, and increased mortality[5–7] The goal of nutritional support in the critically ill patient is to support wound healing and immune function, and prevent malnutrition and its comorbid consequences. Meeting the elevated nutritional requirements of critically ill patients while avoiding the metabolic complications can be difficult. This chapter addresses the many challenges of feeding the SICU patient and provides guidelines for safe and effective nutritional support.

Metabolic Response to Stress

Elevated metabolic requirements and rapid loss of lean body mass characterize the hypercatabolism associated with traumatic injury, sepsis, inflammation, and burns. The release of cytokines and counter-regulatory hormones leads to a cascade of events that profoundly impacts a patient's nutritional status. The metabolic response to injury mobilizes amino acids from lean tissue to support wound healing and the immune response. Critical loss of lean body mass and severe protein calorie malnutrition can develop in as little as 2 weeks in acutely stressed patients – particularly those with closed head trauma and large surface area burns. When self-limited, recovery ensues; but prolonged catabolic illness without nutritional support can lead to significant body protein depletion and complications such as wound infection or dehiscence, sepsis, and multiorgan failure, even in previously healthy, well-nourished individuals.[8,9]

It can be difficult to provide adequate nutrition to this patient population because of alterations in substrate utilization and the limitations of nutrient delivery associated with critical illness.[10,11] Exogenous nutrients are used as fuels to support organ function and heal wounds, but complications of nutrition support are frequently encountered, including azotemia, salt and water overload, and hyperglycemia. Nitrogen losses are predominant. Achieving positive nitrogen balance and improving visceral protein markers is unlikely during this catabolic phase.[12,13] Thus the goal of nutrition support during the period of critical illness is to minimize nitrogen and protein losses. Only when metabolism normalizes will positive nitrogen balance and anabolism become

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apparent. A more realistic goal of nutritional support during this phase is to provide adequate substrate to support organ function, wound healing, and immune competence without causing metabolic derangements or increasing infection risk. Methods to avoid complications of feeding include accurate assessment of needs, close metabolic monitoring, and a multidisciplinary team approach to patient management.

Indications for Nutritional Support

Recommendations regarding the indications for use, timing, and the optimal route of nutritional therapy are based on American Society of Parenteral and Enteral Nutrition (ASPEN) Guidelines.[14] ASPEN summarizes the consensus of clinicians in nutrition support practice on the basis of available clinical and experimental evidence or expert opinion when data are either nonexistent or controversial. Nutrition support is not without the risk of complication/cost, so the decision to initiate must be carefully weighed against the risk/benefit ratio.

Patients are classified as well-nourished, or having mild, moderate, or severe malnutrition in order to determine timing of nutritional therapy. In general, well-nourished or mildly malnourished medical or surgical patients who are not severely metabolically stressed can withstand 7–10 days of starvation and suffer no adverse medical consequences. For these patients the additional cost and increased medical risk of early nutrition therapy may outweigh any potential benefit. Moderate to severely malnourished patients who are unable to eat because of poor gut function, profound anorexia, or anticipated prolonged *nil per os* status may require nutrition support earlier. Severely malnourished patients need prompt nutrition intervention because they are at higher risk of developing sepsis, wound infections, and prolonged SICU stay without nutrition support.[14]

Nutritional Assessment

The purpose of nutritional assessment is to identify malnourished patients and those at high risk for developing malnutrition because of the catabolic nature of their illness or injury. Nutritional status is evaluated by physical assessment, nutrition history, and review of biochemical indices. In the critical care setting, accurate nutritional assessment can be complicated by non-nutritional factors, such as acute metabolic stress and fluid derangements making body weight and serum protein levels difficult to evaluate. The patient's stated usual body weight and information regarding recent oral intake, percent weight loss over 6 months, and functional status are more useful.[15] Physical examination remains the primary nutrition assessment tool. Inspecting the muscle groups such as temporal, deltoids, suprascapular, biceps, triceps, and interossei of the hands can assess protein stores. When tendons can be palpated, greater than 30% of total body protein stores have been lost.[16,17] Edema and ascites are important physical indicators of depleted visceral protein stores. Signs of severe malnutrition include an unintentional weight loss of greater than 10–15% of usual body weight in less than 6 months, a pre-injury serum albumin of <2.5 mg/dl, an emaciated appearance or body mass index (BMI) of less than 18, history of chronic substance abuse, cancer cachexia, and/or evidence of poor wound healing or decubiti.[17]

Serum hepatic protein levels are commonly used to assess nutritional status and response to therapy. Multiple studies demonstrate that serum albumin levels correlate with patient outcome and depressed pre-hospital levels can suggest malnutrition. In acute illness, humoral protein levels will be low because of hepatic reprioritization to synthesize acute phase reactants or to transvascular shifts. In this case, low protein levels are indicators of illness severity, not malnutrition.[18] Routine evaluation of serum hepatic proteins can help identify the sickest patients, i.e., those most likely to develop malnutrition and benefit from nutritional support even if well-nourished prior to injury. Patients with severe protracted catabolic illness, such as head trauma or large body surface area burns with or without malnutrition, will require prompt nutrition therapy.[14] Up to 150 g of protein/day can be lost in septic patients even when nutrition support is provided.[19] Severe protein depletion and the immune consequences can occur in as little as 7 days in this setting. SICU patients requiring nutritional support generally fall into the following categories: major trauma, severe sepsis, or postoperative elective surgery associated with prolonged ileus. While nutrition support plays a vital role in critical care, it should be withheld until resuscitation from shock and hemodynamic stability is achieved. Electrolyte abnormalities and hyperglycemia, common in critically ill patients, must be corrected prior to initiation of nutrition support.

Route of Feeding

"If the gut works use it!" is a well-accepted standard of practice. Enteral nutrition (EN) is preferred over parenteral nutrition (PN) for meeting the needs of critically ill patients with functioning gastrointestinal (GI) tracts, as it is more "physiologic." Technological advancements in enteral formulations and access techniques have greatly expanded the number of patients who can be successfully fed via the enteral route. Compelling reasons to choose enteral over parenteral nutrition include improved host defenses with maintenance of gut-associated lymphoid tissue and enterohepatic circulation of biliary immunoglobulins, reduced infectious complications, maintenance of gut barrier protection, and decreased cost.[20,21] In addition, enteral feeding enables use of disease-specific formulas or immune enhancing diets (IED) supplemented with arginine, glutamine, and omega-3 fatty acids, which may offer an important immunological advantage over PN. Animal models comparing EN to PN demonstrate that administration of EN prevented gut mucosal atrophy and preserved gut integrity, attenuated the stress response, and maintained immune-competence.[22,23] Several human studies comparing route of feeding show reduced septic morbidity in trauma patients.[24–26] Kudsk et al. reported a 76% lower sepsis

rate in a prospective study of abdominal trauma patients when fed EN vs. PN.[25]

EN should be considered early (within the first 24–72 h of severe injury) once fluid resuscitated and hemodynamically stable. Early (vs. late) EN can attenuate the hypermetabolic response and reduce the consequences of catabolism.[27,28] EN can be used safely in patients with minimally functioning GI tracts if careful physical assessment and close monitoring of clinical course guide initiation and advancement.[29,30] When enteral access is delayed or hemodynamic status prevents delivery of enteral feeding, PN may be necessary. Early PN is generally not recommended unless the patient is severely malnourished. Routine early PN may be associated with poorer outcomes than no nutrition in patients with normal to moderate malnutrition.[31] Use of PN should be kept as low as possible. Parenteral nutrition can be safely withheld for up to 5–7 days while the enteral route is attempted in those without severe malnutrition. If EN fails by SICU day 7, PN may be necessary while enteral feeding tolerance is established. On the basis of a review of the literature, a Canadian committee recommended that PN not be initiated in critically ill patients until all strategies to maximize EN delivery (such as use of motility agents or small bowel feeding tube placement) have been attempted.[32] Absolute contraindications to EN are limited to obstruction, massive GI bleeding, peritonitis, and high-output fistula. Relative contraindications include short bowel syndrome, intractable nausea, vomiting or diarrhea, and use of high-dose pressors.[14] Patients with severe protracted diarrhea, increasing abdominal distension, high nasogastric tube outputs, or an unobtainable safe enteral access route are poor candidates for EN and may require PN (Table 37.1).

With the renewed enthusiasm for early enteral feeding in the critically ill patient, new complications from tube feeding have been observed. Evidence suggests that enteral feeding during periods of low blood flow states can result in poor gut perfusion and may promote bowel ischemia.[33–35] Bowel necrosis related to tube feeding might occur in hemodynamically unstable patients on high-dose vasopressors. Normally about 40% of the cardiac output is shunted to the gut in the postprandial state. This is attenuated in the setting of high-dose pressor support. Symptoms include sudden onset of abdominal distension, hypotension, oliguria, metabolic acidosis, and high nasogastric output.[36–38] Non-occlusive bowel necrosis is a rare but devastating complication of EN. It can occur with inappropriate tube feed administration into a poorly perfused gut. Incidence of mesenteric ischemia is less than 1%, but the mortality rate is greater than 50%.[37]

Until recently, PN was provided as the sole source of nutrition for patients with marginal visceral blood flow. Clinical conditions associated with low-flow states include sepsis, cardiac failure, ventilator use with elevated positive end expiratory pressure (PEEP), and use of high-dose vasopressors. Interest in enterally feeding this patient population has emerged because of the known systemic and local benefits to the GI tract, but only if the clinical abdominal exam is benign and tube feeding can be well-tolerated. With appropriate resuscitation, feeding these patients may not be as detrimental as previously thought.[39] In patients receiving a stable dose of pressors, it is reasonable to provide EN, assuming the patient's volume status is replete and mean arterial pressures (MAP) can be sustained above 70 mm/Hg.[37] Surgical intensive care unit staff must pay meticulous attention to the development of GI symptoms such as nausea, emesis, abdominal distention, diarrhea, and elevated gastric residual volumes, which may suggest feeding intolerance. Nasogastric tube output and abdominal exam should be monitored closely. Use of iso-osmolar feeding without fiber and avoiding direct small bowel feeding are recommended.[40] Feedings should be held with sudden onset of hypotension, abdominal distension, or with need for increasing pressor dose or ventilator support.[40]

Combination therapy for nutritional support is often used in this setting. For stable patients unable to tolerate tube-feeding advancement, PN can meet nutritional requirements while EN is reduced to a low rate (trophic infusion) to support intestinal integrity. When GI function improves, tube feeding can be gradually advanced to the required level while weaning off PN.

Table 37.1. Indications for enteral and parenteral nutrition in the SICU.

Indications for enteral nutrition in the surgical intensive care unit
Functional GI tract
Hemodynamic stability
Inability to take oral nutrition in face of malnutrition, increased metabolic stress or prolonged NPO period (>7–10 days)
Indications for parenteral nutrition in the surgical intensive care unit
Unable to obtain safe enteral access
Small bowel feeding not possible (high output fistula, massive small bowel resection, bowel obstruction)
Splanchnic hypoperfusion, acute shock, high-dose vasopressors
Failed enteral feeding trial by SICU day 7

Assessment of Needs

Effective nutrition therapy begins with accurate assessment of requirements because inappropriate feeding can undermine the potential benefits. In the critically ill, the goal of nutrition support is maintenance, not repletion of body protein stores, as many factors limit the efficacy of exogenously provided nutrients. Both under and overfeeding are associated with complications that prolong hospital stay and increase costs.[41,42] Overfeeding is associated with derangements in hepatic, pulmonary, and immunologic function, and may lead to outcomes as detrimental to the injured patient as malnutrition.[41] Hyperglycemia and increased infection risk, hypercapnia and delayed ventilator weaning, and hepatic steatosis may result if attempts to promote anabolism with nutrition support are made inappropriately.[43–45] While deliberate underfeeding to minimize metabolic and infectious complications is a common practice, prolonged inadequate nutritional support will eventually result in malnutrition. For this reason, indirect calorimetry remains the gold standard for energy assessment. Unfortunately, indirect calorimetry equipment and personnel

are expensive and often unavailable. Current recommendations for stressed patients in an ICU/SICU setting remain at 25–30 kcal/kg.[14] However, there is increasing evidence that lower calorie intakes not exceeding 25 kcal/kg (termed permissive underfeeding) may be safer in critically ill patients. Even though patients with the highest levels of metabolic stress (multiple trauma, closed head injury, burns, severe sepsis) can have measured energy expenditures exceeding 40 kcal/kg, feeding at that level significantly increases the risk of metabolic complications that prolong ICU stay. Some studies suggest that an initial caloric goal of 10–20 kcal/kg and 1.5–2 g protein/kg/ideal body weight (IBW) may be warranted during the acute phase response.[46] Benefits relate to good glycemic control and avoiding the detrimental impact of hyperglycemia on infectious outcome. How long a critically ill patient can tolerate hypocaloric feeding is an important question yet to be answered by clinical trials. Extended periods of underfeeding can prove harmful. An accumulated energy deficit of greater than 10,000 kcal has been associated with multiple complications including infection, increased antibiotic treatment days, and prolonged ventilator dependence and ICU stay.[47]

Feeding the critically ill obese patient is an area of much controversy. Since weight is a factor in energy assessment, overfeeding calories can occur. For patients who weigh greater than 25% above their ideal body weight (IBW), body weight is adjusted down to account for adiposity (Table 37.2).

Controversy regarding optimal nutritional support of the critically ill, obese patient persists because outcome data are limited. Obesity in SICU patients is prevalent. Critically ill obese patients are hypermetabolic and can suffer the same consequences of accelerated body protein losses despite abundant fat stores. Following cardiac surgery, patients with BMIs of greater than 30 kg/m^2 have increased rates of respiratory failure and wound infection. Studies have suggested that for critically ill obese patients with BMIs greater than 30 kg/m^2, providing 50% of resting energy expenditure (REE) or 20 kcal/kg adjusted body weight (ABW) and 2 g protein/kg ABW can achieve positive nitrogen balance.[48]

Estimation of protein needs is less controversial. Protein requirements are influenced by degree of metabolic stress, prior nutritional status, steroid use, and protein losses from drains, stomas, and/or wounds. Current recommendations for critically ill patients are to provide 1.5 g protein/kg/day of the IBW (or ABW if obese).[14] Using the example below, the patient would require (81.25 kg × 1.5 g/kg/day) or 122 g/day of protein. Requirements may increase to 2 g protein/kg/IBW in patients with multiple trauma, extensive burns, or head injury; and as high as 2.5 g protein per kg/IBW/day in patients treated with continuous renal replacement therapy (CRRT).[49]

Table 37.2. Calculation of ABW.

Adjusted body weight (ABW) = (Actual body weight − IBW) × 0.25 + IBW
An example: A 220 lb (100 kg) man that is 70 in. (178 cm) tall
IBW is 106 lb for the first 60 in. of height plus 6 lb for each inch
IBW is 106 + 60 = 166 lb (75 kg)
Adjusted body weight = (100 − 75 kg) × 0.25 + 75 kg = 81.25 kg

IBW ideal body weight.

As the catabolic rate exceeds the anabolic rate in critical illness, nutritional support can only limit loss of body protein and energy stores. The magnitude of nitrogen loss varies with the clinical condition and parallels the energy expenditure and stress level. For every gram of nitrogen lost, approximately 6.25 g of protein and 30 g of lean body tissue are lost. With persistent large negative nitrogen losses, ability to recuperate decreases, and increased morbidity and mortality are likely. The goal of nutrition support is to administer sufficient nitrogen to minimize loss of lean body mass and to ultimately promote a positive nitrogen balance. This is best assessed by weekly nitrogen balance studies:

- Free water deficit (in liters) = (1−[140 divided by serum Na]) × (0.6 × body weight (kg))
- Fluid requirements = 1,500 ml + 20 ml/Kg for each Kg > 20 Kg
- Nitrogen balance = (nitrogen intake/6.25) − Nitrogen output + 4
- Nitrogen intake = grams of protein divided by 6.25
- Nitrogen output = 24 h Urinary Urea Nitrogen (UUN) + 4

Once energy and protein needs are determined, the remaining calories are divided between carbohydrates and fat. In general, 15–20% of calories are provided as protein, 50–60% of calories are provided as carbohydrate, and 15–30% calories are provided as fat.[14]

Vitamins and Minerals

There are no current guidelines for vitamin and mineral supplementation in the critically ill patient. Micronutrient needs during periods of metabolic stress are probably higher, but data to support supplementation beyond normal requirements are lacking. All patients should receive a daily source of vitamins and minerals via the enteral or parenteral route. Inadequate amounts of micronutrients will impair ability to utilize macronutrients and maintain the body's defense mechanism. The majority of standard EN and PN solutions contain acceptable levels of vitamins and minerals. Critically ill patients are known to have reduced levels of antioxidants (vitamin C, E, retinol, beta carotene, and selenium),[50] but there is no literature to support that therapeutic doses improve outcome. Furthermore, excess supplementation may be harmful.

Iron supplementation is not recommended during an inflammatory process. Iron is essential for bacterial growth and therefore may theoretically worsen sepsis.[51] Although vitamin C levels may be deficient in critically ill patients, supplementation beyond 200 mg/day can increase iron absorption and infection risk and may contribute to the development of calcium oxalate kidney stones, particularly in patients with renal impairment.[50,51]

Zinc requirements are increased by an additional 2 mg/day in catabolic illness and by 12–17 mg/l of GI losses.[51] Excessive zinc supplementation is not recommended because it can suppress immune function and impair copper absorption. Zinc supplementation beyond normal requirement should be restricted to 10 days.

Fluid Requirements

Standard fluid requirements are estimated at 35 ml/kg, with increased amounts to account for losses from high-output fistulae, stomas, drains, burns, or open wounds. However, critically ill patients have significant gains in total body water compared to unstressed patients. Fluid overload occurs as a result of resuscitative fluid delivery and fluid compartmental shifts. The multiple drips required for providing antibiotics, blood, sedation, and inotropic support can contribute to fluid overload. In addition, the hormonal response to stress causes avid sodium and fluid retention. For these reasons, parenteral and enteral nutrition is provided at maximum concentration to limit fluid burden while providing adequate nutrient delivery. As the patient recovers, fluid is mobilized and intravenous (IV) drips are weaned off. Volume and concentration of PN are then adjusted to meet maintenance fluid needs. Most recovering patients receiving enteral nutrition will require approximately 15–30% of the formula volume in additional free water flushes to meet fluid requirements. Fluid and electrolyte replacement with a separate IV fluid source outside of PN or EN formulas may be necessary when the patient has excessive losses.

Enteral Feeding

The recognition of the gut as an important immunologic factor during critical illness has strengthened the argument for enteral feeding as the preferred route of therapy. The sicker the patient, the greater the importance of maintaining gut integrity.[52] While EN is preferred, it is not without risk. Gastroesophageal reflux and pulmonary aspiration are the most feared complications of tube feeding. Strategies that maximize the delivery of EN while minimizing the risks have the potential to improve outcome in critically ill patients.

Readiness to enterally feed is characterized by a non-distended abdomen on exam, nasogastric tube (NGT) drainage less than 600 ml/24-h period, and hemodynamic stability. The presence or absence of bowel sounds is not a good indicator of bowel function. Fluid and air must be present in the GI tract for bowel sounds to be heard. Therefore, in patients with an NGT to suction, bowel sounds may be absent despite good gut function. Small bowel motility continues in the immediate postoperative period even though a gastric ileus is present for 24–48 h and colonic ileus persists for 3–5 days. Early postoperative enteral feeding is encouraged in high-risk surgical patients who will not resume oral intake within 10 days of surgery. Preoperative nutritional status should be considered before surgery as the enteral route of feeding can be more easily accessed at the time of operation. Options include placement of a nasoenteric or jejunostomy feeding tube if enteral access is anticipated.

Prompt achievement of nutritional goals by tube feeding can be hampered by a number of obstacles. Slow initiation and advancement of infusion rates, and frequent but often avoidable interruptions of feeding, can prevent adequate delivery of nutritional support. A standard tube feeding order form, infusion protocol, and ongoing education of staff can expedite achievement of nutritional goals and avoid unnecessary delays.[53,54]

For patients with gastric or nasointestinal feeding tube access, formula can be initiated at full strength at 20–25 ml/h and advanced by 20 ml increments every 8–12 h until goal is reached. Patients with intraoperatively placed feeding jejunostomy tubes who receive immediate postoperative enteral feeding require more conservative advancement.

Although EN is considered safer than PN, complications can occur. Successful enteral therapy largely depends on the astute clinician who is knowledgeable about assessment, appropriate formula selection, access route, and monitoring guidelines. Tube feeding complications are generally characterized as mechanical, gastrointestinal, or metabolic. Pulmonary aspiration, a potentially lethal complication of EN, deserves special attention.

By strictly adhering to protocols and using available technology, fear of aspiration should not contraindicate tube feeding as the chosen route of therapy. Risk of aspiration increases in patients who are neurologically impaired or have gastroparesis, an incompetent lower esophageal sphincter, or large bore nasogastric tube for feeding.[55] Most aspiration is of oropharyngeal secretions and not gastric contents, so postpyloric access does not offer an advantage over gastric feeding for minimizing aspiration risk.[56,57]

Debate continues regarding the maximum residual volume allowed before tube-feeding infusion is decreased or stopped to prevent aspiration. McClave et al. found that although elevated residual volume was common, most of the time it was an isolated event and did not correlate with physical findings.[58] Authors suggested that for gastric residual volume (GRV) levels exceeding 200 ml, assessment by physical exam and radiography should be done to assess for other signs of intolerance (i.e., abdominal distension, tympany). If no other signs of intolerance can be detected, enteral feeding can generally continue. Increasing abdominal distension and discomfort are worrisome, and feeding should be suspended until GI function is evaluated.[58,59]

To prevent aspiration, one should keep the head of the bed elevated at least 30–45°, monitor GRV every 4 h in gastrically fed patients, add promotility agents, reduce sedation, and position feeding tube lower in the GI tract if necessary. While postpyloric feeding tube placement has not definitively

been shown to reduce aspiration risk,[57] GI tolerance generally improves and nutritional goals are more likely to be achieved. In patients unable to tolerate gastric feeds, access to the small bowel can be obtained at the bedside, during surgery, by endoscopy, or radiology.[60]

Diarrhea resulting from tube feeding is relatively rare. Adhering to infusion protocols, using fiber containing formulas, opting for a closed vs. open feeding system, and practicing good hand washing technique can prevent diarrhea in tube-fed patients. Medications are a common culprit. H2 receptor antagonists, anti-neoplastics, laxatives, antacids, potassium, magnesium, phosphorus supplements, and sorbitol-containing elixirs are medications that commonly contribute to diarrhea. Infection caused by *Clostridium difficile* and antibiotic treatment may also cause diarrhea in the acutely ill. Probiotics such as Lactinex or Florastor may help restore normal gut flora and reduce diarrhea in patients receiving antibiotic therapy.[61–64] Constipation can also occur, particularly in immobilized patients on narcotics when fiber and free water are restricted. Close attention to the abdominal exam, use of fiber-containing formulas, routine bowel regimens, and adequate free water supplementation can prevent constipation.

Formula Selection

The goal of formula selection is to deliver the most clinically appropriate and cost-effective nutrition support. Enteral formulas can be categorized as standard polymeric, chemically defined, and immune enhancing.

Polymeric, high nitrogen, fiber-containing products are acceptable for first-line therapy for most critically ill patients with normal digestive and absorptive functions. Organ-specific formulas for renal, hepatic, and pulmonary insufficiency are available, but data to support improved outcome are lacking.[65] Chemically defined formulas, also known as elemental or peptide-based formulas, are designed for patients with malabsorption syndromes or those who require bowel rest or very low fat intakes. Clinical indications for elemental formulas may include acute pancreatitis, chyle leaks, transition to EN following a prolonged NPO period, and small bowel malabsorption syndromes.[66]

Immune Enhancing Diets

Nutritional therapy has advanced beyond the debate over how much to feed and now focuses on providing specific novel nutrients or "neutraceuticals," which may be necessary to alter the course of the disease or illness and achieve a better outcome. Over the past decade, an abundance of research investigating tissue-specific and immune-enhancing nutrients has been published. These formulas generally contain higher amounts of glutamine, arginine, omega-3 fatty acids, and nucleotides than standard products. Clinical trials comparing immunomodulating formulas to standard products have demonstrated improved outcomes, including reduced septic, infectious, and wound complications, shorter lengths of stay, less time on mechanical ventilation, and reduced hospital costs.[67–77]

However, in a recent extensive meta-analysis, Heyland et al. did not find a statistically significant benefit of immunonutrition on mortality or infectious complications across the board and, in fact, found that they may be potentially harmful.[78,79] Heyland examined 2,400 patients in 22 randomized trials involving IEDs and found that septic patients who received formulas high in arginine, upon subgroup analysis, had a higher mortality rate. Authors concluded that immunonutrition is not associated with clinical benefits in all critically ill patients and may be harmful in some.[78] The Canadian Critical Care Practice Guidelines advise explicitly against the use of diets supplemented with arginine for septic patients.[32]

The US Summit on Immune Enhancing Enteral Therapy, in an attempt to clarify recommendations, proposed a benefit for patients undergoing elective GI surgery who were moderately to severely malnourished and patients presenting with blunt and penetrating torso trauma.[80] Ideally, immune enhancing formulas should be started preoperatively and continued during the immediate postoperative period via small bowel feeding tube. Formula should be advanced to provide 1,200–1,500 Kcal or 50–60% of nutrient goals for no more than 5–10 days. When tube feeding continues beyond this period, a standard enteral product increased to provide 100% of nutrient goals can be initiated. The role and safety of arginine-supplemented formula in critically ill septic patients require further study.[81,82]

Parenteral Feeding

Despite the overwhelming evidence supporting use of EN as the preferred route for nutrition, certain clinical conditions will require PN as the best feeding option. PN is administered to patients whose GI tract is not functioning or cannot be accessed, and to those whose nutritional needs cannot be met with oral diets or enteral tube feeding.[14]

Indication

Nonfunctioning or inaccessible GI tract due to obstruction, peritonitis, profound ileus, short bowel syndrome, high output fistula with either of the following:

1. Prolonged NPO period (>7–10 days). Initiate by SICU day 5–7
2. Severe malnutrition. Initiate as soon as hemodynamically and metabolically stable

Because of its complexity, PN requires careful monitoring by trained clinicians to avoid serious complications. Prior to initiation of PN, patients should be hemodynamically stable, and have good glycemic control and satisfactory fluid, electrolyte, and acid base status.

Careful assessment of calorie and protein needs is critical to avoid the consequences of overfeeding. PN is generally not initiated at goal caloric requirement because of the potential for substrate intolerance from stress-induced diabetes. Protein goals can be met on day 1, but initial maximum dextrose load is limited to 150–200 g to prevent hyperglycemia and/or refeeding syndrome.[83] Refeeding syndrome is characterized by acute intracellular shifts of electrolytes as cell anabolism is stimulated. It can occur in response to large dextrose loads in malnourished or septic patients. Severe hypophosphatemia, commonly observed in refeeding syndrome, can precipitate respiratory failure.[84] Additional symptoms may include congestive heart failure, cardiac arrhythmias, and mental confusion. Refeeding syndrome can be prevented by initiating PN at a rate lower than required goal (primarily by reducing dextrose calories) and by adding supplemental amounts of phosphorus, magnesium, and potassium to the parenteral solution. To help prevent hyperglycemic complications, goal dextrose infusion rates should not exceed 5 mg dextrose/kg/min.

Because of the immunosuppressive nature of currently available lipid emulsions, fat is restricted to 15–30% of energy needs or less than 1 g fat/kg/day and infused slowly over 10–24 h. Lipids are held for triglyceride levels greater than 400 mg/dl.[85] High levels of omega-6 fatty acids, found in commercially available lipid emulsions, when given in large doses over short periods of time, lead to the production of arachidonic acid, a precursor to the family 2 series of eicosanoids and the 4 series leukotrienes. These are potent immunosuppressive agents and act by inhibiting macrophage activity and T-suppressor cell proliferation.[86] Clinical consequences of excessive lipid infusion may include impaired immune function, hyperlipidemia, and hypoxemia. Triglyceride levels above 1,000 mg/dl can cause pancreatitis.[87] Propofol, a commonly administered sedative in SICU patients, can provide a significant source of lipid calories and contribute to overfeeding and immunosuppression. Patients receiving propofol infusion at rates greater than 10 ml/h should not receive intravenous lipid and should have triglyceride levels monitored.[87]

Lipid-free PN regimens (in patients not receiving propofol) are not recommended. In critical illness, persistent hyperglycemia leading to sustained endogenous insulin release or exogenous insulin infusion will reduce lipid mobilization from fat stores, rendering adipose tissue unavailable as an energy source. Without lipid emulsion (even in the presence of obesity) essential fatty acid deficiency can develop. A modest lipid dose (250 ml of a 20% or 50 g lipid emulsion 2–3 times/week) can provide an essential fatty acid source and an important protein-sparing effect, replace a percentage of the dextrose calories to facilitate glycemic control, and help minimize fluid burden.

Patients receiving PN must be monitored closely for fluid, electrolyte, and acid base disorders. PN volume can be expanded or restricted to meet fluid needs, but use of maximally concentrated PN solutions is generally necessary in critically ill patients because of the fluid burden of other therapies. Metabolic acid base disturbances may respond to adjustments in chloride or acetate content of PN, but acid base disorders of respiratory origin respond best to management of the ventilator or underlying disorder.

Table 37.3. Recommended daily electrolyte additions. These electrolytes should be adjusted based on the patient's daily laboratory studies.

Sodium chloride	60–150 mEq/day
Sodium acetate	As needed
Sodium and/or potassium phosphate	15–30 mM/day
Potassium chloride	60–100 mEq/day
Potassium acetate	As needed
Calcium gluconate	9 mEq/day
Magnesium sulfate	8 mEq/day

Table 37.4. Parenteral nutrition (PN) administration guidelines.

Nutrient	Guideline
Calories	Initiate at <20 kcal/kg/body weight, increase gradually
Protein	1.5–2 g protein/kg/IBW, monitor prealbumin, nitrogen balance
Carbohydrate	Initiate at 150–200 g dextrose; gradually increase to goal upon glycemic control
Lipid	<1 g lipid/kg/day, infuse over 12–24 h, hold if triglyceride (TG) level > 400 mg/dl or propofol infusion>10 ml/h
Fluid	Max concentrate to meet nutrient needs, monitor I/Os, weight changes, peripheral edema, tachycardia
Blood work	Monitor daily glucose, sodium, potassium, phosphate, calcium, magnesium, chloride, CO2, blood urea nitrogen (BUN), creatinine, and CBC

Electrolyte abnormalities are common in SICU patients, can impact on organ function, and contribute to respiratory, neuromuscular, and cardiac complications. Fluid and electrolyte status should be monitored closely and provided in amounts to sustain adequate urine output and normal serum electrolyte concentration. Potassium, phosphorus, and magnesium requirements will vary with renal function, GI losses, and medications. Electrolyte and mineral requirements increase with protein synthesis and are carbohydrate-dependant; therefore, repletion doses may be required for the first few days of PN.[89] Early supplementation of these nutrients will prevent metabolic complications (Tables 37.3 and 37.4).

Metabolic Complications of Parenteral Nutrition

Hypophosphatemia

Hypophosphatemia can decrease diaphragmatic muscle contraction and reduce red blood cell 2, 3 DPG, which can impair tissue oxygenation, delay weaning from the ventilator, and

may contribute to respiratory arrest.[89] Common causes include administration of large dextrose loads (due to intracellular shifts), drug administration (insulin, epinephrine, phosphorus binding antacids, sucralfate), phosphorus free PN, refeeding syndrome, and alcoholism. Recommended bolus dosages range from 15 to 60 mmol depending on the severity of the deficiency and renal function. A recent study suggests that a dose of 1 mmol/kg to treat severe hypophosphatemia is safe.[90] Phosphorus should not be replaced too rapidly (7.5 mmol/h), in order to prevent hypocalcemia and metastatic calcium phosphate deposition in tissues.

Hypomagnesemia

Hypomagnesemia can cause hypocalcemia and contribute to refractory hypokalemia. Causes may include diarrhea, diuretics, alcoholism, and antibiotics. Again, repletion dose is on the basis of degree of severity and renal function. Magnesium can be given in 2–8 g doses/24 h.[91] Less than 5% of the total body magnesium is in the intravascular space; therefore, serum magnesium is a poor indicator of total body magnesium stores. Repletion of magnesium should be considered in patients with refractory hypokalemia not responding to potassium repletion.

Hyperglycemia

Hyperglycemic complications of PN (caused by overfeeding, medications, diabetes, metabolic stress, infection, trauma, or surgery) can adversely affect immune function, fluid balance, and, ultimately, outcome. In vitro studies show that even modest elevations of blood sugar are associated with cellular immunity and can negatively impact leukocyte function, chemotaxis, phagocytosis, and intracellular killing. In a 1991 landmark study, the VA Cooperative trial demonstrated that infection rate in PN-fed patients was twice that of controls. The higher infection rate was associated with hyperglycemia and overfeeding.[92] Serum glucose concentrations of 150–200 mg/dl have long been considered acceptable in stressed patients. However, recent data demonstrates that maintaining blood glucose control between 80 and 110 mg/dl reduces complications and improves outcome in SICU patients. Van den Burghe et al. in a prospective randomized controlled trial evaluated effects of intensive versus conventional insulin infusion therapies in 1,548 adult SICU patients. Surgical patients were randomized to receive intensive insulin therapy to maintain blood glucose levels between 80 and 110 mg/dl or to receive conventional insulin regimens to maintain blood glucose levels between 180 and 200 mg/dl. Results showed that intensive insulin therapy was associated with a 34% reduction in overall hospital mortality and 46% reduction in septicemia. Intensive insulin therapies reduced mortality in the SICU from 8 to 4.6%, and in patients who remained in the SICU greater than 5 days, mortality decreased from 20 to 10.6% compared to conventional insulin therapy – a 50% reduction in mortality. Intensive insulin therapy was also associated with reduced morbidity factors such as acute renal failure requiring dialysis, ventilator dependency, and polyneuropathy.[93] Although the risk of hypoglycemia was higher with tight glycemic control, Van den Berghe reported no clinically adverse consequences. Similar yet not so dramatic results have been shown in medical ICU patients.[94]

All patients on PN require close blood glucose monitoring. Even when patients are stable and euglycemic, abrupt hyperglycemia can occur with addition of steroids, epinephrine infusion, peritoneal dialysis, or continuous renal replacement therapy. It is equally important to avoid hypoglycemia. Potential causes include excess insulin dose, abrupt cessation of nutritional support, resolution of the inflammatory process, steroid weaning, and renal failure.[95]

Strategies to prevent glycemic complications:

- Obtain glucose level prior to initiating PN. Do not start PN if serum plasma glucose concentration >200 mg/dl.
- Avoid overfeeding.
- Limit initial dextrose load to 150–200 g.
- Check blood sugar every 6 h and administer sliding scale coverage.
- For diabetics previously treated with insulin or oral hypoglycemic agents, or for patients with 2 or more glucose values above 120–180 mg/dl, add a basal amount of insulin to PN. Start with 0.1 unit of insulin per gram dextrose; i.e., 15 units insulin for 150 g dextrose. If over a 24-h period glucose values exceed goal, increase PN insulin by 0.05 units per gram dextrose/day to a total level of 0.2 units insulin per gram dextrose.
- PN dextrose should not be increased until glucose values for the previous 24 h are in goal range.
- PN insulin should be proportionally adjusted when PN dextrose content is increased or decreased to keep the insulin-to-dextrose ratio the same (example: 30 u of insulin for 150 g dextrose would increase to 40 u insulin for 200 g dextrose. The insulin:dextrose ratio is maintained at 1:5.
- If two consecutive glucose values are above 180 mg/dl, it is reasonable to initiate an insulin infusion.
- Maintaining optimal glycemic control in a critically ill SICU patient is probably best achieved by using an insulin infusion, separate from enteral or parenteral therapy.
- If patients develop hypoglycemia, parenteral dextrose should be administered and PN insulin should be reduced by 50%.

Evaluating Nutrition Support Efficacy

Formulas provide a rough estimate of calorie and protein needs, so the potential still exists for over or underfeeding. Nutritional monitoring can verify calculations and help assure adequacy of the nutrition prescription. There are a variety of testing parameters available. No single test can accurately assess efficacy. Serum albumin, prealbumin, and transferrin are the most commonly monitored serum proteins, but accurate evaluation must

consider the half-life, fluid status, organ function, and presence of infection. Serum albumin concentration is a poor marker of nutritional depletion or repletion given its long half-life of 21 days, but is recognized as an excellent prognostic indicator.[42]

Prealbumin and transferrin have shorter half-lives of 3 and 8 days, respectively, and are considered more sensitive indicators of nutritional response.[96] Baseline levels should be drawn, and then measured weekly while on nutrition support. Observing trends in direction is more useful than assessment of a single level. If prealbumin and transferrin concentrations fail to trend upward, then checking the level of an acute phase reactant such as C-reactive protein (CRP) can be helpful. High circulating levels of CRP indicate that low protein status is due to ongoing stress/infection/inflammation and hepatic reprioritization of protein synthesis, and not inadequate nutritional support. Only when CRP levels fall below 10–18 mg/dl can the liver synthesize other proteins such as albumin, prealbumin, and transferrin. Once CRP levels fall, prealbumin should rise. Expect an increase in prealbumin of 3–7 mg/dl/week with adequate nutritional support. Efficacy of nutritional therapy should be questioned if prealbumin concentrations remain unchanged in face of falling CRP levels.

Improvement in nitrogen balance is the single nutrition parameter most consistently associated with improved outcome. A primary goal of nutritional support is the achievement of positive nitrogen balance. Although the nutritional goal is positive nitrogen balance, it is difficult to achieve in the critically ill patient, especially during the early stages of illness. Only when the underlying illness is controlled or resolved will positive nitrogen balance become feasible.

Nitrogen balance is calculated by subtracting excreted nitrogen (24-h urine urea nitrogen or UUN) plus insensible losses (4 g/day) from nitrogen intake (grams protein divided by 6.25). Measurement of UUN is less reliable in patients with creatinine clearance of less than 50 ml/min, severe hepatic failure, massive diuresis, inaccurate urine collection, or abnormally high nitrogen losses through stool, burns, or fistula.

Other important parameters to assess efficacy of nutritional therapy include rate of wound healing, ability to wean from the ventilator, and the patient's functional status.

Conclusion

Over the past 20 years, the importance of nutritional support in the management of critically ill patients has emerged. Nutritional assessment and early identification of patients who would benefit from nutritional therapy are critical. The complications of PN versus EN (i.e., infections, immunocompromise, metabolic derangements, and probable contribution to bacterial translocation) are well recognized and clearly establish EN as the more favorable route of feeding. Specialized EN with immune enhancing nutrients has been shown to decrease inflammation, improve cell mediated immunity, and influence outcome; however, routine use of these formulas in all critically ill patient populations is not recommended. PN will continue to play an important supportive role in patients who cannot be fed enterally. PN can be life saving, but uncontrolled and inappropriate use can escalate hospital costs and negatively impact patient outcomes such as infectious complications, length of stay, and mortality.

Caloric support should be based on measured energy expenditure or 20–25 kcal/kg/body weight/day. Protein requirements range from 1.5 to 2.5 g/protein/kg/IBW/day in most SICU patients. One should attempt to avoid overfeeding, maintain tight glycemic control, and limit lipid calories (including lipid-based medication such as propofol). Electrolyte status, fluid balance, and renal and liver function should be closely monitored so that appropriate daily adjustments to nutrition prescriptions can be made. Cooperation between SICU intensivists, GI endoscopists, radiologists, and surgeons is vital to develop an interdisciplinary approach to obtaining access for enteral feeding. Multidisciplinary management of nutrition care including a pharmacist and clinical dietitian can optimize nutrition therapy and minimize complications in critically ill patients.

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Part VIII
Nephrology and Electrolytes

38
Acute Kidney Injury

Paolo Calzavacca, Elisa Licari, and Rinaldo Bellomo

Acute kidney injury (AKI) is the new consensus term for various degrees of acute renal injury or failure.[1,2] We will use this term throughout this chapter instead of the previous term "failure" in keeping with such consensus statements. AKI is a frequently diagnosed in patients in the intensive care unit (ICU).[3–5] Unfortunately, until recently, the definition of AKI has been a confounding element in its epidemiology.[6] This is because the diagnosis of AKI is complex and involves data obtained from history, biochemical analysis, body size, sex, hematological information, and imaging. Accordingly, depending on the definition used,[7] the incidence of AKI in ICU is in the range of 1–25%.[8–12] In order to develop a widely accepted definition of AKI to facilitate communication and research in this field, the second International Consensus Conference of the Acute Dialysis Quality Initiative in 2002 proposed a classification scheme for AKI.[2] It produced the so-called RIFLE (risk, injury, failure, loss, and end-stage) criteria for the classification and definition of AKI. These criteria use creatinine and urine output (UO) and consider changes from baseline creatinine value in reaching a classification[2] (Fig. 38.1). Many patients may present with acute renal dysfunction without any baseline measure of renal function. This presents a problem for such a system. However, the simplified Modification of Diet in Renal Disease (MDRD) formula provides a robust estimate of glomerular filtration rate (GFR) relative to serum creatinine on the basis of age, race, and sex. Thus, given a patient without known renal disease and in whom a baseline creatinine is unknown, one can estimate the baseline creatinine clearance. Table 38.1 solves the MDRD equation for the lower end of the normal range (i.e., 75 ml/min per 1.73 m^2). Note that the MDRD formula is used only to estimate the baseline GFR when it is not known.

The RIFLE classification has now been applied to study the epidemiology of AKI in ICU patients[7] and the findings so far confirm the high incidence of this syndrome at 40–67%,[10,13–15] with mortality as high as 50–85%[13,16] for ICU patients. Sepsis has been shown to be the single most common cause of AKI in ICU, accounting for about 50% of cases of AKI.[17,18] Other frequent causes of AKI in ICU are major surgery, which has been described as the trigger in up to 20–40% of cases in some series,[19] radiocontrast nephropathy, low cardiac output, and hypovolemia.[19]

In this chapter, we review the classification, pathophysiology, diagnosis, and management of AKI.

Classification and Pathophysiology of AKI

AKI is a syndrome characterized by an abrupt decrease in glomerular filtration rate (GFR) that leads to a decrease in urinary output and an accumulation of nitrogenous (urea and creatinine) and non-nitrogenous waste products. This, in turn, causes metabolic derangements, namely acidosis through accumulation of nonvolatile acids and chloride, and alteration in electrolytes (sodium, potassium, phosphate, magnesium) and fluid homeostasis. It also has effects on many other organs.[20]

The GFR is a function of the difference in intracapillary and interstitial hydrostatic and oncotic pressure, the so-called Starling forces:

$$\mathrm{GFR} = K[(P_c - P_i)] - \sigma(\pi_c - \pi_I)]$$

where, $Pc - Pi$ is the difference between interstitial and hydrostatic pressure; $\pi c - \pi i$ is the difference between interstitial and capillary oncotic pressure; K is the filtration coefficient; and σ is the reflection coefficient.

Traditionally, AKI has been classified into *pre-renal, renal* (or *parenchymal*), and *post-renal*.[20,21] This classification is on the basis of the presumed pathophysiological mechanisms underlying the syndrome; i.e., if the renal failure is

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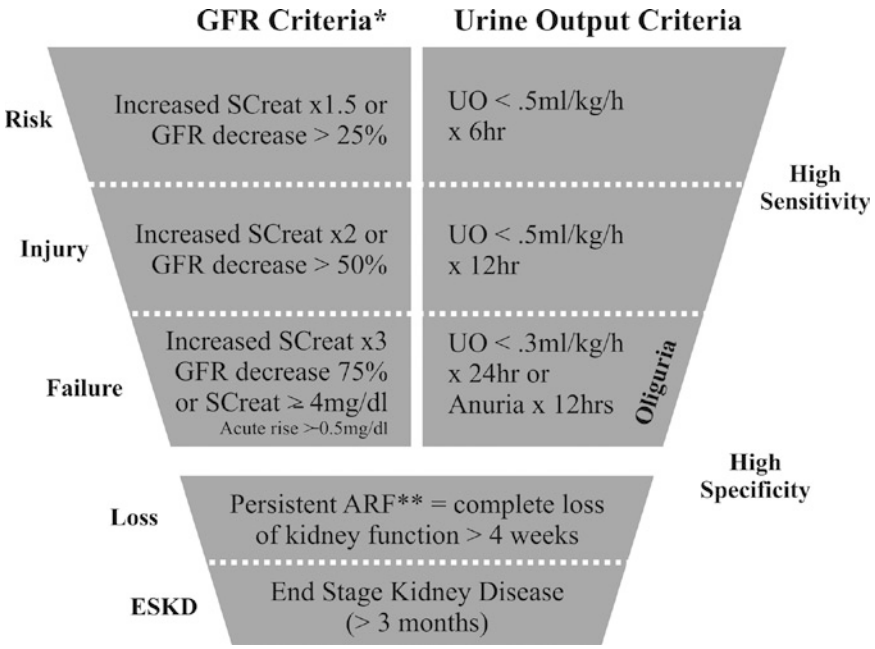

FIG. 38.1. Graphic summary of the RIFLE criteria. *SCreat* serum creatinine concentration; *UO* urine output; *GFR* glomerular filtration rate; *ARF* acute renal failure. Reprinted from ref. 8 with permission from BioMed Central.

TABLE 38.1. MDRD formula to estimate baseline creatinine.

Age (years)	Black males µmol/l (mg/dl)	Other males µmol/l (mg/dl)	Black females µmol/l (mg/dl)	Other females µmol/l (mg/dl)
20–24	133 (1.5)	115 (1.3)	106 (1.2)	88 (1.0)
25–29	133 (1.5)	106 (1.2)	97 (1.1)	88 (1.0)
30–39	124 (1.4)	106 (1.2)	97 (1.1)	80 (0.9)
40–54	115 (1.3)	97 (1.1)	88 (1.0)	80 (0.9)
55–65	115 (1.3)	97 (1.1)	88 (1.0)	71 (0.8)
>65	106 (1.2)	88 (1.0)	80 (0.9)	71 (0.8)

The formula assumes that:
Estimated glomerular filtration rate = 75 (ml/min per 1.73 m^2) = 186 × (serum creatinine [SCr]) − 1.154 × (age) − 0.203 × (0.742 if female) × (1.210 if black) = exp(5.228 − 1.154 × In [SCr]) − 0.203 × In(age) − (0.299 if female) + (0.192 if black).

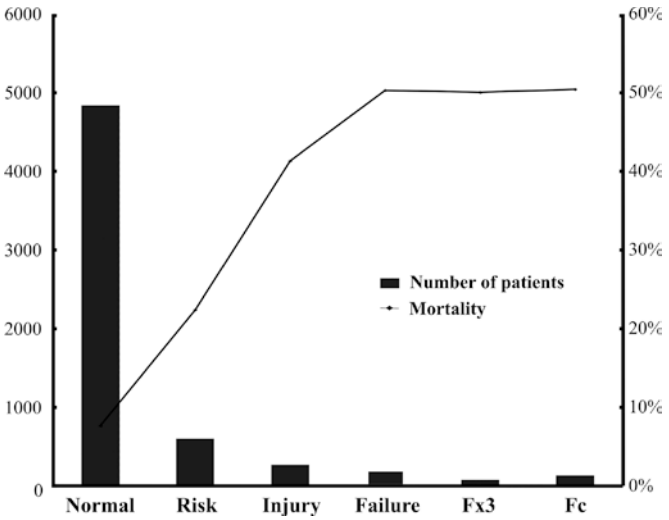

FIG. 38.2. Diagram summarizing the causes of AKI. See text for more details. *RBF* renal blood flow; *IAP* intra abdominal pressure.

due to causes "before" the kidney, in the kidney, or "after" the kidney.

This classification can be useful at the bedside both for diagnostic orientation and treatment purposes. It should be highlighted, however, that the distinction between pre-renal and renal AKI has been traditionally on the basis of a clear division between functional (loss of GFR without histopathological injury) and structural AKI (acute tubular necrosis). New evidence does not support this approach. Moreover, the treatment of these two "types" of AKI should not be different. In Fig. 38.2, we present a possible approach to the patient with AKI, together with a summary of the most common causes leading to AKI in ICU.

Pre-renal AKI

So-called pre-renal AKI is likely the most common form of AKI in the ICU, accounting for 60% of cases of AKI.[20,21] The term pre-renal indicates that the reason for the loss of renal function lies outside the kidney (e.g., decreased cardiac output, hypovolemia, sepsis, or raised intra-abdominal pressure). Thus, pre-renal AKI traditionally implies a physiologic response to decreased renal blood flow (RBF). Systemic hemodynamic disturbances causing pre-renal AKI include true or relative hypovolemia and septic shock. Causes of true hypovolemia include dehydration of any cause (burns, diarrhea, bleeding, vomiting), while causes of relative hypovolemia include congestive heart failure and chronic liver disease. Other causes of pre-renal AKI include drugs affecting renal perfusion. This is the case with NSAIDs, which can induce vasoconstriction of the pre-glomerular arteriole,[22] or ACE inhibitors, which can cause vasodilation of post-glomerular arteriole via blockage of angiotensin II production,[23] thereby decreasing the driving hydrostatic force responsible for GFR.

Unfortunately, there is limited evidence on changes in RBF in septic shock (the most common cause of AKI in ICU), the major pathophysiologic mechanism of AKI. For example, only a few studies have been performed specifically addressing the issue of RBF in septic shock. A recent meta-analysis[24] found no study in which RBF in humans was measured with a suitably accurate method. The few studies show a normal or increased RBF in severe sepsis/septic shock. Moreover, the kidney is able to autoregulate RBF in a wide range of arterial pressure through a combined modification of afferent and efferent arteriolar tone (unless pharmacological interferences, as in the case with ACE inhibitors, cause alteration of this mechanism). Thus, GFR may reflect intra-renal hemodynamic changes rather than systemic hemodynamic changes. From those findings, questions arise about the pathophysiological appropriateness of the term "pre-renal AKI" or "pre-renal azotemia."[25,26]

Renal (Parenchymal) AKI

Intra-renal causes of AKI have traditionally been divided into four groups: glomerular, interstitial, vascular, and tubular. The most common in the ICU may be the tubular form, also known as acute tubular necrosis (ATN). This form, in turn, is considered to be an evolution of pre-renal AKI in which prolonged functional derangement turns into structural damage. The other three forms do not appear as frequently in the ICU and are only briefly reviewed.

Glomerular Disease

Glomerulonephritis and vasculitis can cause glomerular disease. They are characterized by systemic manifestation – such as fever, rash, and arthritis – and renal symptoms like hematuria and proteinuria. Renal biopsy can be necessary for this diagnosis.

Interstitial Disease

Acute interstitial nephritis is typically caused by an "allergic" reaction to a drug[27] or by direct nephrotoxicity of the drug with or without involvement of an immunological mechanism. In Table 38.2, we present a list of nephrotoxic drugs with a presumed causative mechanism. Symptoms and signs of this form of AKI may include rash, fever, eosinophilia, or eosinophiluria. Although uncommon in the ICU, this cause of AKI must be considered, as it is potentially reversible with discontinuation of the drug. Other causes of interstitial disease leading to AKI are autoimmune diseases (i.e., lupus erythematosus, scleroderma), infections, and infiltrative diseases (i.e., sarcoidosis). Corticosteroids can be beneficial. If a drug is suspected, immediate withdrawal is warranted.

Vascular Disease

Aortic dissection, renal artery thrombosis or stenosis, and atheroembolism must be considered in elderly patients. Vasculitis, disseminated intravascular coagulation, thrombotic

TABLE 38.2. Endogenous and exogenous substances and drugs commonly associated with AKI in ICU and presumptive causative mechanism. Some drugs appear in different classes, due to the fact that different mechanisms are supposed to be involved in the genesis of renal damage.

Mechanism	Drug class	Drugs
Interstitial nephritis	Antibiotics	Penicillins, cephalosporins, quinolones, sulfonamides, trimethoprim, rifampin
	Diuretics	Frusemide, thiazide diuretics
	NSAIDs	
	Other	Cimetidine, phenytoin, allopurinol
Nephrotoxins (via production of oxygen radicals?)	Antibiotics	Aminoglycosides, foscarnet, amphotericin B, pentamidine, retrovirals (AZT)
	NSAIDs	
	ACE inhibitors	
	Radiocontrast media	
	Antineoplastic drugs	Methotrexate, cisplatin, ifosfamide
	Other	Hemoglobin, myoglobin, cyclosporine, tacrolimus, cocaine, heavy metals, myeloma light chains
Obstruction (intraglomerular casts)	Mineral calculi	Uric acid, calcium oxalate
	Myeloma light chains	
	Antibiotics	Acyclovir, sulphonamides
	Myoglobin	
Alteration of RBF	NSAIDs, ACE inhibitors	
	Myoglobin	
	Antibiotics	Amphotericin B
Unknown	Vancomycin	

thrombocytopenic purpura, hemolytic uremic syndrome, and microangiopathic hemolytic anemia are other possible causes of AKI of vascular origin.

Tubular Disease or ATN

Ischemia or nephrotoxins are traditionally thought to be the causes of ATN.[28,29] Nephrotoxins are substances that cause renal damage via direct glomerular cell toxicity (for example, myoglobin), through hemodynamic disturbances (radiocontrast media), or by causing an immune-mediated insult (see above, interstitial nephritis). Common risk factors for acute toxic kidney disease are chronic renal derangements, cardiovascular disease, older age, diabetes mellitus, jaundice, and concomitant use of nephrotoxic agents.[30]

Ischemia, on the other hand, is considered a continuum of injury beginning with pre-renal AKI when hypovolemia is not corrected and RBF not adequately restored. Pre-renal AKI, however, according to the traditional view of AKI, is only a functional state, while parenchymal AKI is characterized by structural damage (so-called ATN), in which the histopathology should show a characteristic picture. Unfortunately, although an attractive explanation of AKI physiopathology, the evidence supporting the validity of this concept in modern ICUs is limited. The origin of the definition of ATN, indeed, comes from animal models[31] that poorly reflect clinical situations and from old biopsy data obtained from anuric patients during the Second World War[32] and the Korean War.[33]

The first description of ATN was in postmortem autopsies performed in four patients who died after air-raid casualties in the Second World War.[32] In these patients, rhabdomyolysis due to crush injuries was first recognized as a cause of AKI. Necropsy revealed degenerative changes and casts containing brown pigment in the renal tubules (of note, only in three of the four cases was hypotension reported as being present during the admission and it was not sustained). Oliguria was already present before the drop in pressure in all four cases. During the Korean War[33], similar findings (i.e., patchy tubular necrosis, mostly isolated to the thick, ascending Henle's loop) were found in patients who died after AKI. Hypotension alone could not be incriminated in those cases of AKI as the causative mechanism of the microscopic findings and cells found in the urinary tubular casts of such patients were viable on staining studies, thus partly invalidating the term "necrosis."

Another practice that is coming under close scrutiny is the use and utility of blood and urine tests[34] to classify AKI into pre-renal, renal, and post-renal AKI. Such measurements include urine sodium level, urine/plasma creatinine ratio, urine osmolality, the so-called FeNa and FeU – excretion fraction of sodium/urea: urine Na (or urea) * plasma creatinine/urine creatinine * plasma Na (or urea) – and microscopy analysis of urinary sediment. Two recent systematic reviews[35,36] of all animal and human studies failed to show any evidence of discrimination, predictive ability, or diagnostic accuracy for septic states (which make up close to 50% of all cases). Accordingly, they can no longer be recommended.

Post-renal AKI

Although uncommon (only 5% of cases of AKI are classified obstructive post-renal AKI), post-renal AKI must always be ruled out, as AKI can usually be reversed in this setting. Some patients are more frequently prone to post-renal AKI: elderly patients, males, and patients with only one kidney.

Causes of post-renal AKI are usually mechanic and either extrinsic or intrinsic. They can affect the ureter or the bladder outlet:

- Extrinsic: retroperitoneal fibrosis, abdominal and pelvic cancer obstructing ureters, prostatic hypertrophy, or cancer. An important cause to look for is obstruction of the urinary catheter.
- Intrinsic: bilateral ureteric calculi, ureteric clot, neurogenic bladder (either pharmacologic or posttraumatic).

The treatment is on the basis of resolution of the mechanical obstruction via removal of the obstruction or via catheterization. A common complication of post-renal AKI is the development of marked polyuria after the removal of the obstruction. Appropriate fluid therapy is needed to avoid volume depletion in this setting and secondary kidney injury.

Radiocontrast Nephropathy

This is the third single most common cause of AKI and it accounts for approximately 10–30% of cases of AKI. Mechanisms involved in causing radio contrast-induced AKI (RIA) are likely to be direct renal hemodynamic alterations and direct tubular epithelial cell toxicity, possibly mediated by oxygen radicals.[37] Many trials have been conducted analyzing possible preventive strategies.[38] However, only pre-hydration with normal saline and use of iso-osmolar non-ionic media have been consistently found as protective against RIA[39–41] (see below).

- *Pre-hydration*. Good evidence exists that isotonic intravenous hydration is effective in reducing the incidence of RIA. A large randomized controlled trial (RCT)[42] showed a reduction in incidence of RIA in patients pre-treated with 0.9% saline vs. 0.45% saline in dextrose. The use of a sodium bicarbonate solution instead of 0.9% saline has been shown in a smaller RCT[43] to increase renal protection. Rate of fluid infusion has not been specifically addressed, but most studies have used a rate of 1 ml/kg/h for 6–12 h before and after the procedure. Oral hydration is less effective than intravenous hydration in preventing RIA.
- *Iso-osmolar non-ionic media* have been shown to be associated with a significantly lower incidence of RIA than ionic high-osmolality media in a multicenter RCT[44] in 1,196 patients and are now the standard of care.
- *N-acetylcysteine*. Many trials[45,46] and some meta-analyses[47,48] have been conducted, leading to contradictory findings.[49] Current consensus recommendations do not include *N*-acetylcysteine because, on meta-analysis, no consistent effect can be confirmed.

- *Theophylline*. The rationale in the use of this drug is that adenosine seems to have a role in the pathogenesis of RIA and its blockade with theophylline may be helpful. A recent meta-analysis[50] found a trend toward reduction in the incidence of RIA in patients treated with theophylline. No large RCT exploring the effect of this drug is available.
- *Fenoldopam*. A large, multicentric RCT[51] failed in finding a protective effect of this drug in the setting of RIA.
- *Mannitol*. Only one RCT[52] has specifically addressed the use of mannitol as a treatment to reduce the incidence of RIA, and it found a trend toward harm when mannitol was compared to hydration alone.
- *Hemofiltration* as a prophylactic measure has been shown in one small RCT to reduce incidence of RIA.[53] However, more evidence is probably necessary to recommend this intervention as a routine in high-risk patients.

AKI Associated with Hepato-Renal Syndrome

This condition is a form of AKI, which occurs in the setting of severe liver dysfunction in the absence of other known causes of AKI. It is associated with a high mortality rate. Typically, it presents as progressive oliguria with a very low urinary sodium concentration (<10 mmol/l). Its pathogenesis is not well understood. It is important to note, however, that in patients with severe liver disease other causes of AKI are much more common. They include sepsis, paracentesis-induced hypovolemia, raised intra-abdominal pressure due to tense ascites, diuretic- and lactulose-induced hypovolemia, alcoholic cardiomyopathy, and any combination of the above causes. Thus, these other causes must be looked for, diagnosed, and promptly treated. The avoidance of hypovolemia by albumin administration in patients with spontaneous bacterial peritonitis has been shown to decrease the incidence of AKI in a single center RCT.[54] Small studies also suggest that a vasopressin derivative called terlipressin may improve GFR in this condition.[55,56]

Rhabdomyolysis-Associated AKI

This condition accounts for close to 5–10%[57] of cases of acute renal failure (ARF) in the ICU, depending on the setting. Its pathogenesis involves pre-renal, renal, and post-renal factors. Myoglobin may cause renal toxicity both directly and indirectly through intra-renal vasoconstriction and formation of casts in the tubule. This type of AKI is now typically seen following major trauma, drug overdose with narcotics, vascular embolism, and in response to a variety of agents, which can induce major muscle injury. The principles of treatment are on the basis of retrospective data, small series, and multivariate logistic regression analysis, because no RCTs have been conducted. They include prompt and aggressive fluid resuscitation, elimination of causative agents, correction of compartment syndromes, alkalinization of urine (pH>6.5), and maintenance of polyuria (>300 ml/h). The role of mannitol is controversial.[30]

Diagnostic Tools

The most common clinical picture seen in the ICU is that of a patient who has sustained a major systemic insult (trauma, sepsis, myocardial infarction, severe hemorrhage, cardiogenic shock, major surgery, and the like). This kind of patient is likely to have an extra-renal trigger of AKI. Nevertheless, a careful history of drug administration is mandatory in all patients with AKI to exclude the use of nephrotoxins, as well as to look for possible post-renal obstruction. In some cases of parenchymal AKI (glomerulonephritis, vasculitis), a correct working diagnosis can often be obtained from history, physical examination, and radiological and laboratory investigations. In such patients, one may choose to proceed to a therapeutic trial without the need to resort to renal biopsy. However, if aggressive immunosuppressive therapy is considered, renal biopsy should be considered to confirm the diagnosis. Renal biopsy in ventilated patients under ultrasound guidance does not carry additional risks compared to standard conditions. If a drug is suspected to cause AKI, it should be promptly discontinued. Causes of post-renal AKI must always be ruled out, as they are easily reversed. Ultrasonography and CT scanning of the kidneys can be helpful in diagnosing and treating such conditions.

When looking at creatinine and urea values in plasma, it must be remembered that these tests of renal function are insensitive markers of GFR, as they can be heavily modified by nutrition, use of steroids, presence of gastrointestinal bleed, age, gender, muscle injury, and muscle mass.

More than a third of patients who develop AKI in the ICU have chronic renal dysfunction due to factors such as age-related changes, long-standing hypertension, diabetes, or atheromatous disease of the renal vessels. Such chronic renal dysfunction may be manifested by a raised serum creatinine. However, this is not always the case, especially in elderly patients with decreased muscle mass. In such patients with markedly diminished GFR but "normal" creatinine levels, often what may seem to the clinician to be a relatively trivial insult, which does not fully explain the onset of AKI in a normal patient, is sufficient to unmask lack of renal functional reserve and lead to AKI.

Treatment Options

Unfortunately, a specific treatment for AKI is not available, nor is there convincing evidence that supporting preventive measures have a clear impact.[8] Hence, we will here discuss what are the best options currently available and the evidence available to support their use.

The principles of management of established AKI are the *treatment* or *removal* of its cause and the *maintenance of physiological homeostasis* while recovery takes place.[58] These principles appear sound, rational, and pathophysiologically appropriate, but have not been tested in randomized controlled

trials. Some drugs have been reported to be associated with renal damage.[27] In Table 38.2, some of the most common drugs used in ICU that have been shown to have a potential nephrotoxicity are summarized. They should be removed in patients with AKI. Complications such as encephalopathy, pericarditis, myopathy, neuropathy, electrolyte disturbances, or other major electrolyte, fluid, or metabolic derangement should never occur in a modern ICU. Their prevention may include several measures, which vary in complexity from fluid restriction to the early initiation of extracorporeal renal replacement therapy.

Nutritional support must be started as soon as possible, preferably through the enteral route, unless contraindicated.[59] Although no adequately powered RCTs have been conducted specifically addressing nutritional protocols in AKI, adequate nutrition remains an important component of critical care support of all patients. Thus adequate caloric intake (25–30 kcal/kg/day) as a mixture of carbohydrates and lipids[60–62] and adequate protein intake (about 1.2–2.0 g/kg/day) must be administered.[61–63] The composition of amino acids solutions does not influence the outcome. During continuous renal replacement therapy (CRRT), an amount that approximates 10% of amino acids can be lost through the dialysate. Bearing this in mind, it is important to adjust protein intake accordingly in order to avoid a negative nitrogen balance. Nitrogen balance must be carefully monitored and protein malnutrition must be avoided, as it has been extensively shown to increase risk of death in ICU patients.[64] If increased nitrogen intake leads to an uncontrolled increase in plasma urea concentration, CRRT should be instituted and protein intake should not be decreased. There is no evidence that specific "renal" nutritional solutions are clinically useful. Vitamins and trace elements should be administered at least according to their recommended daily allowance. In renal replacement therapy (RRT) patients, additional amounts of vitamin C, folate, vitamins B1 and B6, and selenium should be considered, as these elements can be lost via CRRT.[65,66]

Hyperkalemia (>6 mmol/l) must be promptly treated either with insulin and dextrose administration or nebulized salbutamol. Bicarbonate infusion is recommended if acidosis is present. If the "true" serum potassium is >7 mmol/l or electrocardiographic signs of hyperkalemia appear, calcium gluconate (10 ml of 10% solution IV) should also be administered. The above measures are temporizing actions, while renal replacement therapy (RRT) is being set up. The presence of hyperkalemia is a major indication for the immediate institution of renal replacement therapy (see following). *Metabolic acidosis* is almost always present but rarely requires treatment. If pronounced, it should prompt immediate consideration for RRT. *Anemia* requires correction to maintain a hemoglobin level of at least >7 g/ml. Use of erythropoietin in ICU patients with AKI remains controversial.[67] More aggressive transfusion requires individual patient assessment. *Drug therapy/dosing must be adjusted* to take into account the effect of the decreased clearances associated with loss of renal function. *Stress ulcer prophylaxis* is advisable and should be based on H2-receptor antagonists or proton pump inhibitors in selected cases. Assiduous attention should be paid to the *prevention of infection*. *Fluid overload* should also be prevented. This can occasionally be achieved with loop diuretics. However, in ICU patients who require fluids for medications and nutrition, the only way to prevent fluid overload may be to initiate RRT. Clinically important (e.g., pulmonary edema) fluid overload is an indication for RRT. *Marked azotemia*: urea > 40 mmol/l (240 mg/dl or blood urea nitrogen [BUN] > 120 mg/dl) or creatinine > 400 μmol/l (4,5 mg/dl) is undesirable and should probably be treated or even prevented with RRT unless recovery is imminent or already under way and a return toward normal values is expected within 24 h.[68] It is recognized, however, that no RCTs exist to define the ideal time for intervention with RRT.

Consideration should be given to the introduction or development of a *rapid response* or *medical emergency team system*. In a single-center before-and-after study, this intervention has been shown as a potentially effective prophylactic measure to prevent AKI in at-risk surgical patients from hospital wards.[69]

What follows is a more detailed discussion and review of evidence for some specific treatments traditionally used for the management of AKI.

- One of the cornerstones of treatment of AKI has always been *fluid resuscitation*, the rationale being restoration of RBF and renal perfusion. This is normally instituted together with invasive monitoring systems in order to guide it. Unfortunately little evidence is available, at least in septic patients, that this practice is truly helpful in preventing and treating AKI.[70,71] In addition, a recent study in 1,000 patients with acute lung injury showed no difference in renal outcome in patients allocated to receive a restricted fluid protocol vs. patients allocated to receive liberal fluid resuscitation.[72] A long-lasting matter of debate has been the use of crystalloid or colloid as a fluid for resuscitation. The SAFE trial (Saline versus Albumin Fluid Evaluation)[73] – a multicentric, randomized, controlled trial that enrolled nearly 7,000 patients – found no differences in new organ failure, UO, or in the number of RRT days in patients treated with albumin or saline for fluid resuscitation. This suggests that there is no intrinsic advantage or disadvantage in terms of AKI from using albumin or saline. The use of starches, on the other hand, deserves a separate discussion. In a multicentric, randomized study published in 2001, 129 patients received medium-weight hydroxyethylstarch 6%. An increased risk of developing AKI or need for RRT when compared to 3% gelatine (O.R. 2.57) was found. These findings are consistent with our recent trial (VISEP trial, Efficacy of Volume substitution and Insulin Therapy in Severe Sepsis), a randomized comparison of crystalloid (Ringer's lactate) and colloid (10% HES) fluid therapy in critically ill patients with severe sepsis.

- *Restoration of MAP* toward near-normal levels may increase GFR, although, once more, randomized controlled evidence is lacking. This can be achieved through vasopressor drugs and/or inotropic drugs.[74–76] When circulatory function is highly compromised and pharmacological treatment is not enough, application of ventricular-assist devices or intra-aortic balloon pump should be considered.
- Another treatment that has been long debated is the use of *low* (or *renal*) *dose dopamine* (LDD). In 1963–1964,[77,78] LDD was described for the first time to increase renal blood flow (RBF) both in humans and animals, and to sustain diuresis and natriuresis. Since then, many studies have been published trying to demonstrate that LDD can increase RBF.[79,80]

Unfortunately, many of the studies performed in the 1970s and 1980s looking at clinical outcomes are uncontrolled or underpowered. In the 1990s, many authors began discouraging its use because of lack of evidence.[81–83]

Since 2000, four meta-analyses,[84–87] several reviews,[88–90] and the first and, so far, only large multicentric double-blind, placebo-controlled RCT[91] have been published. Findings of those meta-analyses and the large RCT trial are as follows:

1. There is no evidence that LDD can reduce mortality or prevent renal dysfunction.
2. If any beneficial effect exists in the use of LDD, it consists of an increase in urine output. This effect, however, is not sustained.
3. Concerns exist on safety of LDD use due to interaction of dopamine with the cardiovascular,[92,93] respiratory,[94] gastrointestinal,[95,96] immune,[97,98] and endocrine[99,100] systems.
4. LDD does not lead to predictable dopamine levels in the critically ill.[101]
5. Increasing diuresis seems to have no apparent benefit on important clinical outcomes.[86,91]

In conclusion, in such a context of no demonstrable advantage and some doubts and concerns about safety, LDD use should now be avoided.

- *Fenoldopam mesylate* is a drug that produces systemic and renal vasodilation.[102] Fenoldopam decreases systemic vascular resistance and it increases RBF[103] in healthy volunteers in a dose-dependent manner, with the greatest effect when infused in the range of 0.03 and 0.1 μg/kg/min.[104] During the last decade, fenoldopam has been studied in many different situations associated with renal dysfunction or as a prophylactic nephroprotective drug in different clinical settings.[51,105–108] Unfortunately, so far, only underpowered studies have been performed.
- *Diuretics* have been traditionally used to try converting oliguric to non-oliguric renal failure.[109] Moreover, loop diuretics are considered to have a function in decreasing oxygen demand of renal cells.[110] Unfortunately, many of the studies available on diuretics are underpowered and have found contradictory findings. Two large multicentric observational studies[19,111] arrived at contradictory conclusions. Two recent meta-analyses[112,113] on use of furosemide and loop diuretics, respectively, failed in finding convincing evidence of decreased mortality or better renal recovery associated with the use of diuretics vs. placebo. Thus, their use remains controversial.
- A biological rationale exists for *mannitol* use. However, no controlled human data exist to support its clinical use. The effect of mannitol as a renal protective agent remains questionable.[52,114]
- *Vasopressin* is an endogenous hormone released in circulatory shock. It exerts a vascular effect (vasoconstriction via stimulation of V1-receptor on smooth muscle[115]) and it has been shown to have renal protection potential in septic patients in low dose (0.01–0.04 U/min in adult), and in association with noradrenaline.[116] Sufficient evidence, nevertheless, is still lacking.
- *Renal replacement therapy* is an artificial substitute for lost renal function. For a detailed discussion of RRT see Chap. 39. There is neither consensus nor a multicenter trial to help define the right timing for RRT in ICU patients. It would be inappropriate, nonetheless, to use the same criteria applied for chronic kidney disease to the initiation of RRT in AKI patients. It seems advisable to institute RRT more promptly in ICU patients than in chronic patients.[117] In Table 38.3, we have summarized proposed modern indications for RRT in the ICU.

Table 38.3. Proposed criteria for initiation of renal replacement therapy in ICU patients with AKI.

Proposed criteria for renal replacement therapy
Acute pulmonary edema
Oliguria: urine output <200 ml over 12 h
Anuria: urine output <50 ml over 12 h
Hyperkalemia: $K^+ > 6.5$ mmol/l or >6.0 with ECG changes
Severe acidemia: pH < 7.1
Azotemia: urea > 30 mmol/l (180 mg/dl or BUN > 90 mg/dl)
Uremic encephalopathy
Uremic neuropathy/myopathy
Uremic pericarditis
$Na^+ > 155$ mmol/l or <120 mmol/l
Hyperthermia
Drug overdose with dialyzable toxin (i.e., digoxin, valproate)

Conversions: urea in mmol/l to urea in mg/dl = multiply by 6.
Urea in mg/dl to urea in mmol/l = multiply by 0.1665.
Urea in mg/dl to BUN in mg/dl= multiply by 0.46.
BUN in mg/dl to urea in mg/dl = multiply by 2.14.
BUN in mg/dl to urea in mmol/l = multiply by 0.357.
Urea in mmol/l in BUN in mg/dl = multiply by 3.

Conclusions

1. Diagnosis of AKI: The RIFLE classification has now created a consensus classification and definition system. The term acute kidney injury (AKI) is now preferred to acute renal failure (ARF).

2. Post-renal causes of AKI must always be ruled out. Nephrotoxic substances must be removed. A search for sepsis, decreased cardiac output, and hypovolemia is mandatory in all patients.
3. No specific drug can be recommended for renal protection.
4. Restorations of plasma volume and perfusion pressure are likely important and should be achieved promptly. Crystalloids and colloids are broadly equivalent. The use of diuretics is controversial.
5. The management of a patient in the ICU with AKI is not different from the treatment of other ICU patients, and should be guided by the principles of the homeostasis.
6. The only treatment of established AKI available is RRT and early institution of this mode of therapy seems advisable.

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39
Renal Replacement Therapy

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Introduction

Endogenous toxins accumulate in blood as a result of many biochemical processes.[1] If their concentration exceeds certain levels, they cause illness. Some toxins are volatile (e.g., CO2, ketones) and can be excreted by the lungs through ventilation; others are lipophilic (e.g., bile acids, bilirubin) and can be excreted by the liver via the biliary system; yet others are water soluble and nonvolatile and are excreted by the kidneys.[2] When acute kidney injury (AKI) occurs, these water-soluble substances (potassium, phosphate, urea, creatinine) and endogenous toxins (methylguanidine, guanidinosuccinic acid, hippuric acid, uric acid, phenols, beta-2 microglobulin, purines, myo-inositol, etc.), which are normally excreted by the kidney, accumulate in blood. If accumulation progresses, AKI becomes severe; and if their removal is not addressed by either renal recovery or the initiation of artificial renal replacement therapy, the patient dies from uncontrolled hyperkalemia or uremia. Unfortunately, AKI requiring renal replacement therapy (RRT) is relatively common in critically ill patients treated in the intensive care unit (ICU) and involves close to 5% of all admissions.[3] When a decision is made that artificial renal replacement therapy is needed, the physician has a variety of techniques at his/her disposal: intermittent hemodialysis (IHD), continuous renal replacement therapy (CCRT), slow extended daily dialysis (SLEDD), and peritoneal dialysis, each with its technical variations. All of these techniques rely on the principle that unwanted solutes and water can be removed through a semipermeable membrane-based separating process. The principles of such process have been extensively studied and described.[4,5]

In this chapter, we summarize some of these principles and technical aspects of RRT. We also discuss several aspects of the practice of RRT, which are particularly relevant to the critical care physician.

General Principles

In general, there is a tendency in intensive care medicine toward a more preventive strategy, which tries to maintain physiologic homeostasis, and avoid any unnecessary deterioration in the patient's physiological state.[6,7] In adult patients with acute renal failure requiring renal replacement therapy in ICUs in developed countries, the major therapeutic options are acute intermittent dialysis (IHD) or continuous renal replacement therapy (CRRT). Peritoneal dialysis remains an option in developing countries and in children. The intensive care physician needs to understand several fundamental principles of these modalities and techniques.

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Dialysis

The process of dialysis as applied to patients typically consists of a combination of ultrafiltration and diffusion. Ultrafiltration drives the movement of water across a semipermeable membrane.

- In peritoneal dialysis, the movement of water from the patient into the dialysate is propelled by an osmotic gradient caused by the high concentration of solutes in the dialysate.
- In hemodialysis (intermittent or continuous), the movement of the water is propelled by a trans-membrane hydrostatic pressure gradient, which is greater than the oncotic pressure in blood and is proportional to the ultrafiltration coefficient of the dialysis membrane (function of its surface area, composition, thickness, and porosity).

Diffusion refers to the movement of small molecules down their concentration gradient.

- In peritoneal dialysis, the diffusion of solutes from the patient into the dialysate is driven by the concentration gradient between plasma and peritoneal fluid.
- In hemodialysis (intermittent or continuous), the diffusion of solutes from the patient into the dialysate is driven by the concentration gradient between plasma and fresh dialysate.

Solute clearance during hemodialysis is mostly a function of four factors:

- Blood flow rate (only blood delivered to the membrane over a unit of time can be cleared)
- Dialysate (sufficient dialysate needs to be delivered to achieve equilibration with blood)
- Membrane surface area and permeability (needs to be appropriate to allow equilibration and the movement of target solutes)
- Time of the treatment (the duration of treatment is clearly important)

The dialysate solution typically consists of sodium, chloride, bicarbonate, calcium, magnesium, potassium, and dextrose in water. The concentrations of sodium and chloride approximate those in plasma. Because the concentration of bicarbonate generally exceeds that of plasma in patients with renal failure, there is a net diffusion of bicarbonate from the dialysate into the plasma. Concentration of magnesium in the dialysate is usually less than that of plasma, so removal of magnesium generally occurs during IHD. The concentration of potassium is variable and can be adjusted depending on the patient's serum potassium level. Also calcium concentration is variable depending on clinical indication. The glucose concentration is generally higher than in plasma, so net diffusion of glucose into the patient often occurs during IHD.

The dialysis membranes are either cellulose-based or polymer-based.

1. Cellulose-based membranes cost less, but tend to have a low ultrafiltration coefficient and a higher level of "bioincompatibility." Some types of cellulose membrane activate complement through the alternative pathway leading to agglutination of white blood cells in the lung and transient hypoxemia.
2. Polymer membranes are costlier, but are more biocompatible. The high porosity of some of these may augment the convective removal of uremic toxins.[8]

Adequate access to blood circulation must be obtained and maintained in patients undergoing hemodialysis to sustain extracorporeal blood flow rates of typically about 200–300 mL/min. In acute renal failure, a double-lumen central venous catheter with two large bore lumens is typically inserted to provide such access. Patients are often given anticoagulation during renal replacement therapy to prevent thrombosis in the extracorporeal circuit (see details below).

Continuous Renal Replacement Therapy (CRRT)

The term CRRT encompasses several techniques. The technical options available are:

- Continuous veno-venous hemofiltration (CVVH)
- Continuous veno-venous hemodialysis (CVVHD)
- Continuous veno-venous hemodiafiltration (CVVHDF)
- Continuous arterio-venous hemofiltration/hemodiafiltration

The principles of CRRT are simple. Blood flows through a semipermeable membrane (as in IHD) driven either by the patient's blood pressure (arterio-venous mode) or by a peristaltic pump (veno-venous mode). In the former case, one needs arterial and venous cannulae for vascular access; in the latter case, one needs a double-lumen central venous catheter. In developed countries, arterio-venous access has essentially been abandoned because of safety concerns, and all therapy is now done with veno-venous techniques. The semipermeable membrane of the filter is typically synthetic and high-flux, and does not allow any significant passage of molecules >30 kD.[9]

If the technique is one of continuous hemodialysis, the principles of intermittent hemodialysis apply. The only difference is that the intensity is lesser with CRRT (typically at a clearance of 30–35 mL/min instead of 300 mL/min) but applied over 24 h instead of 3–4 h.

Continuous hemofiltration, on the other hand, achieves solute and water removal only through the process of "convection" where water is driven across the filtering membrane by the trans-membrane pressure generated by blood flow. Solute moves across the membrane with water in a process called "solvent drag." Such water and solutes need to be replaced with replacement fluids, which contain appropriate buffer and electrolyte concentrations and which must be delivered at a rate sufficient to replace losses. Such fluid can be delivered before (pre-dilution) or after (post-dilution) the membrane.

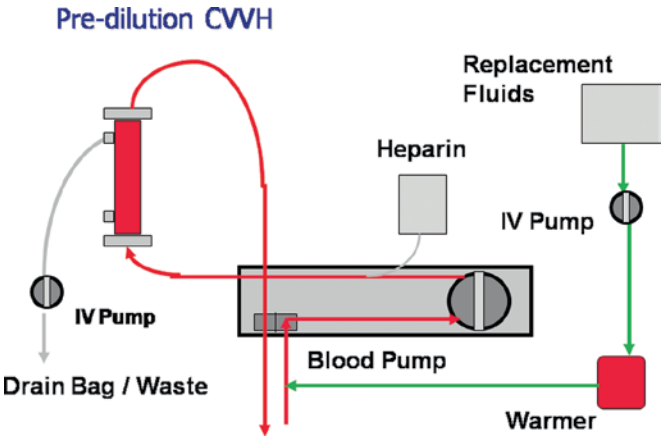

FIG. 39.1. Schematic representation of a continuous veno-venous hemofiltration circuit (CVVH) in pre-dilution mode.

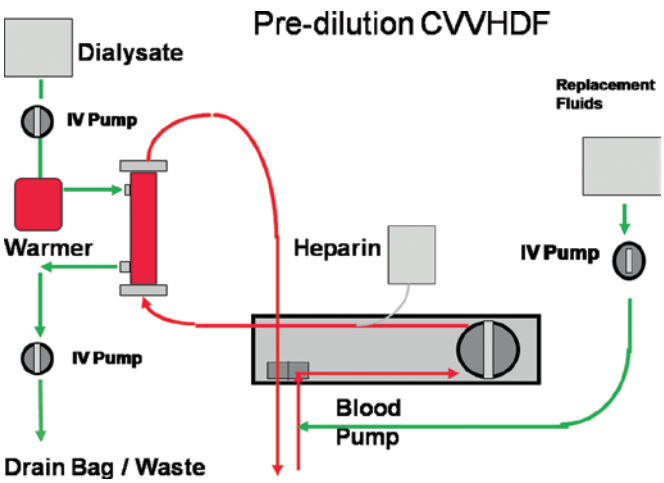

FIG. 39.2. Schematic representation of a continuous veno-venous hemodiafiltration circuit (CVVHDF) in pre-dilution mode.

If fluid loss is desired, then replacement may be set at a rate below losses sufficient to achieve the desired volume loss.

Hemodiafiltration combines both processes and techniques (diffusion and convection or hemodialysis and hemofiltration) by including replacement fluid and dialysate in the circuit.

Schematic representations of several CRRT circuits are presented in Figs. 39.1, 39.2, and 39.3.

The high flux membranes used for CRRT have permeability cut-off points up to 30 kDa. Some of the membranes (especially polyacrylonitrile and polysulfone membranes) have a significant adsorptive capacity. Such adsorption appears to affect several inflammatory mediators.[10,11] Anticoagulation of circuit is necessary to avoid clotting due to the activation of coagulation cascade.

Peritoneal Dialysis

Peritoneal dialysis (PD) is typically a long-term treatment alternative for patients with end stage renal disease. A dialysate

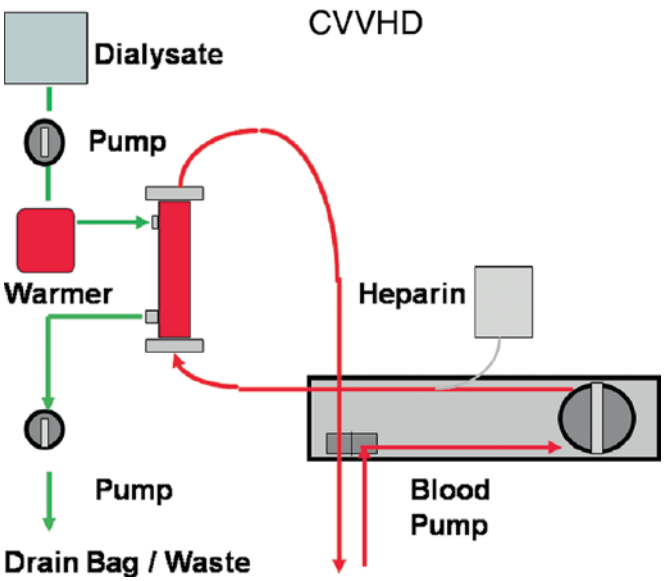

FIG. 39.3. Schematic representation of a continuous veno-venous hemodialysis circuit (CVVHD) in pre-dilution mode.

solution containing balanced electrolytes and high concentration of glucose is introduced in the peritoneal cavity. Uremic toxins diffuse across peritoneal capillaries, through the interstitium, across the peritoneal mesothelial layer and into the peritoneal cavity. Fluid is removed when water in the blood moves across these peritoneal layers into the hyperosmotic dialysate along an osmotic gradient. Toxins and water are removed when the dialysate is drained from the peritoneal cavity.[12]

Several major shortcomings make PD relatively unsuited for the treatment of ARF:

1. Limited solute clearance
2. Risk of peritonitis
3. Hyperglycemia
4. Peritoneal fluid leakage
5. Loss of protein
6. Interference with function of diaphragm

Nonetheless, PD is less expensive than other modalities and can be used in developing countries. It is also particularly more useful in children, where vascular access is difficult and where the surface of the peritoneal membrane is greater relative to body size, than in adults.

Slow Extended Daily Dialysis

This modality has emerged recently in the treatment of ICU patients with AKI.[13] It is known by its acronym (SLEDD). SLEDD is essentially a form of intermittent hemodialysis, where the treatment time has been extended (typically 8–12 h instead of 3–4 h), the intensity of treatment decreased (urea clearances of 100–150 mL/min), and the frequency of treatment delivered daily.

Indications for Renal Replacement Therapy

In the critically ill patient, RRT should be initiated early, prior to the development of complications. Fear of early dialysis stems from the adverse effects of conventional IHD with cuprophane membranes, especially hemodynamic instability, and from the risks and limitations of continuous or intermittent PD. However, continuous renal replacement therapy (CRRT) or slow extended daily dialysis (SLEDD)[13] minimizes these effects. The criteria for the initiation of RRT in patients with chronic renal failure may be inappropriate in the critically ill.[14,15] The recommended criteria for starting RRT are presented in the previous chapter dedicated to AKI.

With either IHD or CRRT or SLEDD there is limited data on what is "adequate" intensity of dialysis. However, this concept should include maintenance of homeostasis at all levels, and better uremic control may translate into better survival.[16,17] An appropriate target urea might be 15–25 mmol/L, with a protein intake around 1.5 g/kg/day. This can be easily achieved using CRRT at urea clearances of 35–45 L/day depending on patient size and catabolic rate. If intermittent therapy is used, daily and extended treatment as described with SLEDD becomes desirable.[15]

Mode of Renal Replacement Therapy

There is a great deal of controversy as to which mode of RRT is "best" in the ICU, due to the lack of randomized controlled trials comparing different techniques. In their absence, techniques of RRT may be judged on the basis of the following criteria:

1. Hemodynamic side effects
2. Ability to control fluid status
3. Biocompatibility
4. Risk of infection
5. Uremic control
6. Avoidance of cerebral edema
7. Ability to allow full nutritional support
8. Ability to control acidosis
9. Absence of specific side effects
10. Cost

CRRT and slow low-efficiency daily dialysis (SLEDD) offer many advantages over PD and conventional IHD (3–4 h/day, 3–4 times/week); while CRRT is almost exclusively used in some centers, only 20–30% of American ICU patients receive CRRT. Some salient clinical aspects of the practice of CRRT, IHD, and PD in ICU require discussion.

Continuous Renal Replacement Therapy

First described in 1977, CRRT has undergone several technical modifications and is now typically delivered by the veno-venous mode. No matter what technique is used, the following clinical outcomes of CRRT are predictable:

1. Continuous control of fluid status
2. Hemodynamic stability
3. Control of acid-base status
4. Ability to provide protein rich nutrition while achieving uremic control
5. Control of electrolyte balance, including phosphate and calcium balance
6. Prevention of swings in intracerebral water
7. Minimal risk of infection
8. High level of biocompatibility

However, CRRT mandates the presence of specifically trained nursing and medical staff 24 h a day. Small ICUs often cannot provide such a level of support. If CRRT is only used 5–10 times/year, the cost of training may be unjustified and expertise may be hard to maintain. Furthermore, depending on the organization of patient care, CRRT may be more expensive than IHD. Finally, the issues of continuous circuit anticoagulation and the potential risk of bleeding have been major concerns.

Dose of CRRT and Circuit Anticoagulation

The optimal dose (expressed at effective effluent/kg/h) of CRRT remains unknown. Several studies suggest that a higher dose may translate into better outcome.[16,18] However, such studies have been single center in nature and require confirmation in multicenter, randomized, controlled trials. Such trials are now under way.[19]

The flow of blood through an extracorporeal circuit causes activation of the coagulation cascade and promotes clotting of the filter and circuit itself. In order to delay such clotting and achieve acceptable operational lives (approximately 24 h) for the circuit, anticoagulants are frequently used.[20] However, circuit anticoagulation increases risk of bleeding. Therefore, the risks and benefits of more or less intense anticoagulation and alternative strategies (Table 39.1) must be considered.

In the vast majority of patients, low-dose heparin (<500 IU/h) is sufficient to achieve adequate filter life, is easy and inexpensive to administer, and has almost no effect on the patient's coagulation profile. In some patients, a higher dose is necessary. In others (pulmonary embolism, myocardial

Table 39.1. Strategies for circuit anticoagulation during CRRT.

1.	No anticoagulation
2.	Low-dose pre-filter heparin (<500 IU/h)
3.	Medium-dose pre-filter heparin (500–1,000 IU/h)
4.	Full heparinization
5.	Regional anticoagulation (pre-filter heparin and post-filter protamine usually at a 100 IU to 1 mg ratio)
6.	Regional citrate anticoagulation (pre-filter citrate and post-filter calcium – special calcium-free dialysate needed)
7.	Low-molecular weight heparin
8.	Prostacyclin
9.	Heparinoids
10.	Serine proteinase inhibitors (nafamostat mesylate) (only in Japan)

ischemia) full heparinization may actually be concomitantly indicated. Regional citrate anticoagulation is effective, but requires a special dialysate or replacement fluid.[21] Regional heparin/protamine anticoagulation is also somewhat complex, but may be useful if frequent filter clotting occurs and further anticoagulation of the patient is considered dangerous. Low molecular weight heparin is also easy to administer, but is expensive. Its dose must be adjusted for the loss of renal function. Heparinoids and prostacyclin may be useful if the patient has developed heparin-induced thrombocytopenia and thrombosis. Finally, in perhaps 10–20% of patients, anticoagulation is best avoided because of endogenous coagulopathy or recent surgery. In such patients adequate filter life can be achieved provided that blood flow is kept at about 200 mL/min and vascular access is reliable.[22]

Many circuits clot for mechanical reasons (inadequate access, unreliable blood flow from double-lumen catheter depending on patient position, kinking of catheter). Responding to frequent filter clotting by simply increasing anticoagulation without making the correct etiological diagnosis (checking catheter flow and position, taking a history surrounding the episode of clotting, identifying the site of clotting) is often futile and exposes the patient to unnecessary risk. Particular attention needs to be paid to the adequacy/ease of flow through the double-lumen catheter. Smaller (11.5 Fr) catheters in the subclavian position are a particular problem. Larger catheters (13.5 Fr) in the femoral position appear to function with greater reliability

CRRT Technology

The increasing use of veno-venous CRRT has led to the development of a field of CRRT technology that offers different kinds of machines to facilitate its performance. Some understanding of these devices is important to the successful implementation of CRRT in any ICU. One can have a simple blood pump with safety features (air bubble trap and pressure alarms), and use widely available volumetric pumps to control replacement or dialysate flow and effluent flow. Such adaptive technology is inexpensive, but is not user friendly. Also, volumetric pumps have an inherent inaccuracy of about 5%, which, in a system exchanging up to 50 L/day, can cause problems.[23] Various manufacturers have now produced custom-made machines for hemofiltration. These machines are safer and have more sophisticated pump control systems, alarms, and graphic displays. They are user friendly, especially with the set-up procedure.

The choice of membrane is also a matter of controversy. There are no controlled studies to show that one of them confers a clinical advantage over the others. The AN 69 is the most commonly used CRRT membrane. The issue of membrane size is also controversial, as no controlled studies have compared different membrane surface sizes. If high-volume hemofiltration is planned, however, the membrane surface needs to be in the 1.6–2 m^2 range.

Intermittent Hemodialysis

Vascular access is typically by double-lumen catheter as in continuous hemofiltration. The circuit is also the same. Countercurrent dialysate flow is used as in CVVHD. The major differences are that standard IHD uses high dialysate flows (300–500 mL/min), generates dialysate by mixing purified water and concentrate, and treatment is applied for short periods of time (3–4 h), usually every second day. These differences have important implications. Firstly, volume has to be removed over a short period of time and this may cause hypotension.[2] Repeated hypotensive episodes may adversely affect renal recovery.[24] Secondly, solute removal is episodic. This translates into inferior uremic control, and acid-base control. Limited fluid and uremic control imposes unnecessary limitations on nutritional support. Furthermore, rapid solute shifts increase brain water content and raise intracranial pressure.[25] Finally, controversy has surrounded the issue of membrane bioincompatibility. However, given the limited difference in cost between biocompatible and bioincompatible low-flux membranes, biocompatible membranes (polysulfone) are now preferred in ARF patients.

The limitations of applying "standard" IHD to the treatment of ARF has led to the development of new approaches (so-called "hybrid techniques") such as SLEDD. These techniques seek to adapt IHD to clinical circumstances and thereby increase its tolerance and clearances.

Peritoneal Dialysis

With peritoneal dialysis, access is typically by the insertion of an intra-peritoneal catheter. Glucose rich dialysate is then inserted into the peritoneal cavity, which acts as the "dialysate." After a given "dwell time" it is removed and discarded with the extra fluid and toxins that have moved from the blood vessels of the peritoneum to the dialysate fluid. Machines that deliver and remove dialysate at higher flows are also available, providing intermittent treatment and higher solute clearances. There have not been any reports of the sole use of PD for the treatment of adult patients with ARF in the last 15 years. A randomized trial comparing PD to CVVH found that PD was associated with increased mortality.[26]

Other Blood Purification Techniques

Hemoperfusion

During hemoperfusion, blood is circulated through a circuit similar to one used for CVVH. However, a charcoal cartridge is perfused with blood instead of a dialysis membrane. In some cases an ion exchange resin (Amberlite) has been used. Charcoal microcapsules effectively remove molecules of 300–500 D in molecular weight, including some lipid soluble

and protein bound substances. Heparinization is necessary to prevent clotting. Attention must also be paid to changes in intravascular volume at the start of therapy because of the large priming volume of the cartridge (260 mL). Glucose absorption is significant and monitoring of blood glucose is necessary to avoid hypoglycemia. Thrombocytopenia is also common, and can be marked. The role of hemoperfusion is controversial, as no controlled trials have ever shown it to confer clinically significant advantages. It may be useful, however, in patients with life-threatening theophylline overdose because it removes the agent effectively.

Plasmapheresis or Plasma Exchange

With this technique, plasma is removed from the patient and exchanged with fresh frozen plasma (FFP) and a mixture of colloid and crystalloid solutions. This technique can also be performed in an ICU familiar with CRRT techniques. A plasmafilter (a filter that allows the passage of molecules up to 500 kD) instead of a hemofilter is inserted in the CVVH circuit, and the filtrate (plasma) discarded. Plasmapheresis can also be performed with special machines using the principles of centrifugation. The differences, if any, between centrifugation and filtration technology are unclear. Replacement (postfilter) will occur as in CVVH using for example, a 50/50 combination of FFP and albumin. Plasmapheresis has been shown to be effective treatment for thrombotic thrombocytopenic purpura (TTP) and for several diseases mediated by abnormal antibodies (Guillan-Barré syndrome, cryoglobulinemia, myasthenia gravis, Goodpasture's syndrome etc.) in which antibody removal appears desirable. Its role in the treatment of sepsis remains uncertain.[27]

Blood Purification Technology Outside of ARF

There is growing interest in the possibility that blood purification may provide a clinically significant benefit in patients with severe sepsis/septic shock by removing circulating "mediators." A variety of techniques including plasmapheresis, high-volume hemofiltration,[28] coupled plasma filtration adsorption,[29] and large pore hemofiltration[30] are being studied in animals, ex-vivo, and in phase I/II studies in humans. Initial experiments support the need to continue exploring this therapeutic option. However, no suitably powered randomized controlled trials have yet been reported.

Blood purification technology, in combination with bioreactors containing either human or porcine liver cells, is also under active investigations as a form of artificial liver support for patients with fulminant liver failure or for patients with acute-on-chronic liver failure. Albumin-based dialysis has been developed to deal with protein bound toxins in patients with liver failure. This system known as MARS (molecular adsorption re-circulating system) has shown benefits in patients with elevated intracranial pressure and/or acute-on-chronic liver failure, but not in patients with fulminant liver failure.[31]

Drug Prescription During Dialytic Therapy

Acute renal failure and RRT profoundly affect drug clearance. A comprehensive description of changes in drug dosage according to the technique of RRT, residual creatinine clearance, and other determinants of pharmacodynamics is beyond the scope of this chapter and can be found in specialist texts. Table 39.2 provides general guidelines for the prescription of drugs commonly used in the ICU.

Conclusion

The field of renal replacement therapy has undergone remarkable changes over the last 10 years and is continuing to evolve rapidly. Technology is being improved to facilitate clinical

TABLE 39.2.. Drug dosage during dialytic therapy.

Drug	CRRT	IHD
Aminoglycosides	Normal dose q36 h	50% normal dose q48 h-2/3 re-dose after IHD
Cefotaxime or Ceftazidime	1 g q8–12 h	1 g q12–24 h after IHD
Imipenem	500 mg q8 h	250 mg q8 h and after IHD
Meropenem	500 mg q8 h	250 mg q8 h and after IHD
Metronidazole	500 mg q8 h	250 mg q8 h and after IHD
Co-trimoxazole	Normal dose q18 h	Normal dose q24 h after IHD
Amoxicillin	500 mg q8 h	500 mg daily and after IHD
Vancomycin	1 g q24 h	1 g q96–120 h
Piperacillin	3–4 g q6 h	3–4 g q8 h and after IHD
Ticarcillin	1–2 g q8 h	1–2 g q12 h and after IHD
Ciprofloxacin	200 mg q12 h	200 mg q24 h and after IHD
Fluconazole	200 mg q24 h	200 mg q48 h and after IHD
Acyclovir	3.5 mg/kg q24 h	2.5 mg/kg/d and after IHD
Gancyclovir	5 mg/kg/d	5 mg/kg/48 h and after IHD
Amphotericin B	Normal dose	Normal dose
Liposomal Amphotericin	Normal dose	Normal dose
Ceftriaxone	Normal dose	Normal dose
Erythromycin	Normal dose	Normal dose
Milrinone	Titrate to effect	Titrate to effect
Amrinone	Titrate to effect	Titrate to effect
Catecholamines	Titrate to effect	Titrate to effect
Ampicillin	500 mg q8 h	500 mg daily and after IHD
Midazolam	Titrate to effect	Titrate to effect

The above values represent approximations and should be used as a general guide only. Critically ill patients have markedly abnormal volumes of distribution for these agents, which will affect dosage. CRRT is conducted at variable levels of intensity in different units also requiring adjustment. The values reported here relate to CVVH at 2 L/h of ultrafiltration. Vancomycin is poorly removed by CVVHD. IHD may also differ from unit to unit. The values reported here relate to standard IHD with low-flux membranes for 3–4 h every second day. d = day; q = frequency; h = hours.

application and new areas of research are developing. CRRT is now firmly established throughout the world as perhaps the most commonly used form of RRT. Conventional dialysis, however – which was slowly losing ground – is reappearing in the form of extended, slow-efficiency treatment, especially in the USA. Two large phase IV trials (>1,000 patients) are underway in the USA and in Australia/New Zealand to compare different dialytic strategies (IHD or SLEDD or CRRT) or to define the optimal dose of CRRT. The results should be available in 2008. Meanwhile, the use of novel membranes and sorbents in conjunction with different intensities of treatment is being explored in the area of sepsis management and liver support. The intensivist needs to keep abreast of this rapid evolution if he or she is to offer his or her patients the best of care.

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40
Disorders of Electrolytes

Flávio Eduardo Nácul

Introduction

Disorders of electrolytes are common in critically ill surgical patients. This chapter will discuss the etiology, diagnosis, and management of abnormalities of sodium, potassium, magnesium, calcium, and phosphorous.

Disorders of Sodium

Sodium is the major extracellular ion and has many important body functions such as regulation of plasma osmolality, participation in chemical reactions, and maintenance of neuromuscular excitability. Serum sodium concentration is the most important determinant of plasma osmolality,[1] which normally remains within a narrow range of 285–295 mOsm/kg. An increase in total body water (TBW) decreases both serum osmolality and vasopressin levels, while a decrease in TBW increases serum osmolality and vasopressin levels.

Hyponatremia

Hyponatremia is a well-recognized complication of the postoperative state[2] that is associated with increased morbidity and mortality.[3] Hyponatremia is defined as a serum sodium concentration of less than 135 mEq/L and is usually associated with hypoosmolality. Serum osmolality in mOsm/kg is calculated from serum concentrations of sodium (Na^+) in mEq/L and glucose and blood urea nitrogen (BUN) in milligrams/deciliter (mg/dL).

$$\text{Osm} = 2 \text{ plasma [Na+]+ glucose/18 + BUN/2.8}$$

Adaptations to hyponatremia occur in all body cells. They are important in the brain, which can expand by only 5–10% before herniation occurs.[4] Decreased serum osmolality results in movement of water into brain cells, which produces cerebral edema. Brain tissue rapidly responds and loses osmotically active solutes to maintain its normal size. Increased intracranial pressure produces a flow of water from the interstitium to the cerebrovascular fluid and then to the systemic circulation.[5–7]

Etiology

The causes of hyponatremia may be classified according to the plasma osmolality and the extracellular fluid status (Table 40.1).[8]

Clinical Manifestations

Hypoosmolality causes neurologic symptoms such as agitation, disorientation, confusion, delirium, obtundation, nausea, emesis, headaches, and seizures. Signs and symptoms are unusual when the sodium serum concentration is greater than 125 mEq/L.

Diagnostic Approach

The differential diagnosis of hyponatremia is based on plasma osmolality, urine osmolality, urine sodium concentration, and the clinical assessment of the extracellular fluid (ECF) (Fig. 40.1).

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Table 40.1. Causes of hyponatremia.

Decreased serum osmolality	
Decreased ECF volume	Diarrhea, use of diuretics, salt-losing nephropathy, Cerebral sodium-wasting syndrome (CSWS)
Normal ECF volume	Syndrome of inappropriate antidiuresis (SIAD), adrenal insufficiency, hypothyroidism
Increased ECF volume	Congestive heart failure, cirrhosis, nephrotic syndrome
Normal serum osmolality	
Hyperlipemia, hyperproteinemia (pseudohyponatremia)	
Elevated serum osmolality	
Hyperglycemia, use of mannitol, use of genitourinary irrigants such as sorbitol or glycine[8]	

ECF extracellular fluid.

Hypotonic Hyponatremia (Serum Osmolality <275 mOsm/L)

Hypotonic hyponatremia is the most common form of hyponatremia and can be divided into three categories based on the extracellular fluid volume: hypovolemic, euvolemic, and hypervolemic.

Hypovolemic

A practical approach is to classify hypovolemic hyponatremia into two groups: (1) patients with urinary sodium >20 mEq/L: diuretic overuse, cerebral salt wasting syndrome (CSWS), and

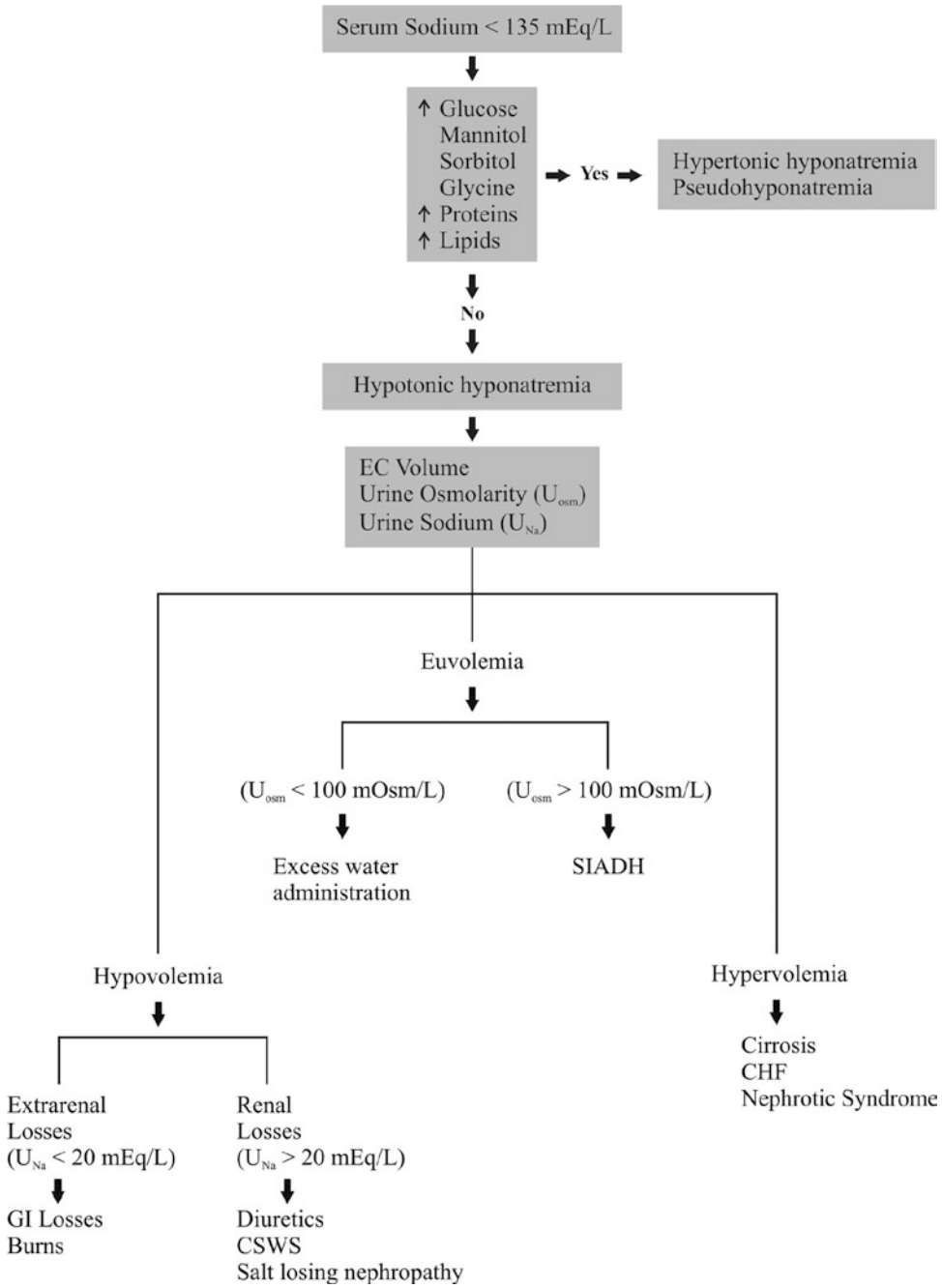

Fig. 40.1. Diagnostic approach to the critically ill patient with hyponatremia.

salt losing nephropathy; and (2) patients with urinary sodium <20 mEq/L: vomiting, diarrhea, sweating, and burns.

Diuretic-induced hyponatremia is probably the most common hyponatremic disorder encountered in clinical medicine, and is mainly associated with the use of thiazide diuretics.[9]

Cerebral salt wasting syndrome is defined as a renal loss of sodium during intracranial disease leading to hyponatremia and hypovolemia. The pathophysiology of CSWS is not yet fully established but is believed to be secondary to increased plasma concentration of natriuretic peptides released from the brain.[10]

Euvolemic

The syndrome of inappropriate antidiuresis (SIAD) is characterized by hyponatremia resulting from dilution of body fluid and increased excretion of sodium.[11,12] The normal response to hypoosmolality is to excrete a maximum diluted urine (osmolality <100 mOsm/kg and specific gravity <1.003). Because of the increased antidiuretic hormone (ADH) activity, the urinary osmolality is inappropriately elevated (>100 mOsm/kg and specific gravity >1.003). SIAD occurs primarily in association with trauma, malignancies, and infections of the central nervous system and lungs; acquired immunodeficiency syndrome (AIDS) and AIDS-related complex[13]; alcohol withdrawal; and the use of drugs such as chlorpromazine, carbamazepine, and opiates. The causes include meningitis, brain abscess, cerebral contusion, subdural and subarachnoid hemorrhage, brain tumors, pneumonia, lung cancer, and tuberculosis. Small-cell carcinoma of the lung is the most common malignancy associated with SIAD.[14] Patients with SIAD present with hyponatremia and low serum osmolality; high urine sodium (>40 mEq/L); an inappropriately concentrated urine (>100 mOsm/L); absence of edema; and normal renal, adrenal, and thyroid function. Because patients with SIAD have hypouricemia, serum concentrations of urate can be used to distinguish patients with SIAD from those with other causes of hyponatremia[15] (Table 40.2).

SIAD may be difficult to distinguish from CSWS because there is considerable overlap in the clinical presentation and laboratory measurements. The primary distinction lies in the assessment of the effective arterial blood volume (EABV). SIAD is a volume-expanded state because of antidiuretic hormone-mediated renal water retention. CSWS is characterized by a contracted EABV resulting from renal salt wasting. Making an accurate diagnosis is important because the treatment of each condition is quite different. Vigorous salt replacement is required in patients with CSWS, whereas fluid restriction is the treatment of choice in patients with SIAD (Table 40.3).[16,17]

Table 40.2. Criteria for the diagnosis of SIAD (only valid if there is no recent use of diuretics).

Hypotonic hyponatremia (serum osmolality <275 mOsm/L)
Urine osmolality >100 mOsm/kg
Urine sodium >40 mEq/L
Plasma uric acid <4 mg/dL
Normal thyroid, renal, and adrenal function
Clinical euvolemia (absence of peripheral edema or dehydration)

Table 40.3. Distinguishing features of SIAD and CSWS. The most important is the plasma volume.

	SIAD	CSWS
Plasma volume	↑	↓
Fluid balance	Positive	Negative
CVP	Normal	↓
BUN/creatinine	Normal	↑
Urine sodium	↑	↑↑

CVP central venous pressure; *BUN* blood urea nitrogen.

Hypervolemic (Edematous Patients)

Hypervolemia is characterized by clinical evidence of volume overload with peripheral edema in patients with congestive heart failure, cirrhosis, or nephrotic syndrome.[18]

Isotonic Hyponatremia (Serum Osmolality 275–295 mOsm/L)

Isotonic hyponatremia is also called pseudohyponatremia since it is an artifact caused by high lipid (e.g., hypertriglyceridemia) or protein (e.g., multiple myeloma, Waldeström macroglobulinemia) in the serum that displaces a portion of the water phase of the plasma.[19,20] Measurement of plasma sodium with ion-selective electrode has reduced this problem.

Hypertonic Hyponatremia (Serum Osmolality >295 mOsm/L)

It is usually caused by an increase in the plasma concentration of a solute that is largely restricted to the ECF compartment (glucose, mannitol, sorbitol, glycine). The resulting osmotic gradient causes water to shift from the intracellular to the ECF, producing hyponatremia.[8] The most common cause of hypertonic hyponatremia is hyperglycemia. The serum sodium decreases by 1.6–2.4 for each 100 mg/dL increase in serum glucose concentration.[21,22]

Treatment

If the osmolality is low and the extracellular volume is decreased, the treatment consists of volume expansion with 0.9% saline. If the osmolality is low and the extracellular volume is normal or elevated, the treatment is fluid restriction with diuretics. If the osmolality is normal or elevated, treatment of hyponatremia is usually not required.

The first-line treatment for SIAD is water restriction. If fluid restriction is ineffective or if hyponatremia is severe, the use of urea and saline or the combination of hypertonic saline with a loop diuretic is a good alternative. Urea has an antinatriuretic effect and produces osmotic diuresis leading to rapid, safe, and effective correction of hyponatremia.

Table 40.4. The sodium content of saline solutions.

Infusate	Sodium (mEq/L)
0.45% NaCl	77
0.9% NaCl	154
3% NaCl	513

Table 40.5. Diagnostic features of diabetes insipidus.

Polyuria (urine output >30 mL/kg/day)
Urine osmolality <300 mOsm/kg
Specific gravity <1.010
Plasma sodium >145 mEq/L

The recommended dosage is 40 g in 150 mL of normal saline intravenously every 8 h associated with intravenous (IV) infusion of normal saline 100 mL/h, but is no longer available in the United States. A more recent option for treating SIAD is conivaptan, a vasopressin antagonist approved by the US Food and Drug Administration in 2005 for intravenous treatment of euvolemic hyponatremia. Vasopressin antagonists cause aquaresis (the electrolyte-sparing excretion of water) rather than diuresis (the concurrent elimination of both water and electrolytes such as sodium). The recommended dosage of conivaptan is 20–40 mg IV daily.[23–29]

Severe hyponatremia (Na+<120 mEq/L or presence of symptoms) requires urgent treatment, and the use of 3% saline to raise the serum sodium concentration is recommended. The amount of sodium to be administered can be calculated according to the following formula (Table 40.4):

$$[Na^+ \text{ administered (in mEq)}] = [Na^+ \text{ desired}] - [Na^+ \text{ measured}] \times TBW$$

For men, TBW = 0.6 × weight (kg), and for women, TBW = 0.5 × weight (kg)

Correction rates of serum sodium greater than 8–12 mEq/day as well as overcorrection of the plasma sodium concentration to above 130 mEq/L within the first 2 days should be avoided.[30,31] Rapid correction of hyponatremia, particularly in chronic hyponatremia (>48 h), can produce osmotic demyelinization that is characterized by disorders of the upper motor neurons, quadriparesis, and pseudobulbar palsy. It is particularly common in menstruant woman.[32–34] Magnetic resonance imaging shows central pontine as well as extrapontine lesions.[35] Because neurologic sequelae may result from inappropriate correction of hyponatremia, re-lowering of the serum sodium in patients after excessive correction of hyponatremia with hypotonic fluids may prevent the development of myelinolysis.[36]

Hypernatremia

Hypernatremia is not an uncommon problem in critically ill patients and has been associated with high mortality rates.[37,38] Because it is generally iatrogenic, resulting from inappropriate prescription of fluids, the incidence of hypernatremia could potentially be used as an indicator of quality of care in intensive care units.[39]

Hypernatremia is always associated with hyperosmolality, in contrast to hyponatremia, in which hypoosmolality is usually but not always present. The normal body response to hyperosmolality is thirst and the release of ADH.[40] ADH increases renal water reabsorption and increases urine osmolality to a maximum value of 800–1,400 mOsm/kg. A urine osmolality of less than 800 mOsm/kg in a patient with hypernatremia indicates at least partial impairment of ADH release.[31] Hypernatremia produces brain-cell dehydration and cellular volume contraction, which is responsible for the clinical manifestations. Following an increase in serum osmolality, organic osmolytes such as glutamate, inositol, and taurine accumulate in the brain to increase intracellular osmolality and restore cellular volume.[41]

Etiology

Hypernatremia may result from either free water loss with inadequate replacement or an increase in sodium intake. The causes of increased renal water loss include hyperglycemia, use of mannitol, a high-protein diet with increased production of urea, and diabetes insipidus. The causes of nonrenal water loss include diarrhea and increased insensible losses such as in fever and burns. Administration of hypertonic sodium may also cause hypernatremia.

Diabetes insipidus (Table 40.5) results from a failure of the hypophysis to secrete ADH (central diabetes insipidus), failure of the kidney to respond to ADH (nephrogenic diabetes insipidus), or excessive administration of water. The causes of central diabetes insipidus include brain trauma, sellar and suprasellar tumors, hypophysectomy, surgery in the suprasellar area, aneurysms, meningitis, encephalitis, histiocytosis, and granulomas. The causes of nephrogenic diabetes insipidus include chronic pyelonephritis, hypokalemia, hypercalcemia, and the use of lithium.

Clinical Manifestations

The clinical manifestations of hypernatremia result from an increased extracellular fluid osmolality and reduced brain-tissue water content. They may include somnolence, lethargy, focal neurologic deficits, seizures, and coma.

Diagnostic Approach

A complete history and physical examination associated with the assessment of urine volume and osmolality are essential in the evaluation of hypernatremia. An appropriate concentrated urine in a hyperosmolar patient (urine osmolality >800 mOsm/kg) usually eliminates the possibility of a renal cause of the disorder in most cases and suggests skin or gastrointestinal water loss. An inappropriately lower urine osmolality in a hyperosmolar patient (urine osmolality <800 mOsm/kg) results from either a solute diuresis or water diuresis. A solute diuresis

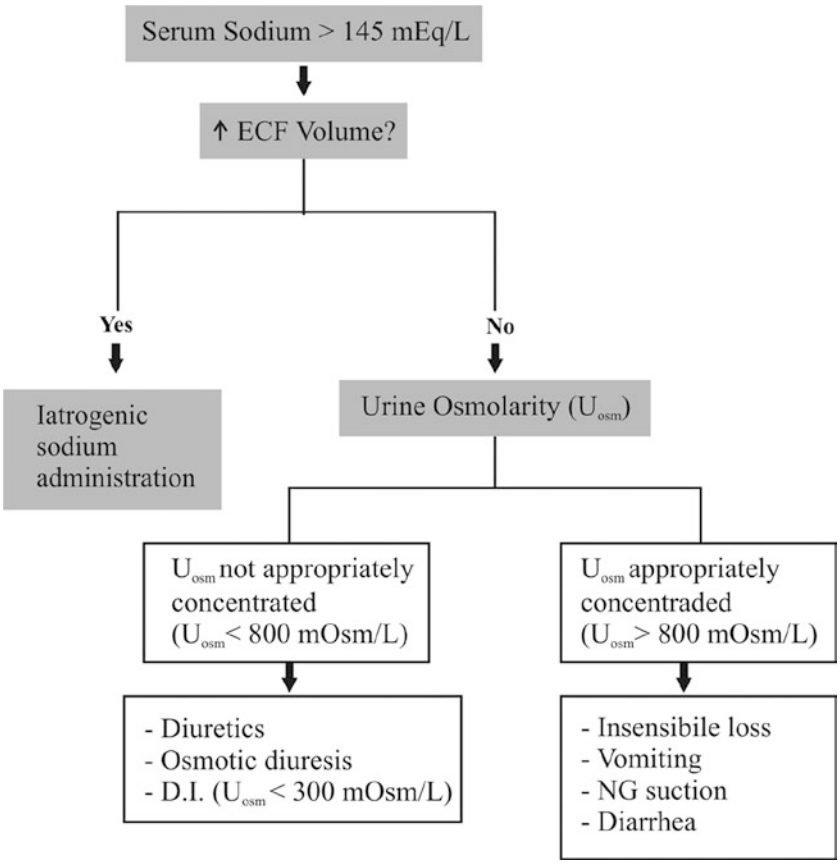

Fig. 40.2. Diagnostic approach to the critically ill patient with hyponatremia (NG suction = nasogastric suction) As in water diuresis, solute diuresis limits urine concentrating ability.

(urine osmolality >300 mOsm/kg) is usually secondary to hyperglycemia or administration of mannitol, whereas water diuresis (urine osmolality <300 mOsm/kg) usually results from diabetes insipidus[41] (Fig. 40.2).

Treatment

The primary goal is to normalize serum osmolality. If hypernatremia is secondary to water loss, the administration of 5% dextrose or 0.45% sodium chloride intravenously or orally is recommended. Except in cases of hemodynamic instability, 0.9% sodium chloride should not be used for managing hypernatremia.[31] The water deficit can be calculated from the following formula:

Water deficit = [(serum sodium – 140)/140] × TBW (liters)

For men, TBW = 0.6 × weight (kg), and for women, TBW = 0.5 × weight (kg).

If hypernatremia results from sodium excess, the treatment consists of administration of a diuretic such as furosemide in association with 5% dextrose. The treatment for central diabetes insipidus consists of the administration of desmopressin 10–20 µg intranasally or 2–4 µg intravenously every 12–24 h. The treatment of nephrogenic diabetes insipidus is a combination of a low-sodium diet and thiazide diuretics.[42]

Disorders of Potassium

Potassium is the most abundant cation in the body and is the major intracellular ion. The normal human body contains about 4,000 mEq of potassium, approximately 98% in the intracellular compartment and 2% in the extracellular fluid. The normal serum potassium concentration ranges between 3.5 and 5.0 mEq/L. The concentration gradient from intracellular to extracellular is maintained by the sodium–potassium ATPase pump. The pump transports sodium out of the cells and potassium into the cells in a ratio of 3 to 2, creating an excess of positive charges outside the membrane that establishes the membrane potential. The normal total body potassium content is determined by the balance between intake and excretion. The average diet contains about 1 mEq/kg body weight/day of potassium, and renal excretion is the major route of elimination. Insulin and stimulation of beta-2 receptors increase cellular potassium uptake by stimulating cell-membrane sodium–potassium ATPase. The ratio between the concentration of potassium in the intracellular and the extracellular fluids is the major determinant of the membrane potential. Potassium plays an important role in cell function and in membrane excitability, and the clinical consequences of potassium disorders are generally related to changes in excitable tissues such as heart, skeletal muscle, and smooth muscle.[43]

Hypokalemia

Hypokalemia is defined as a serum concentration of potassium less than 3.5 mEq/L. It is associated with an increased risk of morbidity and mortality in patients with cardiovascular disease.[44]

Etiology

Hypokalemia results from redistribution of potassium from extracellular to intracellular fluid or loss of potassium. Redistribution of potassium may be secondary to stimulation of beta-2-adrenergic receptors, insulin, and metabolic alkalosis.[45] Renal losses of potassium occur with diuretic therapy, diabetic ketoacidosis, osmotic diuresis, magnesium depletion, the use of amphotericin, and during the recovery phase of acute renal failure. Diarrhea is the most important cause of extrarenal loss.

Clinical Manifestations

The signs and symptoms of hypokalemia relate to abnormal membrane excitability. These may include cardiac arrhythmias, weakness, muscle fatigue, hyporeflexia, paresthesias, flaccid paralysis of the skeletal muscle, constipation, and ileus. If hypokalemia is severe, rhabdomyolysis may occur. Polyuria results from impaired renal concentration ability. The electrocardiogram (ECG) shows depression of the T wave, proeminent U wave, decreased QRS voltage, and ST segment depression.

Diagnostic Approach

A urinary potassium concentration less than 20 mEq/L suggests extrarenal potassium loss, whereas a concentration greater than 20 mEq/L is consistent with renal potassium wasting.

The transtubular potassium gradient (TTKG) calculated from a random urine specimen reflects the ratio of the concentration of potassium in the tubular fluid in the terminal cortical collecting duct to the potassium concentration. It is used to gage renal potassium secretion by the cortical collecting duct, indirectly assessing mineralocorticoid bioactivity in patients who have hypokalemia or hyperkalemia. The TTKG in normal subjects on a regular diet is 8 to 9 and rises above 11 with a potassium load, indicating increased potassium secretion. Hypokalemia with a TTKG >4 suggests renal potassium loss resulting from increased tubular potassium secretion, which can be associated with hyperaldosteronism, whereas a TTKG value <7 in a hyperkalemic patient is suggestive of reduced tubular potassium secretion, which can be associated with hypoaldosteronism.[46]

$$TTKG = [K^+]u \times OSM\ p / [K^+]p \times OSM\ u$$

where OSM p = plasma osmolality; $[K^+]$ u = urinary potassium; OSM u = urinary osmolality; and $[K^+]$ p = plasmatic potassium. This formula is valid as long the urine osmolality exceeds that of the plasma and the urine sodium concentration is above 25 mEq/L.

Treatment

The treatment consists of correcting the underlying disorder and initiating replacement therapy. Intravenous administration of potassium is more appropriate in critically ill patients in a dose of 20–40 mEq of potassium chloride diluted in 100 mL of saline solution infused over 1–2 h.

Hyperkalemia

Hyperkalemia occurs less often than hypokalemia in critically ill patients and is usually associated with renal failure. It is defined as serum potassium greater than 5.0 mEq/L.

Etiology

Hyperkalemia is caused by reduced potassium excretion, redistribution from the intracellular to extracellular space, and potassium administration. Hyperkalemia secondary to diminished renal potassium excretion occurs in renal failure; mineralocorticoid deficiency; and the use of heparin, angiotensin-converting enzyme inhibitors, potassium-sparing diuretics, trimethoprim, nonsteroidal anti-inflammatory drugs, cyclosporine, and tacrolimus. Causes of the intracellular to extracellular shift of potassium include acidosis, hyperosmolar syndromes, cell necrosis, tumor cell lysis, use of beta-adrenergic blockers, depolarizing muscle agents, and digitalis intoxication. Excess exogenous potassium loads occur with high IV potassium administration. Spurious hyperkalemia occurs with blood sample hemolysis or when there is a marked thrombocytosis or leukocytosis.[47]

Hyporeninemic hypoaldosteronism, which is typically asymptomatic, must be considered in any patients with unexplained hyperkalemia. It is characterized by aldosterone deficiency secondary to impaired renin release by the kidney and is associated with diabetes mellitus and chronic interstitial nephritis. Low plasma renin activity and low plasma aldosterone confirm the diagnosis.

Clinical Manifestations

Most hyperkalemic patients are asymptomatic until the serum level is greater than 6.5 mEq/L. Clinical manifestations are usually caused by reduced membrane potential leading to prolonged depolarization that impairs membrane excitability. They include cardiac arrhythmias, muscle weakness, flaccid paralysis, and respiratory insufficiency. The ECG shows peaked T waves, prolongation of the PR interval, and widening of the QRS complex.

Diagnostic Approach

Renal failure, acidosis, and medications that impair potassium excretion should be excluded. Hyperkalemia with a TTKG less than 7 and particularly below 5 suggests a reduction in potassium secretion, which can be caused by hypoaldosteronism.

Treatment

Acute therapy of hyperkalemia includes antagonism of the toxic effects of potassium on cell membranes, redistribution of potassium from the extracellular to the intracellular compartment, and elimination of potassium. Calcium gluconate antagonizes the deleterious effects of potassium on the heart. Dextrose and insulin, beta-2 adrenergic agonists, and sodium bicarbonate drive potassium into the cells. Loop diuretics, cation exchange resins such as polystyrene sulfonate, and dialysis enhance potassium elimination. Each gram of the resin contains approximately 1 mEq of sodium, which is exchanged for about 1 mEq of potassium. Hemodialysis is particularly advantageous in acute renal failure, when patients are volume expanded. Plasma potassium falls over 1 mEq/L in the first 60 min of hemodialysis and a total of 2 mEq/L by 180 min. Rebound occurs after dialysis with about 70% of the reduction abolished after 6 h[48,49] (Table 40.6).

Patients with mild hyperkalemia (K+<6.0 mEq/L) usually require no treatment besides reduction of potassium intake. Moderate hyperkalemia (6–6.5 mEq/L) without ECG changes may be treated with resins and diuretics. Patients with moderate hyperkalemia and ECG changes or patients with severe hyperkalemia (K+>6.5 mEq/L) require urgent treatment, which includes administration of glucose and insulin solution and albuterol. If the ECG displays widened QRS complexes, IV calcium should be given. Sodium bicarbonate is reserved for hyperkalemia associated with metabolic acidosis. Hemodialysis produces the most rapid decline in plasma potassium levels but should be reserved for those patients with severe hyperkalemia unresponsive to more conservative measures.

TABLE 40.6. Management of acute hyperkalemia.

Treatment	Prescription	Onset	Duration
Calcium gluconate	10 mL of a 10% solution IV over 10 min with constant cardiac monitoring. This dose can be repeated after 5 min if the ECG changes persist	Immediate	1 h
Glucose and insulin	100 mL of a 50% solution with 20 units of regular insulin IV over 10 min. Glucose monitoring is necessary to avoid hypoglycemia	15–30 min	4 h
Albuterol	10–20 mg by nebulizer or 0.5 mg IV	15–30 min	2–4 h
Sodium bicarbonate	50 mEq IV over 10 min	15–30 min	2 h
Furosemide	20–40 mg IV every 4–6 h	30 min	2 h
Sodium polystyrene sulfonate	15-30 g in sorbitol orally every 4 h or 50–100 g with 100 mL of 70% sorbitol as retention enema once a day	1–2 h	4–6 h
Dialysis			

[a] Sodium bicarbonate is less effective than glucose and insulin for decreasing serum potassium concentration in patients with end-stage renal failure.
[b] Intestinal obstruction or ileus is contraindication to resin therapy.

Disorders of Magnesium

Magnesium is the fourth most abundant cation in the human body, behind sodium, potassium, and calcium, and the second most common cation in the intracellular fluid.[50,51] The normal human body contains 21–28 g of magnesium[52]; approximately 53% in the bone, 27% in the muscles, 19% in the nonmuscular soft tissues, and only 1% in the extracellular fluid.[53] Normal serum magnesium concentrations range from 1.6 to 2.6 mg/dL. Magnesium has been shown to be an essential component in more than 300 critical enzymatic reactions.[54] Magnesium plays a key role in a number of metabolic processes such as energy production, storage, and utilization in the form of adenosine triphosphate (ATP) and in some enzymatic reactions involved in protein synthesis mechanisms. Magnesium also plays important roles in the control of neuronal activity, neuromuscular transmission, cardiac excitability, and cardiovascular tone.[55] The kidney is the principal organ involved in magnesium regulation.[56] During magnesium deprivation, the kidney conserves magnesium. However, if excess magnesium is taken, it is rapidly excreted in the urine. Phosphate depletion is commonly associated with renal magnesium wasting and hypomagnesemia. The administration of phosphate corrects the abnormality. Magnesium is needed to maintain normal potassium and calcium metabolism; hypomagnesemia results in renal potassium wasting and impairment of the secretion of parathyroid hormone (PTH)[57–59] (Fig. 40.3).

Hypomagnesemia

Magnesium deficiency occurs in about 60% of patients postoperatively.[60] Hypomagnesemia detected at the time of admission of acutely ill patients is associated with an increased mortality rate.[61,62] Experimental findings suggest that magnesium deficiency predisposes to a worse outcome in rats that received endotoxin.[63]

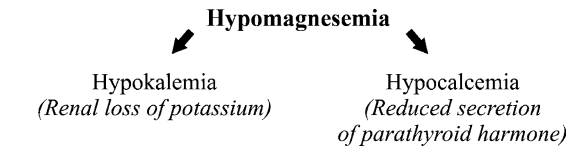

FIG. 40.3. Relation between hypomagnesemia, hypokalemia, and hypocalcemia.

Etiology

Magnesium deficiency may result from intestinal and renal losses. Gastrointestinal losses are caused by diarrhea and intestinal fistula; renal losses by osmotic diuresis (diabetes and use of urea and mannitol), drugs (diuretics, alcohol, aminoglycoside antibiotics, amphotericin B, cyclosporine, foscarnet, and pentamidine), and hypophosphatemia. Magnesium deficiency has been reported in 20% of patients with acute pancreatitis, probably as a result of magnesium deposition in areas of fat necrosis.[64]

Clinical Manifestations

Because patients with hypomagnesemia usually have no specific signs or symptoms, the diagnosis depends on a high index of suspicion.[65] Signs and symptoms of hypomagnesemia, which relate to increased neuronal irritability and concomitant hypokalemia and hypocalcemia, include arrhythmias, tetany, muscle spasms, tremors, seizures, confusion, disorientation, paresthesias, irritability, and muscle weakness. An association between hypokalemia and hypomagnesemia has been reported.[66] In critically ill patients, the most serious neuromuscular manifestation may be weakness of the respiratory musculature.[67] Because low magnesium plasma levels impair repletion of cellular potassium, refractory hypokalemia can be a sign of hypomagnesemia.[68]

Diagnostic Approach

Magnesium is predominantly an intracellular ion, and as a result, the serum magnesium concentration may not reflect the total body magnesium content.[69] However, measurement of the serum magnesium concentration is the most commonly used test to assess magnesium status. The presence of low serum magnesium indicates a deficiency in total body stores, although a normal serum magnesium level may be present despite intracellular magnesium depletion. The magnesium tolerance test may be used to assess magnesium status and is indicated in patients at risk of magnesium deficiency despite normal magnesium serum levels. Following a parenteral load of magnesium sulfate, a patient with normal renal function is capable of excreting in the urine more than 50% of a parenteral magnesium load within 24 h. Retention is greater than normal in both patients with hypomagnesemia and those with normal magnesium levels in the presence of intracellular magnesium depletion.[70,71]

Treatment

Critically ill patients who present with magnesium deficiency should be treated with parenteral administration of magnesium sulfate. An effective treatment regimen is the intravenous (IV) administration of 6 g of magnesium over 3 h for three consecutive days.[57] Magnesium administration may inhibit platelet aggregation, probably by inhibition of fibrinogen binding to the platelet glycoprotein IIb/IIIa receptor on the platelet surface. Large doses of magnesium should be administered cautiously to patients with impaired platelet function and bleeding disorders.[72,73] Magnesium therapy improved respiratory muscle power in patients with hypomagnesemia.[74] Refractory hypokalemia and hypocalcemia caused by concomitant hypomagnesemia respond to magnesium therapy, justifying a trial of IV magnesium in patients with normal magnesium levels with preserved renal function and unexplained hypokalemia and hypocalcemia.[75–78]

Hypermagnesemia

Hypermagnesemia is not common in critically ill patients. It is usually iatrogenic and associated with renal failure, because large doses of magnesium can easily be eliminated in the urine when renal function is normal.

Etiology

The most common causes of hypermagnesemia are the administration of parenteral nutrition and magnesium-containing antacids to patients with renal insufficiency.[79] Treatment of preeclampsia and eclampsia often involves the parenteral administration of large doses of magnesium, which may result in hypermagnesemia.

Clinical Manifestations

The signs and symptoms of hypermagnesemia are related to reduction in neuromuscular transmission and include depressed mental status, respiratory depression, hypotension, and arrhythmias. The first symptom of hypermagnesemia is the loss of deep tendon reflexes, which usually occurs with a serum magnesium concentration above 4 mg/dL. High magnesium serum levels confirm the diagnosis of hypermagnesemia.

Treatment

The treatment of hypermagnesemia consists of the discontinuation of magnesium and administration of saline and diuretics to enhance renal excretion. Dialysis may be needed for patients with severe hypermagnesemia. Parenteral calcium transiently protects against cardiac toxicity.

Disorders of Calcium

Calcium is essential for normal cellular function. It is important for membrane stability, enzyme activation, muscle contraction, secretion of hormones, blood coagulation, and bone structure.[80] The adult human body contains approximately 1 kg of calcium, of which more than 99% is found in the skeleton. Calcium is a major extracellular ion that circulates in the blood

in three distinct forms: about 50% is the biologically active ionized form, 40% is bound to proteins such as albumin, and 10% is complexed to anions. The serum calcium concentration is maintained within normal limits by the actions of PTH and vitamin D, which increase bone resorption and calcium absorption from the renal tubule and the gut.[78]

Hypocalcemia

Ionized hypocalcemia is common in postoperative critically ill patients. It occurs more frequently in patients with sepsis and may be associated with the systemic inflammatory response syndrome.[80]

Etiology

Possible causes of hypocalcemia in critically ill patients include sepsis, acute pancreatitis, rhabdomyolysis (early phase), chronic renal insufficiency, massive tumor lysis, toxic shock syndrome, fat embolism, phosphate infusion, hypomagnesemia, and hypoparathyroidism. The pathogenesis of ionized hypocalcemia is multifactorial. In most patients with sepsis, PTH secretion is increased and vitamin D metabolites are decreased suggesting resistance to PTH action on formation of 1,25 dihydroxycholecalciferol.[80–82] Serum total calcium is not a reliable indicator of calcium status, because it may be low in patients with hypoalbuminemia. Thus, measurement of ionized calcium is preferred.[83]

Clinical Manifestations

Nervous system manifestations of hypocalcemia result from enhanced excitability and include paresthesias, fasciculations, muscle spasms, Chvostek's and Trousseau's signs, tetany, and seizures. Cardiovascular manifestations include decreased myocardial contractility, increased QT interval, arrhythmias, and hypotension. Hypocalcemia may also present as laryngospasm or bronchospasm in critically ill patients, particularly following extubation.[84] An ionized calcium level under 1.13 mmol/L confirms the diagnosis. Hypomagnesemia is an important cause of hypocalcemia, so magnesium levels should be measured. Because hyperphosphatemia may accompany hypocalcemia in patients with hypoparathyroidism, renal insufficiency, rhabdomyolysis, and tumor lysis, phosphate levels should also be monitored.[85]

Treatment

There is no clear evidence that parenteral calcium supplementation impacts the outcome of critically ill patients, so those patients with mild and moderate degrees of hypocalcemia (ionized calcium >0.8 mmol/L) do not generally require treatment.[86] Patients with severe hypocalcemia (ionized calcium <0.8 mmol/L or presence of symptoms) should be treated with IV calcium therapy (100 to 200 mg of elemental calcium diluted in 150 mL of 5% dextrose over 10 min followed by an infusion of 1–2 mg/kg/h of calcium). Calcium chloride provides three times as much elemental calcium as calcium gluconate but because of its higher osmolality, it is phlebitic and should be administered through a central venous line (Table 40.7). Because calcium is implicated in the ischemia-reperfusion syndrome resulting in cellular damage, indiscriminate administration of the cation in critically ill patients should be avoided.[78]

TABLE 40.7. Calcium preparations for the treatment of hypocalcemia.

10 cc of 10% calcium chloride: 1 gm of calcium chloride = 273 mg of elemental calcium = 2000 mOsm/L
10 cc of 10% calcium gluconate: 1 gm of calcium gluconate = 90 mg of elemental calcium = 680 mOsm/L

Hypercalcemia

Postoperative patients can develop hypercalcemia that may require admission to the intensive care unit for better monitoring.

Etiology

Hypercalcemia in critically ill patients is most commonly associated with malignant disorders. Other causes include hyperparathyroidism, adrenal insufficiency, immobilization, rhabdomyolisis (late phase), sarcoidosis, and disseminated tuberculosis. Hypercalcemia usually results from increased bone resorption but can also be secondary to increased gastrointestinal absorption and decreased renal excretion of calcium. Hypercalcemia in patients with cancer usually results from secretion of PTH-related protein by the tumor cells, which leads to increased bone resorption and renal tubular absorption.[87] The resulting hypercalcemic state leads to polyuria and depletion of extracellular fluid, further increasing the serum calcium concentration.[88]

Clinical Manifestations

The clinical manifestations of hypercalcemia are related to the effects of extracellular calcium in cell membranes. These include apathy, drowsiness, obtundation, coma, arrhythmias, constipation, nausea, vomiting, and polyuria. Hypercalcemia should be confirmed by measuring the serum calcium level. Patients with an underlying malignancy have normal PTH levels and the serum chloride is usually lower than 100 mEq/L. In contrast, patients with primary hyperparathyroidism have increased PTH and serum chloride usually greater than 103 mEq/L.[89] The higher the level of serum calcium, the more likely that hypercalcemia is the result of a malignancy.[90]

Treatment

The treatment of hypercalcemia includes rehydration, enhancement of renal excretion of calcium, inhibition of

bone resorption, and correction of the underlying disorder. Correcting any existing volume deficit with isotonic saline is the initial step in the treatment of hypercalcemia.[91] Volume expansion restores the glomerular filtration rate and promotes calcium excretion. The use of a loop diuretic after volume expansion further increases calcium excretion. A convenient schedule is 20 mg of furosemide administered intravenously every 6–12 h. Thiazide diuretics must be avoided because they diminish renal calcium excretion. Calcitonin is a peptide that reduces bone resorption and increases renal calcium clearance. It is administered in a dose of 4 U/kg subcutaneously every 12 h. It has a rapid onset of action; however, resistance after 2–3 days of treatment is commonly seen. Calcitonin occasionally causes nausea, abdominal cramps, and flushing. Bisphosphonates inhibit bone resorption and are safe and effective medications in the treatment of hypercalcemia. A dose of 30–90 mg of pamidronate in 1 L of normal saline or 5% dextrose in water (D5W) is infused over 4–24 h. The mean time to achieve normocalcemia is 4 days.[92] Zolendronate is a newer and more potent bisphosphonate. A single dose of 4 mg in 100 mL of normal saline or D5W is infused over a minimum of 15 min. Retreatment should be considered after 7 days. Glucocorticoids are effective in treating patients with hematologic malignancies and sarcoidosis. The recommended dose is 200–300 mg intravenously of hydrocortisone, or its equivalent, daily for 3–5 days.

For mild and moderate hypercalcemia (calcium <13.5 mg/dL), the administration of saline solution and loop diuretics usually suffices. For severe hypercalcemia (calcium >13.5 mg/dL), the concurrent administration of saline solution, furosemide, calcitonin, and a bisphosphonate is usually necessary. If the hypercalcemia is secondary to hematologic malignancies or sarcoidosis, the administration of glucocorticoids is recommended.[93]

Disorders of Phosphorus

Phosphorus is a major intracellular ion with many important cellular functions. About 80% of the total body phosphorus is found in the bone, and the serum concentrations normally range between 2.5 and 5 mg/dL. Because phosphorus is a predominantly intracellular ion, serum level determination may not reflect total body stores. Phosphorus exists in the serum in monovalent and divalent forms, so it is measured and prescribed either in millimoles (1 mmol = 30 mg) or milligrams rather than in milliequivalents. Phosphorus provides fuel for physiologic processes, regulates enzymatic reactions, and serves as a buffer. Phosphate participates in the formation of 2,3-diphosphoglycerate (2,3-DPG) and ATP; the former is a major determinant of oxygen transport, and the latter plays an important role in all the physiologic mechanisms that require energy for operation. A reduced erythrocyte concentration of 2,3-DPG increases the binding of oxygen to hemoglobin and decreases the delivery of oxygen to the tissues. PTH inhibits the reabsorption of phosphate in the kidneys while insulin and catecholamines promote the transport of phosphate into the intracellular space.[94] Insulin promotes the uptake of glucose and phosphorus in skeletal muscle and liver[95] where phosphate is used for the synthesis of phosphorylated compounds.[96]

Hypophosphatemia

This condition is common in critically ill postoperative patients, is associated with increased mortality, and frequently is not recognized or appropriately treated.[97–99] It is associated with low intracellular stores of ATP,[100] which may produce cellular dysfunction, and with reduced erythrocyte levels of 2,3-DPG that decrease tissue oxygenation.

Etiology

Intravenous glucose administration, hyperalimentation, refeeding syndrome, and respiratory alkalosis produce a shift of phosphorus into the cells, the most common mechanism for hypophosphatemia in critically ill patients.[101–103] During respiratory alkalosis, the increase in intracellular pH stimulates the glycolytic pathway, specifically phosphofructokinase, a key rate-limiting enzyme of glycolysis, resulting in an enhanced consumption pf phosphate, which in turn induces intracellular phosphorous entry.[99] Other mechanisms are increased renal excretion, as in diabetic ketoacidosis or in the diuretic phase of acute renal failure, and impaired intestinal absorption as seen with antacids.

Clinical Manifestations

Patients with hypophosphatemia may present with confusion, seizures, coma, muscular weakness, rhabdomyolysis, respiratory failure, heart failure, hemolysis, or platelet and leukocyte dysfunction. A neurologic syndrome that resembles Guillan-Barré syndrome has been described in association with hypophosphatemia.[104] The reduced cardiac output in hypophosphatemic patients normalizes after phosphate repletion.[105] The development of hypophosphatemia in non-ventilated patients has been shown to precipitate acute respiratory failure probably because a low phosphate level reduces diaphragmatic contractile strength.[106,107] Hypophosphatemia has been associated with the inability to wean from mechanical ventilation.[108]

Treatment

Treatment of hypophosphatemia in critically ill patients requires careful administration of IV phosphorus according to plasma levels (Table 40.8). Adverse effects include hypocalcemia, metastatic calcification, hypotension, and shock.[109,110] Slow infusions over 3 h reduce the risks of phosphorus administration.

TABLE 40.8. Recommended dose of sodium phosphate to treat hypophosphatemia.

Severity	Serum level (mg/dL)	Sodium phosphate (mmol/kg IV)
Mild	2.0–2.5	0.08
Moderate	1.0–2.0	0.16
Severe	<1.0	0.24

Hyperphosphatemia

Hyperphosphatemia occurs less often than hypophosphatemia in critically ill patients and is usually associated with renal failure.

Etiology

Hyperphosphatemia may be secondary to decreased renal excretion of phosphate, increased intestinal absorption, internal redistribution, cellular release, and parenteral administration. The causes of hyperphosphatemia include renal insufficiency, use of phosphate-containing antacids, metabolic and respiratory acidosis, rhabdomyolysis, tumor lysis syndrome, IV phosphate salts, and the use of enemas containing phosphate.[111]

Clinical Manifestations

Clinical manifestations of hyperphosphatemia (serum phosphate >5 mg/dL) are secondary to concomitant hypocalcemia. Calcium levels should also be measured because a calcium–phosphate product above 60 represents a risk of ectopic calcification.

Treatment

Administration of intestinal phosphate binders, such as calcium carbonate or aluminum hydroxide (30 mL by mouth every 6 h) was considered the first-line therapy. Recently, the treatment of hyperphosphatemia patients changed from either calcium- or aluminum-based phosphate binders to new free-calcium and aluminum phosphate binders, such as sevelamer hydrochloride (initial dose of 800 mg by mouth three times a day with meals) and lanthanum carbonate (initial dose of 250–500 mg by mouth three times a day with meals). Volume expansion can induce phosphaturia and reduce phosphate levels if renal function is adequate. Dialysis may be required in patients with renal insufficiency and severe hyperphosphatemia.

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Part IX
Gastroenterology

41
Gastrointestinal Bleeding

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Gastrointestinal bleeding (GIB) in the critical care environment is a relatively common clinical event. The incidence of GIB is 103/100,000 cases per year in the United Kingdom (UK).[1] Of these, 14% occur in patients who are already hospitalized.[1] In the United States (US) the incidence of clinically significant GIB from stress-related mucosal disease (SRMD) has been estimated at 1.5%.[2] GIB can be the primary reason for admission or can develop as a secondary comorbid factor in relation to the primary illness. Patients with this complication can have an increased length of stay and up to a fourfold rise in mortality.[3]

Upper GIB is defined as that originating from a source within the upper gastrointestinal tract proximal to the ligament of Treitz (e.g., esophagus, stomach, and duodenum). It commonly presents as fresh hematemesis and/or melena (offensive, tarry, black stool). A brisk, significant upper GIB can reveal itself as hematochezia (fresh blood per rectum) but this usually represents a colonic source. "Coffee ground" vomiting is an unreliable clinical sign. It may occasionally be mistaken for feculent vomiting, which is associated with bowel obstruction. It is not, however, uncommon for patients in the critical care setting to have fresh or altered blood in their nasogastric (NG) tube.

Bleeding from the nasopharynx should be excluded. It may be equally dramatic and is sometimes confused with an upper GI source. Blood may be passed proximally and vomited, or distally and digested, thus presenting as melena.

This chapter will examine the nature of GI bleeding in critical care, the etiologies and risk factors that may predispose one to GIB, and describe the variety of therapeutic options available to the clinician.

For the purposes of clarity, upper gastrointestinal stress-related mucosal disease (encompasses erosions and ulcers), variceal hemorrhage, and lower GIB will be considered separately.

Etiology

Upper Gastrointestinal Bleeding

Stress-Related Mucosal Disease

The physiological role of the upper GI tract is to aid in digestion and motility, maintain mucosal integrity, and to control acid secretion. The function of the stomach can be divided into motor, secretory, and endocrine. The normal role is to act as a reservoir for ingested food in order to start the initial mechanical mixing and breakdown of food to form "chyme." The food is then emptied at regular intervals through the pyloric sphincter into the small bowel. Histologically, the stomach has three layers: mucosa, submucosa, and muscularis propria. The latter two layers are consistent throughout; however, the mucosal layer has a variable structure and function in different regions. The mucus-secreting epithelial cells are ubiquitous; however, the body of the stomach contains an elongated gastric glandular layer and consists of parietal and chief cells, whereas the antral gastric glands are branched in orientation and secrete mucus and gastrin.[4] The control of gastric acid secretion is complex and involves the interplay of a number of different cells. Initially, gastrin-secreting "G cells" in the antrum stimulate the enterochromaffin-like cells to release histamine. This in turn stimulates an H^+/K^+ ATPase proton pump in the gastric body parietal cells to secrete acid, which has been generated by the dissociation of water into H^+ and OH^-. Acid is secreted into large canaliculi, continuous with the lumen of the stomach. As the local pH level falls, this is a trigger for somatostatin releasing cells, located in the gastric antrum, to inhibit further gastrin production, thereby effecting a negative feedback loop.[5] This physiological

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autoregulation thus provides different opportunities for pharmacological intervention.

Within the mucous layer, carbonic anhydrase converts the hydroxyl ions into bicarbonate, which acts as the mucosal protective buffer against luminal acid and proteolytic enzymes.[6] Chloride ions are actively secreted into the lumen against concentration and electrical gradients. Local prostaglandins also protect the GI mucosa from damage by maintaining mucosal blood flow and increasing mucosal secretion of mucus and bicarbonate.

Pathogenesis of Stress-Related Mucosal Disease

Critical illness imposes severe stress upon the normal mucosal physiological processes described previously. The pathogenesis of stress-related mucosal disease seems to be related to three main factors: mucosal ischemia, increased gastric acid secretion, and reflux of bilious material into the stomach from the upper GI tract.[7]

The stress response of critical illness effects a fall in cardiac output, increased vasoconstriction, and release of proinflammatory cytokines. The resultant splanchnic hypoperfusion induces gastrointestinal mucosal ischemia, reduces gastric motility, impairs protective mucous production,[8,9] and reduces the ability to neutralize hydrogen ions.

Mucosal ulceration can be superficial (erosions) and characterized histologically by loss of surface epithelium, coagulation necrosis of the mucosa, and hemorrhage from superficial mucosal capillaries,[10] which leads to more occult blood loss; or deep (ulcers), which erode through to larger vessels leading to active bleeding and its sequelae. The diffuse superficial disease is generally not amenable to endoscopic therapy.

Cook et al.[2] identified the risk factors for the development of stress ulcers. Analysis of clinical data from more than 2,000 patients demonstrated that 3.7% of those with risk factors experienced GIB compared to only 0.1% of those without. Of all the risk factors analyzed (Table 41.1), the two that demonstrated statistical significance were patients requiring mechanical ventilation for greater than 48 h and those with coagulopathy. The authors also demonstrated that mortality rates were higher amongst the group with clinically significant bleeding (48.5 vs. 9.1%).[2]

Table 41.1. Risk factors for stress-related mucosal disease.[85]

Risk factors
Respiratory failure
Coagulopathy
Hypotension
Sepsis
Hepatic failure
Renal failure
Surgery
Burns
Major trauma

This work was built on the findings of an earlier paper from Hastings et al.[11] One hundred patients with risk factors for stress-related mucosal bleeding were randomly assigned to receive antacid therapy or no prophylaxis. They demonstrated that the incidence of bleeding increased with the number of critical illness-related risk factors present in both groups.

Stress ulceration resulting in significant bleeding may also be a function of the degree of intramucosal pH change measured using gastric tonometry.[12] In the study performed by Fiddian-Green et al. only those patients whose intramucosal pH had fallen below 7.24 suffered from gastrointestinal bleeding.[12]

The combined use of antiplatelet agents, such as aspirin and clopidogrel, is increasing in the setting of acute coronary syndrome and coronary intervention.[13] Aspirin inhibits platelet cyclooxygenase-1 (COX-1) activity, thereby preventing synthesis of thromboxane A2, a promoter of platelet activation. It also inhibits the cytoprotective effects of prostaglandin E2 in the gastric mucosa. These two factors contribute to the increased risks of peptic ulceration.[14] Clopidogrel is a more potent platelet inhibitor than aspirin. It blocks the adenosine diphosphate (ADP) dependent pathway of platelet activation by binding to the P2Y12 receptor. Clopidogrel appears to carry less of a risk of inducing GI bleeding when compared to aspirin.[15] Presumably this is because it has no effect on gastric mucosa. However, the use of clopidogrel has been shown to trigger GIB significantly more often in patients with a previous history of GIB than those without (22 vs. 0%, $p=0.007$).[16]

The use of adjunctive proton pump inhibitor (PPI) therapy has been shown to be of benefit in reducing the incidence of GI bleeding and peptic ulcer disease in patients on antiplatelet therapy.[17] The authors of a recent review article[18] concluded that the antithrombotic benefits and bleeding risks of antiplatelet therapy should be balanced in a manner analogous to anticoagulation; however, the higher the vascular risks the more benefit there is to be gained, thereby outweighing the risk of bleeding. They also stated that PPI therapy is a useful precaution in patients with a recent history of ulceration or bleeding (after ulcer healing and *Helicobacter pylori* eradication).

Selective COX-2 inhibitors theoretically reduce the GI side effects inherent to widespread cyclooxygenase inhibition.[19] This idea has been supported by a number of trials, recently summarized in a review article by Henry and McGettigan.[20] However, the same article suggested that the relative merits of this reduction in GI side effects were ameliorated when balanced against the reported increase in cardiovascular complications[21] with COX-2 inhibitors and the frequent collateral usage of antiplatelet therapy anyway. Chan et al.[22] recently reported the findings of a study that compared the incidence of recurrent ulcer bleeding amongst patients on COX-2 alone (celecoxib) versus COX-2 and PPI (esomeprazole) therapy. Two hundred and seventy-three patients were assessed prospectively in two randomized, double-blinded groups. The incidence of recurrent GI bleeding was 0% in the dual therapy group and 8.9% in the monotherapy group ($p=0.0004$).

It is accepted that *Helicobacter pylori* (HP) infection and nonsteroidal anti-inflammatory (NSAID) use are both independent risk factors for the development of peptic ulcer disease. However, the precise interaction of these two factors remains unclear. There is evidence to suggest that the two factors act synergistically to promote ulcer formation but also conversely that there may be a protective role offered by HP infection.[23]

Equally, the implication of HP in the pathogenesis of stress-related mucosal disease is unclear. Some evidence suggests that the incidence of *H. pylori* seropositivity is increased in ICU patients (67%) versus controls (39%) $p<0.001$.[24] Although there seemed to be no relation to the incidence of GI bleeding, there was a relationship between seropositivity and the severity of bleeding. In another study,[25] 50 ICU admissions were screened for *H. pylori* using a breath test and subsequently underwent endoscopic analysis. Of those with minor mucosal disease, 34.5% were *H. pylori* positive versus 80% in those with major mucosal disease. Both these studies seem to support a relationship between *H. pylori* and the extent of mucosal injury. However, similar studies have failed to support this data.[26]

Although a consensus on best practice in this setting is unresolved, it is recommended that HP eradication should be employed empirically for duodenal ulcers and after confirmation of infection in gastric ulcers.[27]

A meta-analysis by Gisbert and Abraira[28] reviewed the diagnostic accuracy of the various HP tests in the setting of gastrointestinal bleeding. The sensitivities and specificities were respectively: biopsy and rapid urease test (67%, 93%), biopsy and histology (70%, 90%), biopsy and culture (45%, 98%), urea breath test (93%, 92%), stool antigen test (87%, 70%), and serology (88%, 69%). These results suggest that biopsy-based methods have a low sensitivity but high specificity and that the accuracy of the urea breath test remains very high. On average, the most practical tests for the critical care population are stool antigen and serology, which have a similar diagnostic performance. Treatment regimens normally consist of "triple therapy" containing a proton pump inhibitor and two antibiotics. Current first-line treatment, which is successful in 80% of cases, is the combination of amoxicillin and clarithromycin.[29] Failure of eradication often requires "quadruple" therapy including a bismuth agent.

Esophageal motility has been shown to be reduced in sedated critically ill patients.[30] In addition to this, it is recognized that nocturnal gastroesophageal reflux disease[31,32] is related to supine positioning. It could therefore be postulated that these factors, in combination, could expose critical care patients to not only a risk of esophageal mucosal erosive disease and hence ulceration, but also chemical lung injury and nosocomial pneumonias. Prolonged use of wide bore NG tubes has also been suggested as an etiological factor in esophagitis among patients in hospital.[32]

There have been published observational studies to suggest that selective serotonin reuptake inhibitors (SSRIs) may be a risk factor for upper GI bleeding.[33] However, a meta-analysis on the same topic[34] suggested that the overall evidence was weak and really only supported the idea that SSRIs used concurrently with NSAIDs or aspirin increased the risk of upper GIB.

With specific reference to critical care patients, there is some evidence to suggest that mechanical ventilation can affect venous return and cardiac output[35] thereby causing a fall in splanchnic perfusion with theoretical implications for SRMD. However, the effect of positive end expiratory pressure on GI bleeding is not known. Drugs, including opiates and sedatives, can also have a similar deleterious effect on hemodynamics.

Variceal Hemorrhage

Portal hypertension is a complication of cirrhosis.[36] It accounts for life-threatening conditions including gastroesophageal varices and subsequent bleeding. Portal hypertension generates reversal of portal venous flow (hepatofugal), which diverts venous blood in a cephalic direction through the left gastric vein to the venous plexus of the esophagus. Therefore, portal hypertensive varices are more common in the lower third of the esophagus, especially at the gastroesophageal junction. Gastric fundal varices can also develop in this setting, but can also rarely be caused by splenic vein thrombosis.[37]

Variceal hemorrhage is often associated with clinical stigmata of chronic liver disease (spider naevi, gynecomastia, palmar erythema, etc.). At the time of diagnosis, 40% of compensated cirrhotics and 60% of those with ascites have varices.[38] A small number (4.4/100,000 per year) of patients with cirrhosis suffer with variceal bleeding as their first presenting feature.[39] Due to advances in pharmacotherapy and endoscopic intervention, there has been a significant reduction in in-hospital mortality over the past two decades from 42 to 14%.[40] Immediate mortality from uncontrolled bleeding is between 5 and 8%.[41] The poor prognostic indicators related to failure to control bleeding include: active bleeding at endoscopy,[42] hepatic venous pressure gradient >20 mmHg,[43] and bacterial infection.[43]

Other

Other vascular abnormalities that can result in upper gastrointestinal blood loss include portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE) (see also Table 41.2).

TABLE 41.2. Incidence of different endoscopic diagnoses in acute upper gastrointestinal hemorrhage.[2]

Diagnosis	%
None made	25
Peptic ulcer	35
Malignancy	4
Varices	4
Mallory Weiss tear	5
Erosive disease	11
Oesophagitis	10
Other	6

PHG is a phenomenon that can affect up to 65% of all patients in the setting of portal hypertension of any etiology.[44] Diagnosed endoscopically, in the early stages PHG has an erythematous, edematous, and sometimes "snakeskin-like" mucosal appearance most commonly affecting the fundus. In the later stages, cherry red spots can appear and are very friable.[45] PHG is more likely to cause chronic blood loss (10.8%) than to bleed acutely (2.5%).[46] The pathophysiology of this condition is poorly understood, but is believed to represent a complex interplay between local changes in nitric oxide production, TNF-alpha synthesis, prostaglandin inhibition, and altered gastric blood flow.[47] The only definitive treatment for portal hypertension in the setting of cirrhosis is liver transplantation, after which PHG has been shown to reverse.[44] There is mixed evidence for pharmacological treatments including propranolol and somatostatin analogues[47] and no supportive evidence for H2 blockers or Sucralfate.[48]

GAVE syndrome was first accurately described in 1984 by Jabbari et al.[49] Multiple red patches are present in an erratic or linear distribution within the stomach antrum. It is otherwise known as "Watermelon stomach." GAVE can be distinguished from PHG due to the anatomical distribution and classical features on biopsy. Around 30% of patients with GAVE will have cirrhosis,[50] a fact that can sometimes create diagnostic uncertainty. GAVE is also more likely to produce chronic blood loss but to a greater extent than PHG. Among the non-cirrhotic patients with GAVE, there is an increased prevalence of autoimmune disorders and chronic kidney disease.[51] The etiology of GAVE is also unclear, but some theories, based on histological findings of fibromuscular hyperplasia,[52] suggest that a mechanical stress injury similar to intussusception may affect the mucosa.[49] Pharmacological treatments including estrogen therapy and tranexamic acid (a synthetic antifibrinolytic drug) are supported by case report evidence.[53,54] More recently the endoscopic therapy of argon plasma coagulation (APC) has prompted supportive comment.[55]

There are other rarer abnormalities such as Dieulafoy's lesion. This is an abnormally large submucosal artery that erodes into the stomach lumen. It is usually found in the proximal stomach and accounts for up to 4% of upper GIB.[56] Two groups have reported case series[56,57] of up to 70 patients. Initial endoscopic hemostasis (injection therapy and hemoclipping) was successful between 91.3 and 100%, with overall mortality between 0 and 4%.

Lower Gastrointestinal Bleeding

The incidence of lower GIB is 22 per 100,000 adults in the United States[58] and it accounts for 24% of all GI bleeding episodes.[59] Around 90% stop spontaneously, although 35% require transfusion and 5% acute surgical intervention.[60] Lower GIB generally occurs in older patients. The mean age lies between 63 and 77 years.[58]

The most common etiology in the western world is diverticular disease (40%). After this, inflammatory bowel disease (20%), malignancy (15%), and benign anorectal disease (hemorrhoids) (10%) account for the rest. Up to 5% of apparent lower GIB cases actually arise from the small bowel.[60] Other rarities include angiodysplasias and Meckel's diverticulum. It is also important to mention post-polypectomy bleeding as a notable cause. This is normally immediate but can be a delayed presentation, and has been shown to occur in 0.5–2.2% of polypectomies.[61,62]

General Management

Assessment and Scoring Systems

The initial assessment of the patient with GI bleeding should focus on the general principles that are applied to any hemorrhagic condition. Evaluation of airway patency, respiratory compromise, and management of circulatory dysfunction are the primary goals.

A number of scoring systems exist for the calculation of severity and risk of mortality from acute upper GIB. Perhaps the best known of these was devised by Rockall et al. in 1996.[63] A total of 5,810 patients with upper GIB were prospectively studied. Logistic regression techniques identified six clinical features that were individually predictive of mortality. Using this information, a simple numerical scoring system was developed that stratifies patients into different levels of mortality risk (see Table 41.3a and b). The precise risks of mortality vary depending on whether this score is calculated pre- or

Table 41.3a. Rockall Scoring System for Upper GIB. Risk assessment after acute upper gastrointestinal hemorrhage.[63]

Score	0	1	2	3
Age	<60	60–79	>80	
Shock	No shock	HR > 100	HR > 100, SBP < 100	
Comorbidity	Nil		Cardiac failure, ischemic heart disease	Renal failure, liver failure, disseminated malignancy
Diagnosis	Mallory Weiss, no lesion, no SRH	All other diagnoses	Malignancy of upper GIT	
Major stigmata of recent hemorrhage (endoscopy findings)	None or dark spot		Fresh blood, adherent clot, visible or spurting vessel	

Table 41.3b Percentage rebleeding and mortality based on Rockall score.[63]

Score	0	1	2	3	4	5	6	7	8+
Total (%)	4.9	9.5	11.4	15	17.9	15.3	10.6	9.0	6.4
Rebleed (%)	4.9	3.4	5.3	11.2	14.1	24.1	32.9	43.8	41.8
Death (non rebleed) (%)	0	0	0.3	2.0	3.5	8.1	9.5	14.9	28.1
Death (rebleed) (%)	0	0	0	10.0	15.8	22.9	33.3	43.4	52.5
Death (total) (%)	0	0	0.2	2.9	5.3	10.8	17.3	27.0	41.1

post-endoscopy. This scoring system has since undergone both internal and external validation. These efforts have confirmed the ability of the score to predict mortality, but have shown that it is less reliable when assessing risk of rebleeding in high-risk patients.[64]

A separate group led by Blatchford et al.[65] developed a predictive model that would identify a patient's need for treatment including blood transfusion or intervention to control bleeding, rebleeding, or dying. Based on these results they developed a simplified fast-track screen for use at initial presentation.

Airway

The presence of shock, agitation, hematemesis, and other clinical factors may influence the decision to protect the airway and intubate promptly or to reassess at a later stage. There is no definitive evidence to support routine intubation.[66] However, if there is any concern about adequate airway protection then this is the preferred action. Patients with variceal bleeding are more likely to require airway protection due to the volume of blood, associated encephalopathy, and potential insertion of a Sengstaken Blakemore tube.[67]

Resuscitation

In the setting of critical care, all patients, by definition, should have intensive physiological monitoring. This guides adequate resuscitation and fluid balance.

Gastrointestinal bleeding can often be underestimated because unlike a traumatic or operative source of bleeding it cannot be "seen." Resuscitation is therefore guided by clinical and physiological parameters. There is evidence that these conventional parameters (pulse, blood pressure) do not always correlate with the degree of shock. Mismatch may be seen in the case of the young, old, and patients on beta blockade. There are times, therefore, when patients are inadequately resuscitated. GIB can occur with varying severity and a straightforward approach to assessment of vital signs is recommended. Table 41.4[68] shows a clinical guide to assessment of hypovolemic shock.

There is ongoing debate regarding the timing and volume of fluid administration for patients with bleeding. It can be difficult to strike a balance between restoration of blood pressure and the potential for disrupting clots, reopening bleeding points, and, hence, worsening bleeding.

Table 41.4. Classification of hypovolemic shock.[68]

	Class I	Class II	Class III	Class IV
Blood loss (ml)	750 ml	750–1,500 ml	1,500–2,000 ml	>2,000 ml
Blood loss (% blood volume)	<15%	15–30%	30–40%	>40%
Heart rate	<100	>100	>120	>140
SBP	No change	No change	Reduced	Very low
DBP	No change	Raised	Reduced	Unrecordable
Resp Rate	<20	>20	>30	>40
Urine output (ml/h)	>30	20–30	10–20	<10
Extremities	Normal	Pale	Pale	Cold
Mental state	Alert	Anxious	Aggressive/drowsy	Confused/unconscious

SBP systolic blood pressure; *DBP* diastolic blood pressure.

A recent Cochrane review evaluating the effects of early versus delayed, and larger versus smaller volumes of fluid administration in trauma patients with bleeding proved inconclusive.[69] Therefore, we advise that resuscitation should be focused on reducing the state of shock and returning parameters to normal limits.

In patients with a large bleed and/or cardiac comorbidities, central venous access is felt to be a necessary adjunct to management, although this has not been the subject of a formal clinical trial.[70] Current accepted emergency practice for patients without comorbidities is placement of a large bore (16 G) intravenous cannula in each antecubital fossa.

Crystalloids and volume expanders should be used initially, with additional blood products in the setting of class III/IV shock, active hematemesis, or for initial hemoglobin concentrations of less than 10 g/dl.[70] There is data from the critical care setting that suggests that mortality is reduced in younger ICU patients who receive a more cautious, restrictive administration of blood[71] rather than a liberal transfusion. This study was not, however, carried out in the setting of hemorrhage and its results should therefore be treated cautiously.

Resuscitative efforts for variceal bleeding should be more controlled. Anecdotally, it is recommended that one should aim for an "adequate but conservative" approach. This statement illustrates a theoretical concern that rapid volume resuscitation will have a detrimental effect on portal pressure and, hence, bleeding; however, there is evidence against this idea.[72] An alternative strategy is to maintain the hematocrit at 25–30%.[73]

Coagulopathy

Coagulopathy will exacerbate any kind of hemorrhage. Elevation of the INR (international normalized ratio) should be reversed with fresh frozen plasma or clotting factor concentrates in the setting of active hemorrhage.[74] Intravenous

vitamin K should be supplemented, especially if the patient is icteric as they may be malabsorbing fat soluble vitamins and therefore be deficient. It can also be used in more controlled circumstances.[74] There are very few studies that have defined the optimum doses of these products or indeed the relative evidence for one over the other.[75]

The use of recombinant factor VII in the setting of uncontrollable gastrointestinal hemorrhage is still under assessment. There have been very few randomized clinical trials and the only one that stood up to a recent Cochrane assessment[76] failed to demonstrate a reduction in the risk of death from gastrointestinal bleeding in patients with cirrhosis.[77] It could, therefore, be considered as an additional therapy for patients unresponsive to standard treatment; however, lack of strong evidence and cost currently precludes routine use. The incidence of thrombotic events with use of factor VII has been reported at 1.5% in a study of 11,000 patients. Almost all of these events occurred in non-hemophiliacs and those with other underlying risk factors for thrombosis. All case mortality was 0.3%.[78,79]

Specific Management of Stress-Related Mucosal Disease

Pharmacological Management

Maintaining a luminal pH between 3.5 and 4.5 is an accepted endpoint used in many studies and should be the minimum goal of effective prophylactic therapy.[80] Although reduced pH is only one factor contributing to SRMD, controlling excess luminal acid levels in at-risk patients is an important factor in the reduction of bleeding episodes.[81]

Cook et al. reported in a meta-analysis[82] on the subject of prophylaxis that the incidence of overt GIB was reduced with the use of prophylactic agents including antacids, sucralfate, and H2 blockers versus no therapy. The same group also studied a direct comparison between ranitidine (H2 blocker) and sucralfate prophylaxis and found that the former significantly reduced the chances of clinically significant GI bleeding (1.7 vs. 3.8 %, p 0.02).[2]

H2 blockers act by inhibiting histamine-stimulated gastric acid production from the parietal cell. They are highly selective, having little effect on other systemic histamine receptors. Proton pump inhibitors (PPI) inactivate the H^+/K^+ ATPase at the secretory surface of the parietal cell regardless of the source of paracrine stimulation.[83]

Proton pump inhibitors are known to be effective in the general treatment of acid related disease. They are, however, not yet formally approved as prophylaxis against stress ulceration. They have been favorably evaluated in studies with intensive care unit patients; however, these studies used small numbers of patients and lacked control groups.[84,85]

Very few trials have directly compared H2 blockade with PPI therapy. When compared with H2 blockade, PPI therapy is associated with reduced bleeding episodes.[86] In healthy volunteers, omeprazole infusion was significantly superior to ranitidine by producing a higher gastric pH. The same study also showed that ranitidine has a rapid loss of antisecretory activity on days 2 and 3, rendering it inappropriate for situations in which high intragastric pH levels appear to be essential.[87] There are also theoretical concerns that H2 blockers can induce the cytochrome P450 system and culminate in renal failure. With these patterns in mind, the use of proton pump inhibitors as a stress ulcer prophylactic agent has increased in recent years.[88] All of the data so far has been on oral PPI therapy. Studies on IV therapy are needed.

The Surviving Sepsis Campaign has recently published a series of measures that are thought to improve patient outcome.[89] This group represents the collective opinions of the European Society of Intensive Care Medicine, the International Sepsis Forum, and the Society of Critical Care Medicine.[90] The "bundle" concept, a collection of clinical interventions applied to all patients meeting specific criteria, has now been applied to the management of sepsis. The idea was originally developed by the institute of healthcare improvement (IHI), which considered a collection of evidence-based interventions for patients on mechanical ventilation otherwise known as the "ventilator bundle." These measures included, among others, peptic ulcer disease prophylaxis and elevation of the head of the bed. Although instituted to prevent ventilator associated pneumonias (VAP) the general importance of acid prophylaxis has been clear for some time within the critical care community.

The theoretical concerns that raising luminal pH could, however, be a risk factor for the development of nosocomial pneumonias is controversial. Recent prophylaxis trials failed to demonstrate any increase in the rate of nosocomial pneumonias.[2]

Regarding the route and method of drug administration in stress ulcer prophylaxis, studies have demonstrated that continuous infusions are more effective in keeping luminal pH above 4.0 for longer than intermittent bolus therapy.[91] However no work has been done to measure the effect on clinical outcomes. The exact approach to the administration of prophylaxis does vary with local practice, but the evidence, as discussed, points to the suggestion that patients should be assessed for risk factors and treated accordingly.

Following a study reported in 2000,[92] it has become accepted practice that intravenous PPI therapy should accompany endoscopic therapy for treatment of bleeding peptic ulcers. Blood clots are less stable in an acid environment and a pH of 6 or more is necessary for platelet aggregation.[69] Lau et al.[91] demonstrated that rebleeding rates, blood transfusion requirements, and duration of hospital stay were all reduced in patients who received IV omeprazole (80 mg stat followed by an infusion of 8 mg hourly for 72 h) versus placebo. The same group has recently published evidence that demonstrates that intravenous PPI infusion pre-endoscopy accelerated the resolution of signs of bleeding in ulcers (ulcer with clean

base $p = 0.001$) and reduced the need for endoscopic therapy ($p = 0.007$) when compared to placebo.[93]

Further studies are in progress to evaluate this theory using the newer PPIs. However, a recently published meta-analysis concluded that there is currently strong evidence to support the use of PPI therapy to treat peptic ulcer bleeding as well as reducing the rates of rebleeding.[94]

Endoscopic Management

Esophagogastroduodenoscopy (OGD) plays an important part in the management of GIB. It can offer both diagnostic information and the opportunity for therapeutic intervention.

Endoscopy should be undertaken within 24 h in low-risk patients and as soon as blood pressure has normalized in those with massive bleeding. Cooper et al. demonstrated a reduction in rebleeding, surgical intervention, and length of hospital stay in patients who underwent endoscopy within the first 24 h of admission.[95]

If required, for ventilated patients, the endoscopy can take place in the critical care unit itself. It is, however, preferable for those patients who can move to undertake it in the normal specialist surroundings of a dedicated endoscopy unit. It is important that the endoscopist is assisted by specialist endoscopy nursing staff who are familiar with the equipment and techniques required. If there is a possibility of the patient needing emergency surgery then it can be beneficial to undertake the procedure in the operating theater. This allows for surgical involvement and immediate procession to a laparotomy if required.

Endoscopic evaluation of mucosal ulcerative disease should be straightforward; however, excessive active or residual blood pooling can obscure adequate views of the mucosal surfaces. Changing the patient's position (prone, right lateral) can help to clear the fundus of residue if required. The highest risk, and indeed frequently missed sites, for ulceration are the gastric lesser curve and the posterior wall of the second part of the duodenum. These areas should be carefully inspected before the endoscopy can be considered complete. Indeed, one should consider the use of a side-viewing duodenoscope, normally used for endoscopic retrograde cholangiopancreatography (ERCP), for greater assessment and management of lesions in the latter area.

The different endoscopic therapies available include adrenaline injection, heat treatment/diathermy, endoscopic clips, and argon plasma coagulation.

Injection therapy with adrenaline rather than a saline solution aims to provide local tamponade with the advantage of additional vessel and tissue vasoconstriction. Saline can be used for emergency tamponade; however, it is likely that the lesion will rebleed once this effect is lost.[96] Adrenaline is used in a concentration of 1:10,000. Up to 10 ml can be injected in four quadrants around the ulcer and finally into the central bleeding point.

The newest and preferred modality for heat treatment is the use of bipolar electrocoagulation via a Gold probe. The alternative technique, still used in many institutions, is known as the heater probe. This uses direct application of thermal energy (~30 J) rather than an electrical source. The bipolar Gold probe catheter also has a needle in the central channel through which injection therapy can be applied. This removes the need to change catheters when applying both injection and heat therapy.

In summary, for the treatment of ulcers, if there is evidence of fresh bleeding, adherent clot, or a visible vessel in the ulcer base, intervention is indicated[97] as these lesions confer a high risk of rebleeding. Attempts should be made to remove adherent clot from the ulcer base before treatment with either a water jet or cold snaring. A clean ulcer base or one with black or red spots can be safely left alone and managed conservatively as they have a low risk of rebleeding. The use of "dual" therapy, that is, adrenaline injection and thermocoagulation together, is now the recommended best practice.[98] A recent meta-analysis has confirmed that this combined treatment is superior to injection therapy alone in reducing the risk of rebleeding and emergency surgery.[99] As mentioned previously, the adrenaline injection therapy should be applied in four quadrants around the bleeding point before finally being injected into the central vessel itself. Thermocoagulation should then be applied repeatedly until bleeding has stopped and a blackened area has formed.[70] The energy settings and length of application differ between the Gold and heater probes.

Endoscopic clips are a relatively recent useful adjunct to current therapies. A study in Taiwan compared the combined use of endoscopic clips and injection therapy with injection therapy alone.[100] They found that the rebleeding rates were significantly higher in the monotherapy group (3.8 vs. 21%, p 0.008). In practice, endoscopic clips are probably best targeted at larger visible vessels where it is actually possible to obtain an effective mechanical grip on the vessel. This is not always achievable in the setting of a large fibrotic ulcer base. It should be acknowledged that this technique is more technically demanding and requires both a skilled operator and assistant.

There is very little evidence currently to support the use of argon plasma coagulation in the setting of non-variceal upper GI hemorrhage.[101] Equally it has no role in the setting of acute variceal hemorrhage, although preliminary small studies have suggested that it may be an effective therapy in the prevention of variceal recurrence after initial banding therapy.[102]

In those patients in whom initial endoscopic techniques have failed (5–20%), the evidence suggests that one further attempt at endoscopic therapy should be tried before progressing to open surgical intervention.[103] If it is not possible to remove the overlying clot during the initial endoscopy then repeated assessment should be undertaken after a trial of promotility agents. This may help the clot to move on if stability has been achieved.

It is common practice that any repeat endoscopy should occur in close liaison with the duty surgeon. If repeat endoscopic therapy fails, it will at least offer a guide to the anatomical location of the bleeding vessel.

Capsule endoscopy has come into prominence in recent years as an important tool used in the investigation of hemodynamically stable obscure gastrointestinal bleeding.[104] This technique utilizes wireless miniature camera technology contained within a pill-sized capsule. It enables the physician to identify small bowel lesions, which previously would have been unreachable with standard endoscopic modalities.

Radiological Management

Although the main method to diagnose and treat GIB is endoscopy, interventional radiology (IR) techniques may be very useful if endoscopy is unsuccessful in either locating the bleeding site or in the application of its therapy. Unless patients have catastrophic hemorrhage, IR methods should be used as second-line management before recourse to surgery. The methods for diagnosis and treatment are broadly similar for both upper and lower GIB.[105]

The role of imaging is to locate the site of hemorrhage. The main modalities are conventional angiography, labeled red cell imaging, and CT angiography.

Angiography

Angiography involves selective catheterization of the celiac artery, the superior mesenteric artery (SMA), and the inferior mesenteric artery (IMA) with a variety of shaped catheters. The vessel targeted first for selective angiography depends on the clinical suspicion of the site of hemorrhage; although in practice, angiography of all three vessels is usually performed. Definite angiographic signs of hemorrhage are the accumulation of contrast after all the contrast has disappeared from the other vessels and the passage of contrast into recognizable bowel. Suggestive signs of the site of bleeding are abnormal vasculature (e.g., irregular vessels, dilated vessels, abnormal blush) or early venous filling. Conventional angiography detects hemorrhage if patients are bleeding at a rate of 1 ml per minute or more. If patients are bleeding more slowly or not at all at the time of the study, abnormal vessels may indicate the bleeding site. However, a positive result in a patient who is not bleeding at the time of the study is uncommon. Therefore, angiography should generally only be performed in patients who have ongoing hemorrhage at the time of the procedure. Acute bleeding is visualized angiographically in 37–97% of cases. The detection of acute hemorrhage is more common in upper gastrointestinal bleeding than in lower gastrointestinal hemorrhage.[106,107] In the individual patient, the critical factor in the success of angiography is whether the patient is bleeding or not at the time of the study.

Radionuclide Imaging

This study involves attaching a radionuclide marker to a sample of the patient's own red cells and reinjecting them into the patient. The tracer accumulates at the site of bleeding where it can be imaged by the detector. Red cell imaging is sensitive at lower rates of bleeding than angiography and may be used in stable patients when angiography is negative.

CT Angiography

With the development of multi-slice CT scanners, the ability of CT to image small vessels has improved substantially. Although the technique continues to evolve, it appears that CT angiography can locate sites of bleeding in a significant proportion of patients and, where available, should probably be used early on in the diagnostic evaluation of patients.

Embolization of GIB is one of the most technically demanding procedures performed by interventional radiologists. The aim of embolization is to occlude the vessel supplying the site of hemorrhage by delivering one of several blocking or embolic agents through a catheter. This requires passing a catheter from the femoral artery into the peripheral branches of the celiac artery, SMA, or IMA. Embolization can be performed through standard sized catheters. However, to access very peripheral vessels, it is usually necessary to use microcatheters and guide wires, which are passed coaxially through the larger bore standard catheters.

The main embolic agents used to treat GIB are coils, particulate matter (PVA or polyvinyl alcohol), and gelatin sponge (Gelfoam). Gelfoam is a temporary occluding agent and dissolves after a few days, while the other agents are permanent. The choice of which agent to use depends on the anatomical site of the bleeding and the ability (or not) to pass a catheter to the bleeding site.

The procedure differs slightly depending on whether the vascular territory supplying the site of hemorrhage is an end-artery or not. End-arteries supply a segment of bowel and do not have additional supply from adjacent vessels (e.g., large bowel). On the other hand, the duodenum is supplied by a rich anastomotic network of vessels from the celiac artery and SMA. End-artery territories can be embolized by simply occluding the vessel supplying the site of bleeding (Fig. 41.1a, b). Patients bleeding from vessels that have several contributories, such as the duodenum, require occlusion of all of the vessels supplying the bleeding site. In practice, this requires closing the vessel from either side of the bleeding site (the so-called "front and back door").

Patients with a negative arteriogram and a high clinical suspicion that the site of hemorrhage is located in the upper GI tract may be offered embolization of the gastroduodenal artery or left gastric artery with coils or Gelfoam. Complications of such prophylactic embolization are uncommon, although the evidence for the efficacy of this approach is limited.[108,109] Prophylactic embolization should not be performed for bleeding distal to the ligament of Treitz.

Most recent series report high success rates for the cessation of hemorrhage by embolization in around 85–90% of patients. These high success rates are achieved in upper and lower GIB.[110–114] Recurrent hemorrhage occurs in 10–20%

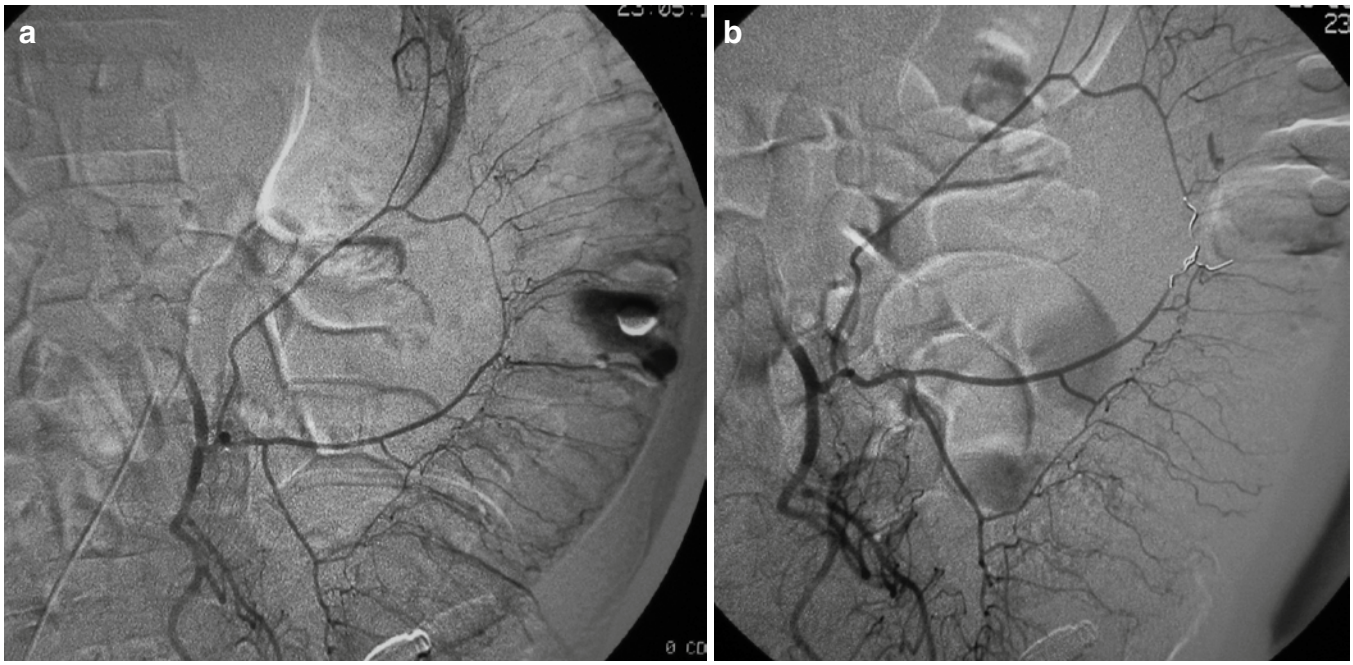

FIG. 41.1. Acute diverticular hemorrhage. (**a**) This selective inferior mesenteric arteriogram shows active extravasation of contrast from the left colic artery. (**b**) A microcatheter was advanced to the site of hemorrhage and the bleeding was stopped by coil embolization. Angiography after the embolization shows no further evidence of hemorrhage.

in the majority of series and can be treated by repeat embolization procedures in the majority of patients. Rebleeding is more common in patients with angiodysplasia, and the presence of multiple lesions in many patients is usually an indication for surgery.

Although ischemic stricture or bowel perforation was the complication feared by interventionalists and clinicians alike in the early experience of embolization, clinically evident ischemic complications after embolization are very uncommon, occurring in 1–2% of patients. In most patients, small ischemic or infarcted areas of bowel visible endoscopically are asymptomatic and do not require surgery. Transient abdominal pain occurs in around 10% of patients.[111–115]

Specific Management of Variceal Bleeding

Pharmacological Management

Infection has been shown to be a significant cofactor and possible precipitant in the patient with variceal bleeding. It affects between 35 and 66% of patients within 2 weeks of the event.[116,117] A combination of reduced small bowel motility, bacterial overgrowth, and increased permeability gives rise to higher levels of gut bacterial translocation, and, hence, endotoxemia and spontaneous bacterial peritonitis in these patients.[118] The mechanisms linking this endotoxemia to increased rates of variceal bleeding are believed to be related to worsening liver dysfunction, increased portal pressure, and decreased hemostasis.[118] Prophylactic broad spectrum antibiotic administration at the time of bleeding has been shown to reduce the risk of rebleeding at 1 week.[119] The most frequently studied and successfully used antibiotics are those active against enteric bacteria.[120]

Varices are a pathophysiological result of portal hypertension. The use of vasopressin analogues (terlipressin) to produce splanchnic vasoconstriction, and thus reduce the hepatic venous pressure gradient and variceal pressure, is now common practice in the acute management of bleeding varices. It has been shown to be superior to placebo in the control of variceal bleeding and to reduce mortality.[121] Terlipressin has been shown to have fewer of the systemic side effects (myocardial infarction, mesenteric ischemia) that were a concern with vasopressin.[122] In situations where endoscopy is unavailable terlipressin should be given; however, the benefits of combining the two therapies are still undemonstrated in the literature.[123]

Somatostatin (octreotide) has also been shown to be better than placebo in controlling variceal bleeding[124] and of equivalent efficacy to vasopressin.[121] Overall, there is not enough trial data, however, to strongly recommend the therapy either way. Suffice to say it is not regularly used in clinical practice, but could be considered as an alternative in patients intolerant to terlipressin.

The use of propranolol (beta blockade) as a long-term treatment for increased portal pressure has been shown to be equivalent to variceal band ligation in the reduction of rebleeding rates.[125] Those patients who do not respond to monotherapy have shown benefit from additional treatment with isosorbide mononitrate.[126]

Endoscopic Management

Historically, the endoscopic therapy of choice was sclerotherapy (submucosal injection of a sclerosant, e.g., ethanolamine); however, over the last 10 years the technique of endoscopic variceal band ligation has taken preference.

Despite a long history of clinical use, there are substantial differences in established sclerotherapy technique and hence a wide variation in results.[127] Sclerotherapy has been shown to be more effective at controlling bleeding than balloon tamponade[128] but no better than pharmacological therapy.[129] It is, however, not without potential complications such as esophageal ulceration and perforation, predisposition to infections, and pleural effusions.[127] Two meta-analyses to date[130,131] have appeared to suggest that variceal band ligation is superior to sclerotherapy on its own and in conjunction with vasoactive therapy in controlling bleeding and reducing rates of rebleeding, mortality, and complications.

The data discussed previously relates to the treatment of esophageal varices. Gastric varices, however, present a slightly different challenge. Their different anatomical location results in different technical hurdles. The evidence for band ligation in this setting is not as strong; however, the emerging use of endoscopic glue therapy (cyanoacrylate) appears especially useful.[132] The glue polymerizes on contact with the hydroxyl ions present in water. Double bonds present in the monomer become single bonds, causing multiple linkage, hence changing the liquid to a hard brittle acrylic plastic[133] thereby physically occluding the lumen of the varix. There are risks of embolization to lung, spleen, or brain, which have been reported in the literature.[134,135]

Non-endoscopic Management

Insertion of a Sengstaken Blakemore tube can act as an effective bridge to definitive treatments in the case of massive uncontrollable bleeding. This technique was first described in 1950.[136] The authors reported the use of an expandable balloon to provide tamponade and hence cease bleeding from the collateral variceal venous network. This technique is highly effective, temporarily arresting variceal bleeding in 90% of cases,[137] but is not suitable as a definitive measure. Up to 50% of patients will rebleed after deflation of the balloon at 24 h.[137]

Patients should ideally be intubated before tube insertion. The tube can be passed nasally or orally, although the latter is the more logical route in the intubated patient. Contrary to anecdotal advice, prior refrigeration does not aid passage of the tube.[138] Once fully passed, the gastric balloon should be inflated with 150–200 ml of air and traction applied and maintained.[120] Confirmation of correct placement pre-insufflation can be obtained either endoscopically[139] or ultrasonographically.[140] This is preferable in order to avoid inflation of the gastric balloon within the esophagus and risk esophageal rupture[141] or extrinsic compression of the trachea.

There is clinical debate, but little evidence about the type of traction applied. There are anecdotal concerns about pressure necrosis and luminal rupture associated with excessive force. Traditionally, the tube was allowed to hang over the head of the patient's bed with bags of fluid used as traction. Theoretically, however, this could result in variable traction and inadvertent movement of the tube. More recently the trend has been to fix the tube to the patient's cheek using a waterproof medical adhesive tape.

Although the tube also has both esophageal and gastric balloons, the authors do not recommend that the former is used. The gastric balloon alone is sufficient for compression of the gastric cardia, thereby tamponading the variceal supply; and, as discussed, concerns exist regarding rupture and pressure necrosis associated with esophageal balloon inflation.

Linton–Nachlas tubes are an alternative for effective control of gastric varices. This tube has a larger gastric balloon (600 ml), which provides tamponade throughout the gastric fundus. The evidence for their use is limited and has not been repeated recently, but does seem to suggest an advantage over the Sengstaken–Blakemore tube in this setting.[142]

Radiological Management

Establishing a connection between the portal venous system and the systemic supply (hepatic vein) allows for decompression of raised portal venous pressure. This phenomenon was first described in 1969, although it has only been featured as a formal clinical intervention over the past 10 years. This technique, known as transjugular intrahepatic portosystemic shunt (TIPSS), is a radiologically guided insertion of a self-expanding metallic stent into the liver parenchyma, via the internal jugular vein, to connect the portal and hepatic veins.

It is indicated as a rescue therapy in patients with uncontrollable acute variceal bleeding who have failed conventional endoscopic therapy, or for recurrent bleeding in patients intolerant to standard medical treatments.[143] In patients with a hepatic venous pressure gradient (HVPG) >20 mmHg, TIPSS has been shown to reduce early rebleeding risk and 6-week mortality.[144] Indeed the ideal HVPG should be <12 mmHg. There is increasing evidence that TIPSS also has a role to play in the management of both refractory ascites and hepatic hydrothorax.[143]

The main complications of TIPSS include stent failure, either due to thrombosis or intimal hyperplasia, and worsening encephalopathy. Stent thrombosis occurs in 10% of cases,[145] generally within the first 24 h post insertion. Both forms of blockage can be identified with Doppler ultrasound and released with repeat radiological catheterization. Procedural-related complications such as intraperitoneal bleeding, hepatic infarction, and formation of biliary-venous or arteriovenous fistulas are rare. Up to a quarter of patients experience new or worsening encephalopathy after TIPSS.[146] This should improve with standard medical management, but newer

percutaneous techniques include stent occlusion or reduction of patency with coils or stent grafts.[147]

It is important to remember, however, that this technique is not widely available and is mainly found in dedicated hepatology units. The indications for insertion and decision to proceed should normally take place under the direction of a specialist hepatologist.

Specific Management of Lower Gastrointestinal Bleeding

Endoscopic Management

The role of urgent colonoscopy in these cases is controversial. Endoscopic views may be obscured by blood or stool and, as mentioned previously, 90% of cases spontaneously settle.

A recent study[148] randomized 100 patients to undergo either urgent purging and colonoscopy or "standard" management with angiography and planned colonoscopy. Urgent colonoscopy identified the cause of bleeding significantly more often (OR 2.6) than standard management. There were, however, no significant differences in mortality, hospital stay, transfusion requirements, or rebleeding rates between the two groups.

The therapeutic options available will vary depending on the pathology.[149] The treatment of bleeding from diverticular disease will depend on the stigmata of hemorrhage, but is essentially identical to that of mucosal ulcerative disease in the upper GI tract (adrenaline injection, heat therapy, hemoclipping). The same approach can be applied to solitary rectal ulcers and colonic angiomas. Hemorrhoidal bleeds can be managed with thermocoagulation; however, band ligation has recently found favor.[150]

Each case should be judged on the relative clinical merits at the time, in discussion with the local colorectal surgical team, and be based on individual experience and local expertise.

Radiological Management

Mesenteric angiography can be both diagnostic and therapeutic (embolization). This technique should be considered in the case of uncontrolled bleeding from an unidentified source. A full discussion of the radiological techniques involved is included in the earlier section.

Surgical Management

Surgical intervention is required in 18–25% of patients who require a blood transfusion.[151] A segmental colectomy is the preferred operation, provided a bleeding point can be identified preoperatively. If not, then subtotal colectomy should be performed. The average mortality for segmental colectomy is 10% and for subtotal 20%.[151] Case series have been described[152] that report the role of laparoscopic surgery in an "acute setting," but within these there was no description of its role in the management of colonic hemorrhage. Open surgery remains, therefore, standard practice.

Conclusion

As we have highlighted in this chapter, gastrointestinal hemorrhage is a significant and challenging problem when encountered in the critical care setting. The potential etiologies are numerous, but core aspects of clinical management remain constant. The evidence base for specific therapeutic interventions is large and continues to develop.

Progress within the field of endoscopic and drug therapy has advanced to the extent now that the requirements for emergency gastroduodenal surgery are increasingly rare in modern practice. Perhaps the most significant of these was the advent of proton pump inhibitors, which has revolutionized the management of peptic ulcer disease. The fall in mortality rates for variceal bleeding over the past two decades is also a victory for developments in endoscopic technique (variceal band ligation) and pharmacological intervention (vasopressin analogues).

Specialist training in endoscopy is gaining prominence in the UK, with recently established national training centers and educational programs bringing a much needed formal and standardized approach to training. More hospitals are also establishing emergency 24-h endoscopy rotas in light of the evidence that demonstrates improved outcomes with earlier intervention.

The interface between critical care medicine and the medical specialties is increasing. The specialist knowledge and practical contributions that can be provided by physicians with a background in medical specialties such as gastroenterology should not be underestimated and demonstrates the importance of multidisciplinary working.

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42
Acute Pancreatitis

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Acute pancreatitis is an inflammatory disease of the pancreas, which can be either localized or affect the whole pancreas, and is a disease with a typically unpredictable course. The spectrum of disease severity of acute pancreatitis varies from benign with only mild symptoms to patients who require treatment in an intensive care unit (ICU) for a prolonged period. The wide spectrum of signs and symptoms, and the lack of clear definitions have made it very difficult in the past to compare different studies regarding patient management and risk stratification. In 1992, a Consensus Conference was held to provide a number of descriptions of different classes of the disease process. The main result of this meeting was the differentiation between mild acute pancreatitis and severe acute pancreatitis, a classification scheme which is now widely used.[1] Essentially, mild acute pancreatitis is a self-limiting disease with no local or systemic complications, and has a low to 0% mortality rate. Severe acute pancreatitis on the other hand, is more severe due to either local complications or systemic complications and often associated with one or more organ dysfunction(s). The validity and usefulness of these definitions have been questioned, and a revision is scheduled for 2008–2009. A more detailed and strict definition of organ dysfunction in patients with severe pancreatitis, and a clearer distinction between early and late events is urgently needed.

Natural History of Acute Pancreatitis

Most of the patients, estimated at about 80–85%, develop only mild pancreatitis,[2] which resolves within 3–5 days and carries a low morbidity and mortality rate. There is no necrosis present, only pancreatic edema to some extent, and systemic effects are limited.

However, about 15–20% of patients with acute pancreatitis progress to the severe form, which is associated with organ failure and/or local complications as necrosis, abscess formation, or pseudocysts. Typically, the Ranson score[3] (Table 42.1, see also below) is 3 or above, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score[4] on admission is 8 or higher. Pain that lasts beyond the first few days of admission can be indicative of local complications. Patients with the fulminant variant of the disease develop multiple organ dysfunction syndrome (MODS) within 24–72 h after admission due to a systemic inflammatory response syndrome (SIRS).

Complications in patients with acute pancreatitis typically occur in two phases. Complications arising in the first days after the onset of disease are caused by the inflammatory reaction, and may lead to MODS, similar to organ dysfunction described in patients with severe sepsis. At this point, tissue hypoperfusion may set in, and may be the cause of problems later in the course of the disease, although often no necrosis is documented on abdominal computed tomography (CT) scan.

1–2 weeks after the onset of symptoms, complications are mainly caused by the residual pancreatic tissue. Pancreatic necrosis, and more importantly infection of the pancreatic and peripancreatic tissue, is the most feared complication. It has always been associated with considerable morbidity and mortality, and as infection obviates a surgical intervention, multiple strategies have been devised to prevent this from happening. The formation of pancreatic pseudocysts is also

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Table 42.1. Variables included in the Ranson score.[3]

On admission	During the 48 h after admission
Age >55 years	Decrease in hematocrit >10%
White blood cell count >16,000/μL	Calcium <8 mg/dL (2 mmol/L)
Glucose >200 mg/dL (11 mmol/L)	paO_2 <60 mmHg
Lactate dehydrogenase >350 IU/L	Blood urea nitrogen increase >5 mg/dL
Aspartate aminotransferase >250 IU/L	Base deficit >4 mEq/L
	Estimated fluid sequestration >6,000 mL

Table 42.2. Causes of acute pancreatitis.

Gallstones including microlithiasis
Alcohol
Drugs (estrogen, furosemide, sulfonamides, aminosalicylates, tetracyclines, thiazides, valproic acid, steroids, metronidazole, cyclosporin A, azathioprine, L-asparaginase
Trauma
• Endoscopic retrograde cholangiopancreatography
• Sphincterotomy
• Blunt and penetrating trauma to the pancreas
Infections
• Viral infections (mumps, human immunodeficiency virus, Coxsackie virus, cytomegalovirus, hepatitis B virus)
• Bacterial infections (*Salmonella typhi, Legionella*)
• Parasitic infections (*Ascaris lumbricoides*)
Obstruction of the pancreatic duct
• Sphincter of Oddi obstruction (ampullary tumor or stricture)
• Intraductal stone and stricture
Ischemia (hypotension, hypothermia)
Autoimmune disease
Metabolic (hypertriglyceridemia, hypercalcemia)
Anatomic congenital abnormalities (pancreas divisum, choledochal cysts, diverticula)
Idiopathic

an important source of late morbidity, but in most cases, the outcome of patients with this complication of severe acute pancreatitis is good. Patients with complicated disease often stay in the hospital for prolonged periods of time.

Complications are important in patients with acute pancreatitis, because they are the main cause of morbidity and mortality, both in hospital and after discharge. Medical problems after discharge from the hospital include diabetes, abdominal pain, chronic pancreatitis, polyneuropathy, and problems related to chronic alcohol abuse. Diabetes and polyneuropathy have been reported to be important problems in particular, indicating also a significant economic burden after discharge from the hospital.

Despite this, patients rate their quality of life rather good. The long-term outcome in patients with acute pancreatitis has been studied in the past. One study reported that the health related quality of life in 145 severe acute pancreatitis patients was not different from the overall health related quality of life of the general population, although the scoring system used did indicate that patients scored slightly worse[5]; a considerable number of patients died, however, after hospital discharge, mainly from alcohol-related problems and injuries.

Mortality in mild AP is low and estimated below 1%,[2] and related most often to exacerbation of chronic underlying problems such as COPD or chronic heart failure. Mortality in severe acute pancreatitis on the other hand is higher, but highly variable in the literature, depending obviously on the patients studied.

Epidemiology and Etiology

The incidence of acute pancreatitis varies considerably, and ranges from 5 to over 80 per 100,000 population per year.[6,7] This incidence seems to be largely determined by the prevalence of the typical risk factors in the population, such as alcohol intake and gall stone disease. It has been suggested that the incidence is increasing in some regions, but data are limited and this observation may also be attributed to improvement in and increased use of diagnostic aids to confirm the diagnosis.

Causes of acute pancreatitis are numerous (Table 42.2); biliary tract stones and alcohol intake outnumber all others, and together account for about 70–80% of the episodes of acute pancreatitis. Remarkably, in some countries, excessive alcohol intake is responsible for as many as 80% of the episodes of acute pancreatitis. There seems to be an important variation in etiology across different geographic areas, with Europe as a striking example – in northern Europe, alcohol intake is by far the leading cause of acute pancreatitis, whereas in Greece, biliary tract stones accounted for the majority of the episodes of acute pancreatitis,[7] and in Italy, alcohol accounts for only 7% of all episodes of acute pancreatitis.[2]

Less frequent causes of acute pancreatitis include hypertriglyceridemia, hypercalcemia, endoscopic retrograde cholangiopancreatography (ERCP), drug toxicity, pancreatic and duodenal tumors and congenital abnormalities (e.g. choledochus cyst, pancreas divisum), abdominal trauma, and viral or parasitic infections. In a considerable number of patients, up to 20% of patients in some studies, no clear cause can be identified; these patients are classified as suffering from idiopathic pancreatitis.

An increasing number of genetic causes of pancreatitis are being identified, mainly inducing a loss of protection against spontaneous trypsinogen activation.[8]

Often, patient characteristics may point to the cause of pancreatitis. Gallstones are often responsible for acute pancreatitis in female patients above age 50, whereas alcohol abuse should be suspected in the younger male patient.

Pathophysiology

Acute pancreatitis can be limited to a local inflammatory disease of the pancreas, or can evolve to severe acute pancreatitis with systemic complications. Three different phases can

be distinguished in the development of acute pancreatitis: the first two take place in the pancreas itself, while in the third and final phase extrapancreatic symptoms may occur. However, not all patients will progress to the second and third phase, and in patients who develop mild disease, the disease will not spread outside the pancreas.

The first phase takes place in the acinar cell of the pancreas itself; the acinar cell is damaged and this leads to cell death; this initiates the second phase of local inflammation of the pancreas, which causes the typical local signs and symptoms. These first two phases occur to some extent in all patients, but in a number of them, this local process activates the SIRS, which makes up the third and final phase. This SIRS response leads to distant organ damage.

Phase 1: Cellular Damage

Premature conversion of trypsinogen into trypsin, a proteolytic enzyme responsible for activation of a number of digestive enzymes in the gastrointestinal lumen, is considered the starting event in the development of acute pancreatitis.[9] This activation of trypsinogen is normally mediated by enterokinases, and normally occurs in the gastrointestinal tract. In pathological conditions, this is initiated in the acinar cells of the pancreas, but the exact mechanisms remain unclear. Likely, co-localization of cathepsin B – a proteolytic enzyme, under normal conditions responsible for degrading unneeded cellular material and stored in a separate compartment – with trypsinogen in the same intracellular vacuoles is the initiating event, but several other factors play a role. The level of intracellular calcium for instance is very important for this premature activation,[10] and decreased secretion, and thus accumulation of trypsinogen in the acinar cell, mediated by disruption of the actin cytoskeleton also plays a role.[11] It is also assumed that the inhibition of the cellular mechanisms that protect against spontaneous or accidental trypsinogen activation, such as trypsin inhibitor and proteases that degrade activated trypsin, plays a role in the development of pancreatitis.

Genetic factors may also contribute to the pathogenesis of this first phase in some patients. Several forms of hereditary pancreatitis have been described; the common feature of these diseases is the inhibition of cellular mechanisms that protect against spontaneous or accidental trypsinogen activation.[8]

In recent years, the cellular reaction to this damage has been intensively investigated. Especially the role of apoptosis (i.e., programmed cell death) in acute pancreatitis, as opposed to necrosis, as a reaction to damage seems to be important.[12,13] In normal conditions, apoptosis is mediated by a group of proteases, the caspases, that may serve both as an initiator, as well as an effector of this process.[14] The local conditions will largely determine whether apoptosis or necrosis will occur, and several mediators are involved – among them trypsin itself, nuclear factor (NF)-κB, cathepsin B, so-called inhibitors of apoptosis and poly(ADP-ribose) polymerase (PARP)[15] – that lead to necrosis. The level of ATP depletion is very important in this respect.[16] High levels of adenosine triphosphate (ATP) depletion will lead to necrosis, whereas lower levels of depletion are associated with apoptosis. Again, calcium is a key factor. Higher and sustained high levels of calcium in the acinar cell are likely to result in necrosis.[17] The form of cell death, either necrosis or apoptosis determines the severity of pancreatitis, at least in animal models; apoptosis is associated with mild disease, whereas necrosis is associated with severe acute pancreatitis.[18]

Phase 2: Local Inflammation in the Pancreatic Tissue

This phase is characterized by attraction and activation of neutrophils and macrophages in the pancreas. This inflammatory process is initiated by the NF-κB pathway,[19] which initially leads to the local production of Interleukin (IL)-1β and TNF-α both in the acinar cells and local macrophages. These cytokines set off a whole inflammatory cascade[9,20] involving different cell types (such as neutrophils, lymphocytes, macrophages, and endothelial cells) and a multitude of pro-inflammatory – such as IL-6, IL-8, intercellular adhesion molecule (ICAM)-1, complement components, platelet activating factor (PAF), reactive oxygen species, kallikrein, nitric oxide, prostaglandins, substance P – and anti-inflammatory mediators (e.g., IL-2, IL-10), of which the complex interactions are not yet fully understood.[21]

Anatomically, these processes are characterized by inflammation and edema of the pancreatic tissue.[22] This may be associated with vasospasm in both intra- and extra-pancreatic vessels.[23] In some cases, the microcirculation is compromised, and ischemia, hemorrhage, and necrosis may develop[24]; many of the previously mentioned pro-inflammatory mediators have been associated with changes in the microvasculature,[25] and platelets seem to play a crucial role.[26]

Phase 3: Systemic Inflammation

Systemic complications of acute pancreatitis are caused by a systemic inflammatory response syndrome, which is similar to the reaction observed in patients with sepsis, trauma, or burns. Once these pro-inflammatory mediators enter the systemic circulation, remote organ dysfunction may develop, which is responsible for the majority of severe complications seen early during the course of acute pancreatitis. In addition to the cytokines mentioned earlier, monocyte chemoattractant cytokine (MCP-1), macrophage migration inhibitor factor 1 (MIF-1), and cyclooxygenase 2 (COX-2) induction among many others are involved in the development of distant complications. In animal models, selective inhibition of these cytokines has resulted in a decreased severity of distant complications, but so far, only one human study in established pancreatitis has been performed. In this large human study, lexipafant (a PAF antagonist) was tested, but could not ameliorate the severity of disease or improve outcome.[27]

Different mechanisms can lead to all or some of the previously described pathophysiological processes. It is also highly questionable whether the different mediators identified in acute pancreatitis have the same role when different causes of pancreatitis are considered.

In rodents, for instance, alcohol has a multitude of effects on the described processes.[28] First, the expression and activity of cathepsin B, responsible for the premature conversion of trypsinogen in the acinar cell, is increased. The activity of the various caspases involved in the apoptosis process is also decreased, and deleterious effects on the microcirculation have been described. The metabolism of alcohol to fatty acid ethanol esters is also considered to contribute to the development of pancreatitis, as it causes intracellular trypsin activation, and an increase in the intracellular calcium concentration.[29] It is unknown whether these mechanisms are also involved in human alcoholic pancreatitis.

Biliary tract obstruction on the other hand, causes pancreatitis through the reflux of bile salts in the pancreatic duct. These bile salts increase intracellular calcium concentration, causing mitochondrial dysfunction leading to cell death through necrosis.[30] Whether this mechanism is also partly involved in isolated obstruction of the pancreatic duct without bile reflux is not clear.

Finally, hyperlipemia causes pancreatitis through a direct toxic effect of free fatty acids that come from the hydrolyzed triglycerides in the pancreas. Apart from the direct toxic effect, the microvasculature is also compromised.

Most of the knowledge about the pathophysiology of acute pancreatitis comes from animal, most of them rodent, models. In these models, the role of different enzymes or cytokines involved in either of the prior steps has been studied individually by inhibiting their activity, or by knocking out the gene coding for their synthesis. This has taught us a great deal about the pathophysiology of pancreatitis in the mouse and rat, but it remains unclear if this can be extrapolated to humans. For instance, receptors for cholecystokinin (CCK) in rodents and humans are expressed differently, and supraphysiological doses of CCK, a commonly used model for experimental acute pancreatitis, are not able to induce pancreatitis in humans.

Clinical Presentation

Clinical presentation is quite straightforward in most patients. Acute epigastric pain is the most striking symptom, often associated with referred pain in the back, and nausea and vomiting. The severity of the pain increases over a few hours, and can last for several days.

In some patients, acute pancreatitis may mimic acute peritonitis, and in cases of clinical uncertainty, more investigations such as abdominal CT scan may be needed to exclude problems such as perforated gastric ulcer or other causes of secondary peritonitis. . A minority of patients present with the typical findings of discoloration of the periumbilical area (Cullen sign) or both flanks (Grey–Turner sign). This indicates involvement of the peripancreatic tissues, and is suggestive of advanced disease.

On rare occasions, patients with acute pancreatitis may present with overt organ dysfunction, without obvious abdominal symptoms. Most commonly involved organ systems are the cardiovascular, the respiratory, the kidneys and the central nervous system, resulting in hypotension, hypoxia, agitation, or decreased level of consciousness. Fever is also often present due to systemic release of pro-inflammatory mediators.

Diagnosis

The diagnosis is suspected based on the combination of the above typical clinical features, and elevated serum levels of amylase or lipase in most patients.

Biochemistry

Increased pancreatic enzymes (> 3 times the normal upper limit) are the mainstay of the biochemical confirmation of pancreatitis. Amylase is most often used, but is also increased in a number of other conditions ranging from other pancreatic disorders, intestinal ischemia and perforation to parotitis and acute renal failure.[31] The specificity of elevated lipase is reported to be higher, but far from perfect. Daily follow-up of these enzymes does not add to the management of the patient once the diagnosis has been established, and they cannot be used to assess the severity of pancreatitis or as a marker of improvement. In patients with low serum amylase levels but suspected pancreatitis, urinary amylase may be more appropriate to confirm the diagnosis.[32]

Other enzymes have been studied as diagnostic tools such as urinary trypsinogen-2 and serum pancreatic elastase, with especially high negative predictive values for both.[33] The tools are not yet used on a broad scale to diagnose pancreatitis.

Imaging

Imaging techniques such as ultrasonography or abdominal CT scan are not necessary in establishing the diagnosis of acute pancreatitis in the majority of the patients, and should only be used on admission to exclude gall stone disease in patients with suspected biliary pancreatitis, or to exclude other diagnoses. So far, imaging techniques have not been able to predict disease severity at the time of admission to the hospital.

The role of CT scan and magnetic resonance imaging (MRI) lies in the detection of complications of acute pancreatitis, such as pancreatic necrosis, peripancreatic fluid collections, or pseudocysts; the presence of these complications can also be used to predict the severity of the disease.

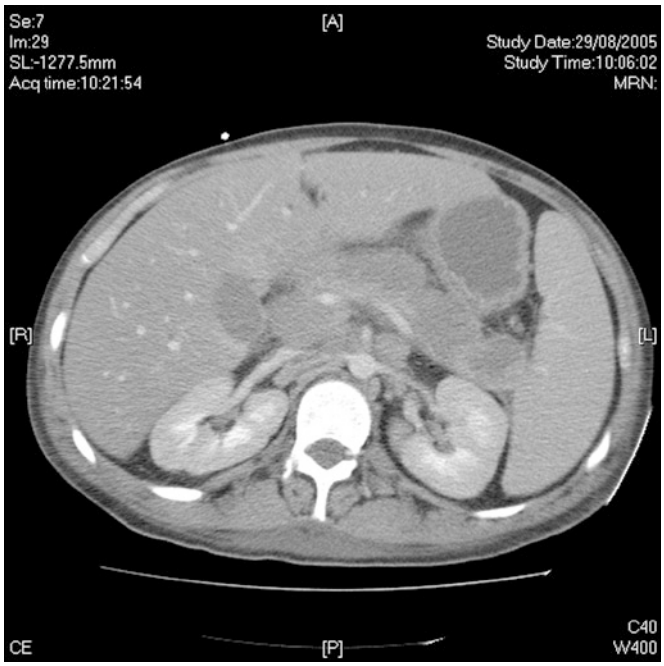

FIG. 42.1. Abdominal CT scan of a patient with severe acute pancreatitis showing pancreatic necrosis and retropancreatic inflammation.

CT Scan

In some cases, such as high clinical suspicion with normal enzyme levels or unexplained MODS, abdominal CT scan can be used to establish the diagnosis in suspected acute pancreatitis. Specific pancreas protocols should be used to increase the diagnostic yield. On CT scan, findings may vary from localized edema with or without pancreatic tissue inflammation to necrosis of the pancreatic tissue, with extensive peripancreatic fluid collections (Fig. 42.1).

MRI

MRI can also be used to diagnose acute pancreatitis and can distinguish accurately between necrotic and non-necrotic tissue.[34] It is particularly well suited to visualize the pancreatic duct and detect the presence of lithiasis without the need for ERCP. In clinical practice, MRI is rarely used on a routine basis, because of limited access and the practical problems relating to transportation of critically ill ventilated patients to the MRI lounge.

Ultrasound

Ultrasound cannot be used in most patients to assess the pancreas for the presence of inflammation or necrosis. The value of ultrasonography lies in the detection of gall stone or dilatation of the biliary tract, indicative of obstruction due to a retained gall stone. Endoscopic ultrasound has a high sensitivity for detecting microlithiasis that may be missed on transabdominal ultrasound.

TABLE 42.3. Modified Glasgow criteria.[35]

Within 48 h after admission
Age >55 years
White blood cell count >15,000/μL
Glucose >180 mg/dL (10 mmol/L)
Lactate dehydrogenase >600 IU/L
Calcium <8 mg/dL (2 mmol/L)
paO_2 <60 mmHg
Blood urea nitrogen >44.8 mg/dL (16 mmol/L)
Albumin < 32 g/L

Risk Stratification

The goal of early risk stratification is to predict which patients are more likely to benefit from early admission to an ICU or high dependency unit for monitoring and supportive care. It may also help physicians to select patients for targeted interventions in order to limit the damage caused by pancreatitis.

The Ranson criteria (Table 42.1) were developed in the 1970s, and are still widely used today. A combination of clinical and biochemical parameters obtained at admission and during the first 48 h after admission provides an estimate of the risk for mortality.[3] Although the high predicted mortality rates no longer apply, the Ranson score reflects the extent of metabolic derangement, and can be expected to relate to mortality in patients treated today. The modified Glasgow criteria have been derived from the same criteria, but the number of variables have been reduced to 8 (Table 42.3).[35] Both are at a disadvantage in that some of the variables are only evaluated at 48 h, and therefore are of limited use in the emergency room.

Several biochemical markers that may predict the severity of pancreatitis have been studied. C-reactive protein at 48 h, but not at admission, has been shown to be a useful parameter, with sensitivity and specificity ranging between 57–89% and 55–82% respectively.[31] Other markers include procalcitonin, IL-6, trypsinogen activation peptide, polymorphonuclear elastase and carboxypeptidase B activation peptide; however, these markers are not yet widely available. Hematocrit, and persistent hemoconcentration in particular, has been found to be an indicator of pancreatic necrosis and organ failure,[36] but may also be an indicator of poor initial resuscitation with organ dysfunction inevitably resulting from it.

The importance of necrosis and infected necrosis has been well documented, but as both occur only at least 2–3 days after the start of symptoms, they cannot be used on admission to guide patient disposition. Radiological scores based on the presence of necrosis, such as the CT severity index[37] (Table 42.4), should therefore not be used within the first days of symptoms to guide patient treatment. However, both scoring systems have been found to be reliable to predict outcome in terms of mortality in patients with acute pancreatitis[38]; as one of the main determinants of outcome, necrosis and the extent of it, is an essential part of both scoring systems, this is to be expected. It should be noted however, that

Table 42.4. The CT severity index.[37]

Element	Finding	Points
Grade of acute pancreatitis	Normal pancreas	0
	Pancreatic enlargement	1
	Inflammation involving pancreas and peripancreatic fat	2
	Single fluid collection or phlegmon	3
	Two or more fluid collections or phlegmons	4
Degree of pancreatic necrosis	No necrosis	0
	Necrosis of one third of pancreas	2
	Necrosis of one half of the pancreas	4
	Necrosis of more than one half of the pancreas	6

an important number of patients with pancreatic necrosis, will never develop organ dysfunction.

Intra-abdominal Hypertension

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) have been described most often in patients with abdominal trauma or after emergency abdominal surgical procedures such as aortic aneurysm repair. IAH is defined as a sustained or repeated pathologic elevation of the intra-abdominal pressure (IAP) above 12 mmHg, whereas ACS is described as the sustained elevation of IAP above 20 mmHg in combination with newly developed organ dysfunction. Although the typical symptoms of ACS, i.e., rapidly evolving MODS (most often a combination of respiratory failure, hemodynamic compromise, and acute renal failure) are often found in patients with severe acute pancreatitis, it was not until recently that the importance of IAH has been recognized.

The true incidence of IAH in patients with severe acute pancreatitis is not yet completely clear, but figures as high as 80% have been reported.[39] A causal relationship could not be demonstrated, but the case series reporting excellent outcomes in patients undergoing abdominal decompression suggest that IAP may be a target for early intervention.[40] When it occurs, IAH develops early in the course of the disease, after a median of 1 day, and is maximal on the second and third day. It has also been found that in non-survivors, IAP remained elevated during the first week whereas survivors had high IAP on day 1, but showed a progressive decrease in IAP in the following days.[41] The role of the dynamics of IAH in patients with SAP is probably a key factor.

It has been suggested that IAP can also be used as a predictor of the severity of the episode of acute pancreatitis. Maximal IAP correlates well with the severity of pancreatitis and the development of a maximum IAP >14 mmHg can adequately predict mortality.[42] However, IAP should not be used to guide patient disposition in the emergency room or within the first few hours or days. The sensitivity and specificity reported for the development of intra-abdominal collections (sensitivity 78%, specificity 86%) and the need for surgery (sensitivity 88%, specificity 86%) using the same cutoff of 14 mmHg, may be indicators that IAH does play a role in the development of pancreatic necrosis and infection as well.

The development of IAH in patients with severe acute pancreatitis is initiated by the inflammatory process in the retroperitoneum leading to the development of pancreatic and visceral edema, peripancreatic acute fluid collections, and ascites. The combination of capillary leakage and large volume fluid resuscitation further increases the development of intra-abdominal edema. Additionally, paralytic ileus and upper gastrointestinal tract obstruction by the pancreatic collections may also aggravate IAH. Reduced abdominal wall compliance due to edema may also play a role.

A subset of patients with severe acute pancreatitis who develop early multiple organ dysfunction syndrome (MODS) within a few days after the start of symptoms has been described, which is associated with increased mortality. Although the exact mechanisms of early MODS are not completely understood, IAH may be a potential contributing factor to the development of early organ failure seen in patients with severe acute pancreatitis. Tao et al. reported an incidence of ACS (defined as an IAP >15 Hg) in as much as 78% of patients with early SAP; 90% of the fatalities in this group had developed ACS.[43]

The symptoms caused by IAH in patients with acute pancreatitis are not very different from other conditions associated with IAH. Hemodynamic instability requiring vasoactive drugs, acute renal failure, and respiratory failure are the most obvious clinical signs and symptoms that have been associated with IAH. The association between IAH and development of organ dysfunction in severe acute pancreatitis is well documented.[41] One study found higher mean and maximal IAPs in patients who developed MODS, and reported a sensitivity of 86% and specificity of 84% for an IAP ≥15 mmHg to predict MODS.[42]

Complications in Severe Pancreatitis

Necrosis

Hypoperfusion of the pancreatic tissue due to changes in the microvasculature may lead to tissue necrosis. The occurrence of necrosis has long been considered the most important determinant of outcome, but organ dysfunction seems to have replaced this at least for mortality as an endpoint. Symptoms caused by necrosis may vary considerably, and it should be noted that up to half of the patients with necrosis do not develop organ dysfunction.[44] Local complications such as pseudocysts and infection of necrosis, however, can only occur after the development of necrosis, and therefore necrosis should be considered a substrate for subsequent complications.

The extent of the necrosis on the other hand, seems to be related to the development of local and systemic complications;

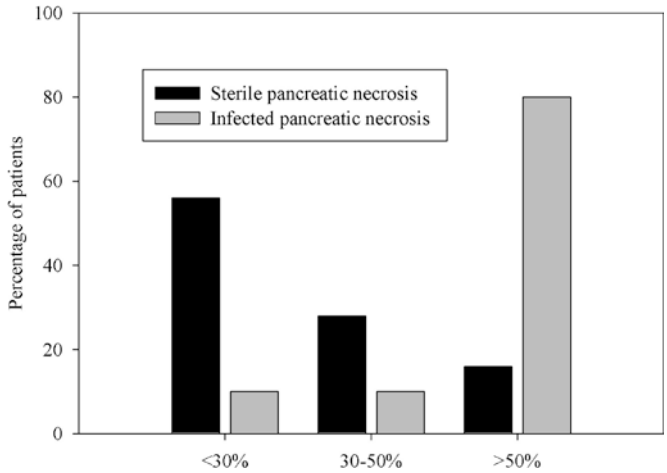

FIG. 42.2. Relation between extent of pancreatic necrosis and infection.[45]

as an example, infection of necrosis seems to occur more often in patients with more than 50% necrosis of the gland (Fig. 42.2)[45]; also organ dysfunction is more frequent in patients with more extensive necrosis.[46]

Extensive necrosis may also cause obstruction of the upper gastrointestinal tract, and produce discomfort in the upper abdomen. The consistency of pancreatic necrosis will change over time from a solid mass to a more viscous collection, often encapsulated by a fibrotic wall, which may finally resolve without intervention.

Infected Necrosis

Infection of the necrotic pancreatic tissue is the most feared complication of severe acute pancreatitis,[47] because it is associated with increased morbidity and mortality.[46,48,49] It occurs in 20–40% of patients with severe disease. Typically, enteric gram-negative bacteria cause infection in these patients,[50] although recently, a shift toward gram-positive organisms and fungi was observed.[51]

Bacterial translocation from the gut is presumed to be the main threat for patients with severe acute pancreatitis. In laboratory experiments, an incidence of bacterial translocation of up to 100% has been found.[52] Some of the factors involved in translocation may be ileus, the use of prophylactic antibiotics, and intra-abdominal hypertension, which is increasingly documented in patients with severe acute pancreatitis (see above). IAH and ACS are associated with an increased translocation rate,[53] but mechanisms are not clearly understood. Poor perfusion pressure of the gastrointestinal tract leading to gut barrier failure can also be a plausible explanation.[54]

Other causes of secondary infection of pancreatic necrosis are bowel perforation, causing direct infection or hematogenous dissemination of distant foci of infection such as pneumonia or catheter-related infections. One additional factor involved may be reflux from the bile ducts, which is associated with the occasional fulminant deterioration of patients with acute pancreatitis after ERCP.

ICU Management of Patients with Severe Acute Pancreatitis

ICU Admission

Selecting patients who will require ICU care remains very difficult, due to the lack of early adequate predictors of the development of organ dysfunction. Patients at risk for severe disease may not necessarily benefit from ICU admission, as only patients with organ dysfunction, and not pancreatic necrosis alone, seem the most logical candidates for monitoring and close follow up in an ICU.

From a practical point of view, patients who present with organ dysfunction at admission – most often hypotension, respiratory insufficiency, and acute kidney injury – should be admitted to an ICU or high dependency unit, as well as patients with severe metabolic derangements or significant underlying disease that may aggravate acute organ dysfunction such as heart failure or chronic renal insufficiency. ICU care for patients with severe acute pancreatitis consists of five different aspects:

- Monitoring for the development of complications (i.e., organ dysfunction and local pancreatic complications such as necrosis and infection)
- Support for organ dysfunction
- Limiting the progress of the disease
- Prevention of infection
- Treatment of complications

Monitoring

Monitoring of vital signs is the most obvious aspect of care in an ICU environment. Parameters should include heart rate, blood pressure, respiratory rate, oxygen saturation, urinary output, and consciousness on a regular basis, and biochemical evaluation of organ function should also be performed.

This will alert the treating physician to impending organ dysfunction, which should trigger strategies to support failing organ systems, and to prevent further damage (see below).

Monitoring for the development of local complications is equally important. As discussed before, the development of necrosis and infection of the necrosis are associated with increased morbidity and mortality. Pancreatic necrosis is documented on contrast enhanced CT scan, and although the detection of pancreatic necrosis will not alter treatment significantly, it should be considered in patients who do not improve after ICU admission, to exclude other causes or early pancreatic infection.

Infection of pancreatic necrosis is difficult to predict, and especially difficult in the early phase of the disease. The SIRS reaction related to pancreatitis itself makes differentiation between inflammation and infection very difficult. Regular screening for peripancreatic infection by means of repeated CECT scan, with FNA if necessary, is the most logical solution

for this problem. So far, biomarkers have been useless to discriminate between infection and inflammation.

Because of the association between organ dysfunction and IAH in patients with SAP, IAP monitoring is logical. IAH is related to the development of complications, and may be a simple and reliable tool to predict complications in AP. A maximal IAP≥14 was found to be predictive of MODS as well as infected collections and the need for surgery,[42] with especially high specificity for most endpoints.

Support of Organ Dysfunction

Hypotension is one of the most common presentations of organ dysfunction in patients with severe acute pancreatitis, and often these patients require aggressive fluid resuscitation. This is largely due to fluid loss in the "third space," which may lead to systemic hypoperfusion and, therefore, further contribute to end organ dysfunction. Rapid restoration of intravascular volume is therefore essential, and can be accomplished using colloid or crystalloid transfusion. Some patients may require several liters of fluids over a few hours to correct hypovolemia.

Oliguria is often present in patients presenting late after the onset of symptoms. Reduced fluid intake because of nausea and abdominal pain combined with third space losses as previously described and systemic inflammation contribute to acute kidney injury. Most patients respond well to fluid administration, and often renal replacement therapy can be avoided.

Respiratory insufficiency is rarely present on admission, and often only develops after fluid resuscitation. Acute lung injury or acute respiratory distress syndrome with bilateral pulmonary infiltrates on chest X-ray may develop; pleural effusion and reduced thoracic compliance may further compromise respiration. Supplemental oxygen may help some patients to relieve respiratory failure, but ventilatory support is often unavoidable. Noninvasive ventilation via a face mask may be tried; but in case of persistent hypoxic or hypercapnic respiratory failure, invasive mechanical ventilation using lung protective strategies is necessary.

Pain relief is often necessary in patients with SAP, not only to make the patient more comfortable, but also because the pain per se impairs oxygenation and may even contribute to ongoing organ dysfunction. The parenteral route is generally preferred, and intravenous administration of opioids is often necessary. Previously, morphine was considered to cause sphincter of Oddi dysfunction, but this has not been documented in humans, and morphine is now considered to be safe in humans.[55] Epidural administration of analgesics has proven to be very effective, but should be used judiciously in patients with hypotension.

Limiting Disease Progress

A lot of effort has been spent on devising strategies to limit progression of the disease and thereby preventing complications. Most of these strategies, although beneficial in experimental pancreatitis, had no effect on relevant endpoints such as morbidity or mortality. Probably, most of these interventions come too late when applied to patients who present with established pancreatitis.

Putting the pancreas at rest by prohibiting oral intake or withholding enteral nutrition has traditionally been one of the first steps when patients present with acute pancreatitis. Although most patients will not tolerate oral feeding due to nausea and abdominal pain, there is no evidence that this is indeed beneficial. Pancreatic secretion is presumed to be inhibited by the disease itself, and prescribing "nil per mouth" has no added value. The contrary is probably true: early enteral nutrition, even intragastric feeding is feasible in patients with severe acute pancreatitis, and has been shown to limit organ dysfunction and reduce the rate of infection.[56]

Pharmacologic inhibition of pancreatic secretion using protease inhibitors or antisecretory drugs such as somatostatin or analogues has extensively been investigated, but no convincing effect on morbidity or mortality could be demonstrated in patients with acute pancreatitis.[57]

Anti-inflammatory compounds aimed at dampening the local and systemic inflammatory process have attracted much attention recently. Lexipafant is an antagonist of platelet activating factor (PAF), one of the pro-inflammatory cytokines involved in the local and systemic response. PAF is present in high concentration in the inflamed pancreatic tissue, which is released from neutrophils and also from acinar cells when stimulated with phospholipase A2. Lexipafant has been studied in several studies,[58,59] but failed to demonstrate a reduction in the frequency of organ failure or mortality in a controlled randomized trial of 270 patients with predicted severe pancreatitis (APACHE II score of 6 or more).[27] The authors blamed the high baseline incidence of organ dysfunction for the inability to show an advantage of treatment with lexipafant, and suggest that patients may benefit if they are treated earlier in the course of the disease.

Furthermore corticosteroids have potent anti-inflammatory effects, and have successfully been used in experimental pancreatitis.[60,61] Recently, a small case control study also suggested a possible role for hydrocortisone in acute pancreatitis patients with vasodilator shock,[62] but the role of steroids in acute pancreatitis patients remains to be elucidated.

In patients with biliary tract stones as the cause of pancreatitis, removal of residual lithiasis from the common bile duct should be attempted when documented or when indirect signs of this, such as jaundice and bile duct dilation on abdominal or endoscopic ultrasound, are present. As surgery in this setting has been associated with increased mortality, ERCP with sphincterotomy is the most elegant way to reach this goal. ERCP notably has beneficial effects in patients with severe forms of pancreatitis, with reduced incidence of complications, such as biliary sepsis.[63] When performed later than 72 h, ERCP may induce infection in pancreatic necrosis, and should therefore be avoided.

In some patients with pregnancy-related hypertriglyceridemia or type IV or V hyperlipoproteinemia and high level of serum triglycerides (>1,500 mg/dL despite conservative

treatment), plasmapheresis may be necessary to prevent ongoing damage to the pancreas.

Prevention of Infection

Prophylactic Antibiotics

Prophylactic antibiotics have been the most intensely debated topic in the treatment of patients suffering from SAP. Although once considered a life-saving intervention based on a number of small unblinded trials, and eagerly adopted by the medical community, in two recent controlled randomized trials – the only blinded studies that have been performed to date – this practice could not demonstrate any benefit. Table 42.5 provides an overview of the relevant studies regarding this issue.

In the 1980s and 1990s, a number of trials were performed that investigated the use of different antibiotics to reduce the incidence of pancreatic infection. Only one trial showed an effect on mortality. In a small study, Sainio et al. studied the use of cefuroxime and reported a reduced mortality rate in treated patients when compared to patients who had not received prophylactic antibiotics (1/30 vs. 7/30, $p=0.03$).[64] The incidence of pancreatic infection was no different, however, and the high number of patients that did receive antibiotics makes interpretation difficult. Peripancreatic coagulase-negative staphylococcal infections were frequent, and also the high number of catheter-related infections suggests problems with intravenous catheter management in these patients.

Similar studies found no effect on mortality, and different end points are used in every single paper. Pederzoli compared imipenem with placebo, and found a decrease in the incidence of pancreatic sepsis, but no effect on mortality.[65] Bassi randomized patients to either treatment with pefloxacin or imipenem, and, not surprisingly, also found no difference in outcome.[66] Another recent trial found no effect on mortality or peripancreatic infection rate, but the overall (pancreatic and non-pancreatic) infection rate was reported to be lower.[67] The total cost of antibiotics in the intervention group was about double the cost in the placebo groups.

The beneficial effects of prophylactic antibiotics – albeit on questionable endpoints in most studies – have not been confirmed in the only two blinded randomized controlled trials to have recently been performed. The largest trial, comparing a combination of ciprofloxacin and metronidazole with placebo in predicted severe pancreatitis did not show a difference in incidence of pancreatic infection, extrapancreatic complications, or mortality, and was stopped after an interim analysis.[68] More recently, a large multicenter controlled randomized trial has shown no effect of prophylactic meropenem in patients with SAP.[69] Also, the use of meropenem did not delay the pancreatic infection. Whereas the early use of non-study antibiotics was very frequent in the placebo group of the Isenmann study, this was not the case in the study by Dellinger et al., making the placebo group indeed worth the name.

In both randomized controlled trials, antibiotic prophylaxis did affect the susceptibly of the microorganisms isolated to the antibiotic administered. In the Isenmann study, 18 out of 23 isolates were resistant to ciprofloxacin. The Dellinger study only had data on six isolates of infected patients in the intervention group; five of these were resistant to meropenem.

So far, no trial has undeniably shown an effect on mortality, and in the randomized trials, no effect on pancreatic infections was found; therefore, the use of prophylactic antibiotics, although widely practiced and still recommended by some societies[70,71] and experts in the field,[72,73] cannot be supported in patients with pancreatic necrosis.

Selective Digestive Decontamination

As the bowel is evidently the source of infection in patients with infected pancreatic necrosis, the use of selective digestive decontamination (SDD) may be a logical solution to decrease the load of microorganisms that can potentially infect the peripancreatic tissues.

Luiten et al. studied the effect of selective digestive decontamination – a combination of topical antibiotics and antifungal agents consisting of colistin, tobramycin and amphotericin

TABLE 42.5. Overview of clinical trials of prophylactic antibiotic strategies in patients with severe acute pancreatitis.

First author	*n*	Treatment in intervention group	Blinded	Pancreatic infection rate (intervention vs. placebo)	Mortality (intervention vs. placebo)
Sainio[64]	60	Cefuroxime	No	9/30 vs. 12/30	1/30 vs. 7/30*,[a]
Pederzoli[65]	74	Imipenem	No	5/41 vs. 10/33[b]	3/41 vs. 4/33
Delcenserie[99]	23	Ceftazidime, amikacin + metronidazole	No	7/12 vs. 0/11*,[c]	3/12 vs. 1/11
Nordback[100]	58	Imipenem	No	NA	2/25 vs. 5/33
Isenmann[68]	114	Ciprofloxacin + metronidazole	Double blind	7/58 vs. 5/56	3/58 vs. 4/56
Dellinger[69]	100	Meropenem	Double blind	9/50 vs. 6/50	9/50 vs. 10/50
Rokke[67]	73	Imipenem	No	3/36 vs. 7/37	3/36 vs. 4/37

*$p<0.05$.
[a]See text for comment.
[b]Pancreatic infection rate defined as a combination of infected pancreatic necrosis, pancreatic abscess, and infected pseudocyst.
[c]Pancreatic infection rate defined as severe sepsis (pancreatic infection and septic shock.

B – together with intravenous cefotaxime for a mean of 7.4 days. They found that the infection rate of pancreatic necrosis was reduced from 38 to 18%.[74] In particular, the occurrence rate of gram-negative infections was decreased, whereas gram-positive infections did not change significantly.[75] Moreover, mortality in 102 patients included in this trial was reduced from 35 to 22%, which was not statistically significant, but multivariate analysis showed that treatment with SDD had an odds ratio of 0.3 (p=0.048). The question remains however, whether this effect should be solely attributed to the use of SDD, as the patients also received a 7.4 day course of cefotaxime. Also, the high rate of intestinal fistulas and colonic resections may be alternative explanations for the high rate of infections in the control group.

Enteral Nutrition

Whereas it was once considered dangerous to feed the patient enterally to avoid stimulation of the exocrine pancreas, the early use of enteral nutrition is now generally accepted for patients with acute pancreatitis. Apart from the obvious advantages as compared to total parenteral nutrition in critically ill patients, such as reduced cost and lower catheter-related and other infections,[76] it is also considered to reduce morbidity specifically related to pancreatitis. In a recent meta-analysis, McClave et al. found that the use of enteral nutrition results in better outcome when compared to parenteral nutrition.[56] Not only is it assumed that enteral nutrition modulates the inflammatory response, but a number of studies demonstrated that enteral nutrition compared to parenteral nutrition decreases the incidence of infectious complications and even mortality associated with it.[56,77] Although part of the effect may be due to the side effects of parenteral nutrition in the control groups, it is assumed that enteral nutrition improves gut mucosal integrity and therefore reduces the rate of bacterial translocation; however, a recent study in humans did not find such evidence.[78] Enteral nutrition also results in a better glucose control than parenteral nutrition, which may also add to the beneficial effect observed.[79]

Treatment of Complications

Sterile Pancreatic Necrosis

Whereas pancreatic necrosis per se was considered an indication for early debridement in patients with unresolving symptoms in the 1980s, several studies have shown that sterile pancreatic necrosis can be safely managed nonoperatively in the majority of the patients, with low mortality rates (Fig. 42.3). Moreover, high mortality rates have been described in patients with sterile necrosis who were managed surgically[80]; and subsequent infection of previously sterile pancreatic necrosis may occur in as many as 75% of patients operated for sterile pancreatic necrosis.[81]

Currently, there is little disagreement that the management of patients with sterile necrosis should be primarily nonoperative.[82] However, surgery should be considered in cases of persistent obstruction of the gastrointestinal tract due to mass effect, or in case of IAH with overt MODS.

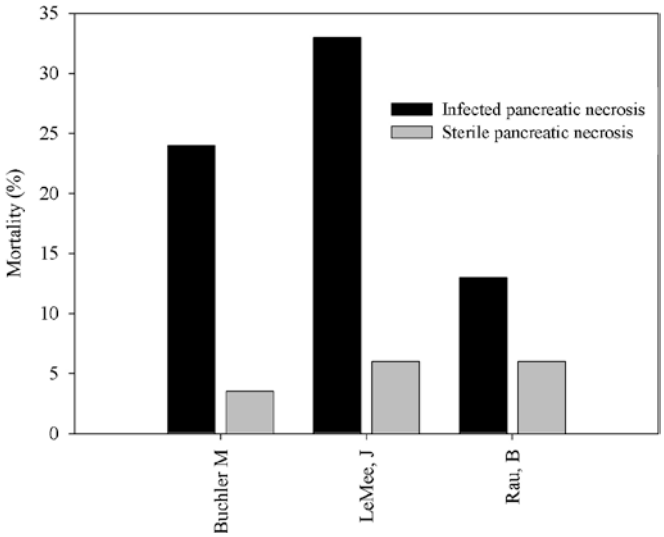

FIG. 42.3. Mortality in patients with sterile and infected pancreatic necrosis.[45,49,101]

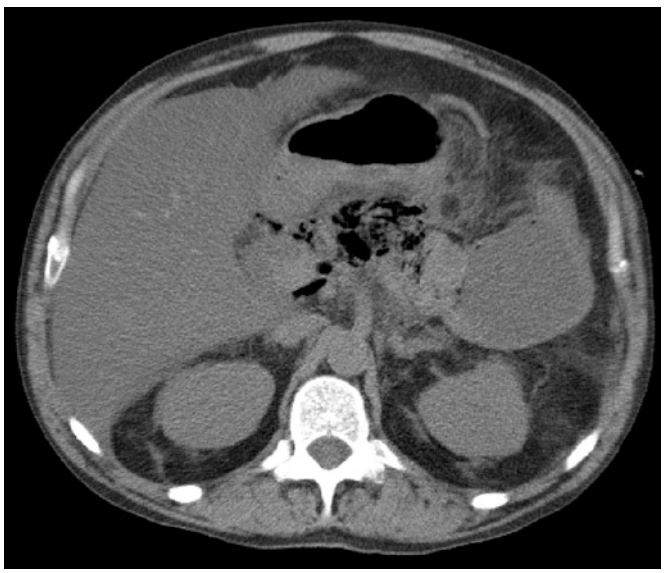

FIG. 42.4. Retroperitoneal gas indicative of infected pancreatic necrosis.

Infected Pancreatic Necrosis

Microbiology of Infected Pancreatic Necrosis

The microorganisms involved in infection of pancreatic necrosis are most often enteric gram-negative bacteria, although an increase in gram-positive infections has been described.[83] This observation, and also observations of the organisms described in most series, may have been blurred by the extensive use of antibiotic prophylaxis, often broad-spectrum antibiotics such as carbapenems or quinolones.

Interesting data on this topic have emerged from two blind studies on antibiotic prophylaxis.[68,69] Figure 42.4 displays the organisms isolated from the combined placebo and intervention groups of these studies. From this chart it is clear that

the organisms recovered from patients in the placebo group are different from those recovered from the intervention group: notably, more infections with nosocomial gram-negative organisms (such as *Pseudomonas*, *Acinetobacter*, and *Enterobacter spp*.) were found, and also more enterococcal infections were present in patients who were given antibiotic prophylaxis. It should also be noted that an important number of patients in the placebo group were switched to antibiotics on suspicion of pancreatic infection or extrapancreatic infection, so the effect of selection may even be underestimated.

Diagnosis of Infection in Acute Pancreatitis

The diagnosis of infection in patients with pancreatic necrosis is notoriously difficult. Fine needle aspirate, either CT[84,85] or ultrasound[86] guided, is an elegant method for excluding pancreatic infection. It is very important that Gram staining is immediately performed; but infection cannot be ruled out based on this alone, as, in a considerable number of patients it may produce a false-negative result, especially after empirical treatment with antibiotics. Culture reports should also be awaited. In some extreme cases, retroperitoneal gas may point to infection of the peripancreatic tissue (Fig. 42.5).

It is important to realize that clinical criteria such as fever, tachypnea, or tachycardia are very sensitive, but not very specific in patients with suspected infection, as are elevated leukocytes or C-reactive protein. These should not be used as a guide to start empiric antibiotic treatment, but should rather prompt the search for infection using either one of the techniques described previously. Infection, however, is rare in the first 7–10 days after the start of symptoms, and as any puncture carries an inherent risk of introducing infection into sterile pancreatic necrosis, FNA should be used judiciously in this setting.

Source Control

Infected pancreatic necrosis should be treated according to the principles of source control. Classically, source control should consist of drainage, prevention of ongoing contamination and restoration of premorbid anatomy and function. In acute pancreatitis, this should include proper drainage of pus and proper removal of pancreatic and peripancreatic necrotic tissue – known as debridement. This can be achieved using a variety of surgical techniques, none of which is demonstrably superior.[87] Recently, minimally invasive techniques have proved to be associated with minimal morbidity and mortality,[88,89] but randomized studies should be awaited before drawing any conclusions.

In contrast with other intra-abdominal conditions such as abdominal abscess, infected pancreatic necrosis is not usually

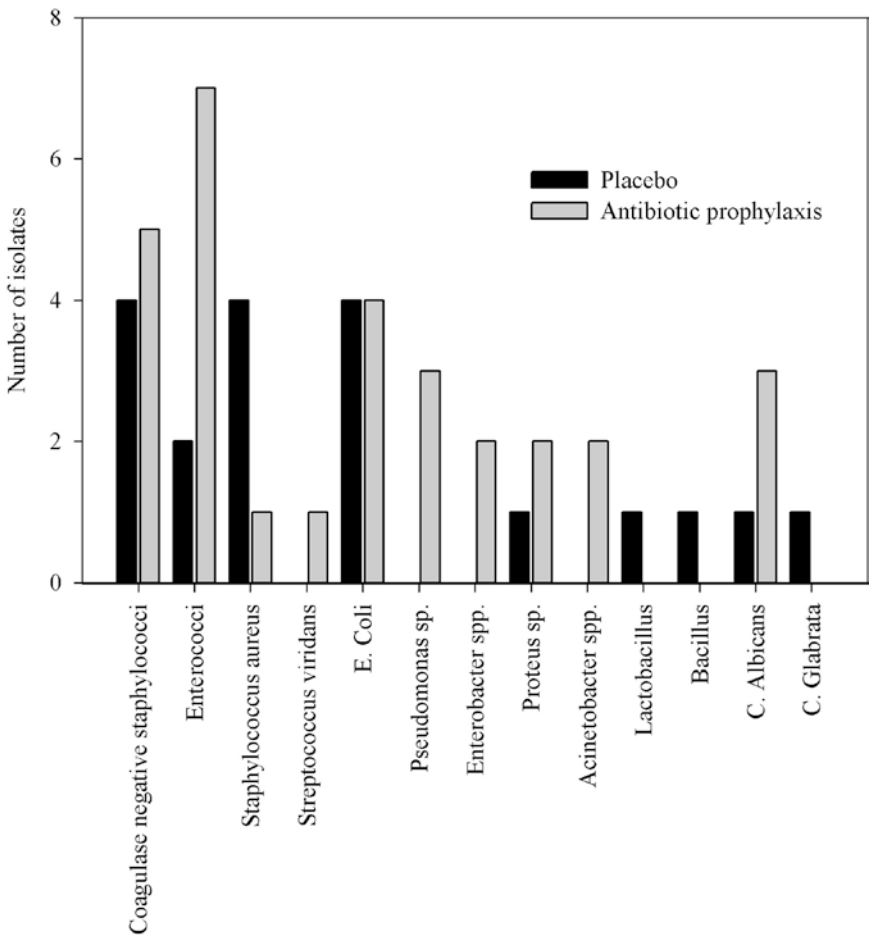

FIG. 42.5. Microbiology of infected pancreatic necrosis. Pooled data from two randomized controlled trials of prophylactic antibiotics.[68,69].

amenable to percutaneous drainage in the early phase, as pancreatic necrosis is solid at this stage. Ultrasound- and CT-guided drainage may be considered at a later stage in case of walled-off "organized pancreatic necrosis," or for treating pancreatic abscesses, especially in those patients who have undergone prior debridement for pancreatic necrosis.

If possible, surgery should be avoided in the first week(s) of pancreatitis, as demarcation of the necrotic tissue may be incomplete at this stage, increasing the risk of collateral damage to surrounding structures and bleeding complications. It should be noted, however, that the evidence for delaying surgery beyond the first 2 weeks is based on a small unblinded study,[90] and retrospective studies with the inclusion of sterile pancreatic necrosis patients as a clear confounder.[91] In the case of severe sepsis or septic shock with documented pancreatic infection, prompt source control should be pursued, preferably via a formal surgical procedure.

Some patients with infected pancreatic necrosis have been managed without intervention; these patients did, however, receive systemic antibiotics.[92] No clear selection criteria exist, but patients who seem to tolerate the infection well, without overt organ dysfunction or deterioration at the moment of diagnosis of the infection may be treated conservatively. Caution should be exercised, as no definite criteria have been identified to select patients who may be treated without intervention. Infected pancreatic necrosis is a continuum starting with bacterial translocation and ending with a collection of pus in the necrotic pancreatic bed. When diagnosed early, some patients may be spared from developing the classical picture of infected pancreatic necrosis with ensuing severe intra-abdominal infection and sepsis.

In the past, source control meant surgery, but now more than ever, several strategies can be used and a combination of these may be employed. Therefore, diagnosing and controlling infection in patients with pancreatic necrosis is a multidisciplinary process, and early and repeated interaction with surgeons, gastroenterologists, and interventional radiologists experienced in the management of pancreatitis, is essential. The variability of the localization, consistency, and the extent of pancreatic necrosis mean that any procedure for either diagnosis or treatment, at any stage in any patient should be tailored to the individual patient.

Antibiotics

Generally, little attention has been paid to the choice of antibiotic for established infected pancreatic necrosis. A number of studies have been performed on the penetration of parenteral antibiotics into the normal pancreas, with generally good results for carbapenems and quinolones.[93,94] The situation is obviously different in pancreatic and peripancreatic necrosis and subsequent superinfection. There is no reason, however, why infected pancreatic necrosis should be treated differently from any other complicated intra-abdominal infection, and using any compound or scheme that has proven to be effective in complicated intra-abdominal infections is also a good choice in infected pancreatic necrosis.[95]

Fungal Infections and Infected Pancreatitis

In recent years, fungal involvement in infected pancreatic necrosis has increasingly been described, and in the most recent studies, fungal infection was shown to occur in about 30–40% of patients who develop infected pancreatic necrosis.[51,96,97] *Candida albicans* was isolated from most patients. There seems to be a relationship with the use of prophylactic antibiotics, and with the duration of prophylactic antibiotic treatment in a lot of reports. One study showed that early antifungal treatment reduced the incidence of fungal infection without affecting mortality. The impact on mortality of fungal infected pancreatic necrosis is variable with mortality rates reported between 0[96] and 63%,[98] with an overall mortality of 27%. Secondary infections, occurring after one or more surgical procedures for infected pancreatic necrosis are particularly frequent, and in these patients, prophylactic antifungal treatment should be considered.

Abdominal Compartment Syndrome

In patients with large volumes of pancreatic ascites, percutaneous drainage of the intraperitoneal exudates can lead to a significant drop in IAP. Routine screening for fluid collections amenable for percutaneous drainage seems a logical first step.

Intra-abdominal fluid collections are not always present and therefore decompressive laparotomy and temporary abdominal closure is the most effective way of decreasing IAP.[3,6,11,15,16] Although the role of decompressive laparotomy has not been studied prospectively, multiple case series report impressive survival rates when the abdomen is timely decompressed. In one of the largest series on the topic with 18 patients who were decompressed, Tao et al. reported survival rates as high as 84% in patients with MODS and severe acute pancreatitis.

The most common approach to decompressive laparotomy is through a long, vertical midline incision, but a transverse incision to anticipate later pancreatic surgery may also be used. Because of the risk of introducing infection to the peripancreatic space and the absence of demarcated pancreatic necrosis, it is not necessary and even dangerous to explore the pancreas at this stage. Leppäniemi et al. introduced an alternative to a formal laparotomy, based on subcutaneous linea alba fasciotomy preserving the skin as a cover.[40] Utilizing three transverse 2–4 cm long skin incisions placed about 10 cm below the xiphoid and about 5 cm above and below the umbilicus, the subcutaneous tissue is incised and the linea alba divided vertically in the midline under visual control using a scalpel and scissors.

The management of the open abdomen following decompression in severe acute pancreatitis is challenging. The best currently available technique is the utilization of the vacuum-assisted closure technique aiming for gradual closure of the abdominal wall. The use of a vacuum-assisted closure system guarantees a perfect seal of the peritoneal cavity, avoiding possible superinfection of the pancreatic or peripancreatic necrosis.

Conclusion

Acute pancreatitis, and especially severe acute pancreatitis, may be a relatively rare disease, but the high rate of morbidity and mortality rate in a generally young patient population obviates the need for further research into the mechanisms that may lead to local and systemic complications. The management of severe acute pancreatitis patients in the ICU remains a challenge, as the course is highly variable and notoriously unpredictable. The focus should be on monitoring of organ function, supporting failing organs if necessary, and prevention of complications. Although early organ dysfunction seems to be the most important determinant of outcome, infection of pancreatic necrosis still is the most feared complication. Prevention of infection using prophylactic antibiotics does not reduce the rate of infection, but early enteral nutrition may be more effective to reduce infectious complications. When infection of pancreatic necrosis occurs, it should be managed based on the principles of source control. Further elaboration of the role of IAH in the pathophysiology of organ dysfunction is necessary, and may help to identify patients who may benefit from abdominal decompression.

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Part X
Surgery, Trauma, and Transplantation

43
Trauma

Michael S. Rosenblatt

Trauma is the leading cause of death in the United States for individuals from ages 1 to 44 years; and overall, is the fifth leading cause of death for the entire US population.[1] In 2000, 16% of the population reported needing treatment for an injury. One patient in 100 required hospitalization, and approximately 10% of these patients met criteria for trauma center admission. Most of the more severely injured received care in a surgical intensive care unit (SICU). Trauma accounts for 10% of measurable healthcare expenditures, but probably has a significantly greater impact if other measures such as value of life lost to premature mortality, loss of patient and caregiver time, nonmedical expenditures (e.g., wheelchair ramps), insurance costs, property damage, litigation, decreased quality of life, and diminished functional capacity are factored into the calculation.[2]

The purpose of this chapter is to review general concepts in the evaluation and management of adults admitted to the SICU following trauma. This chapter is not intended to be an all-inclusive discussion of the care of the traumatized patient; a number of excellent books address trauma care more completely.[3–6] Initial evaluation and resuscitation recommendations are based upon concepts emphasized in the American College of Surgeons Advanced Trauma Life Support Course™, completion of which is strongly recommended for anyone involved in the care of trauma patients.

This chapter focuses on: (1) prioritization in resuscitation and diagnosis of injuries, (2) the concept of staged resuscitation of the critically injured patient and the role of the SICU in this approach, (3) the implication of specific documented or potential injuries in the care of the patient while in the SICU, and (4) special considerations associated with the trauma patient.

Principles of Prioritization

Initial management of trauma patients follows the airway, breathing, and circulation sequence that is universally applicable to any patient with acute cardiorespiratory decompensation. First, a patent airway needs to be ensured and adequate oxygenation and ventilation must be confirmed. Ensuring both an adequate airway and breathing may require establishing an endotracheal airway, mechanical ventilation, and/or closed tube thoracostomy to correct tension pneumo- or hemothorax to allow for effective breathing, either spontaneous or mechanical. Attention is then directed toward determining whether adequate circulation is present. If there is evidence of circulatory compromise, the focus of the resuscitation shifts to identifying and correcting the cause. Shock is most commonly the result of hemorrhage, but other forms of non-hemorrhagic shock – such as obstructive shock from cardiac tamponade, or neurogenic shock from spinal cord injury – are not uncommon and often present a diagnostic challenge in the face of multiple injuries. Once the circulatory status has been stabilized, which may require surgical intervention, the trauma work-up must continue to eliminate or treat other life-threatening injuries. Ultimately, once life-threatening injuries have been addressed, attention is directed first at limb-threatening injuries and finally at soft-tissue injuries.

Airway

There are several concerns associated with evaluating and controlling the airway in trauma patients.[7] First, these patients are often at risk for cervical spine injury. This complicates standard oral endotracheal intubation techniques in that the

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patient with a documented, suspected, or potential cervical spine injury must be intubated with restricted movement of the neck. Patients involved in high-velocity decelerations who have injuries that are the result of direct trauma to the head or neck are at the greatest risk for cervical spine injury. Intubation in this setting requires experienced personnel. The neck must always be stabilized throughout the procedure, preferably with two-person in-line traction. Direct visualization of the vocal cords and oral intubation, fiber optic-assisted intubation, or use of laryngeal mask ventilation as a bridge to endotracheal intubation in the difficult airway has been described. Removal of the front of the cervical spine collar facilitates intubation in all cases and is safe as long as attention is directed at maintaining the cervical spine in a neutral position.

Second, victims of trauma frequently have a reduced ability to protect their airway. This may be secondary to either head injury or alcohol or drug intake. These patients often are also at an increased risk for aspiration because of a full stomach, bag mask ventilation in the field, or an associated trauma-related ileus. Care must be taken in this situation to prevent aspiration. Patients with a Glasgow Coma Scale (GCS) of 8 or less, suggestive of severe head injury, should be intubated prior to leaving the emergency room. Patients who are hemodynamically unstable should have their airway controlled with an endotracheal tube early in the course of resuscitation.

When a patient cannot be intubated orally, nasotracheal intubation may be attempted, as long as no evidence of maxillofacial trauma is present. Prolonged nasotracheal intubation is associated with the development of sinusitis[8] and nosocomial pneumonia[9] and, therefore, should be avoided if possible. If neither oral nor nasal tracheal intubation is successful, the next steps are dependent upon resources and expertise available. A fiber optic-assisted intubation might be attempted. If the cords are obscured by swelling or blood then, depending upon resources, either a laryngeal mask airway (LMA) or Combitube can be attempted. If these are not available, or are unsuccessful at controlling the airway sufficiently, then a surgical airway should be performed. Traditionally, performing a cricothyroidotomy has been recommended, but under emergent circumstances a tracheostomy is acceptable.[10] The increase in practitioners, facile with performing percutaneous tracheostomies, using the dilatational technique has added percutaneous tracheostomy into the armamentarium of emergent airway techniques.[11]

Breathing

A patent airway does *not* ensure adequate breathing. Breathing difficulties in the trauma patient may be related to a number of issues. First, pneumothorax or hemothorax may prevent adequate lung expansion. These are both treated expeditiously with a closed thoracostomy tube. Second, chest wall expansion may be insufficient for adequate breathing. This may be the result of direct chest wall damage, as in a flail chest or open pneumothorax, or may be secondary simply to the pain associated with rib fractures. Breathing may be impaired secondary to neurologic deficits, both centrally with coma, and peripherally with spinal cord injury. In the early stages of resuscitation of a critically injured patient, mechanical ventilation is the safest method to ensure adequate gas exchange. When the injury is clearly isolated to the chest wall, and pain is the main contributor to diminished breathing, early placement of an epidural catheter for pain control effectively improves breathing patterns and reduces the need for mechanical ventilation.[12] The use of non-invasive ventilator circuits, such as a continuous positive airway pressure (CPAP) mask, may also be considered, but only in select patients.[13]

Circulation

Once the airway and breathing have been controlled, the trauma evaluation moves to the circulatory status. Adequate circulation is more than an adequate systolic blood pressure. Signs and symptoms of inadequate perfusion include confusion, lethargy, cool or mottled skin, and tachycardia. Initial urine output is misleading because it represents the contents of the bladder at the time of voiding or catheterization and does not represent continued kidney perfusion. When a patient has a systolic blood pressure below 90 mmHg or other signs of hypoperfusion, judicious fluid resuscitation should be initiated, through either peripheral or central venous access. Depending on the magnitude of suspected volume deficit, crystalloid or a combination of red cell transfusions and crystalloid should be used for resuscitation. Resuscitation should aim at elevating the systolic blood pressure above 90 mmHg with improvement in the markers of organ perfusion.[14] If the patient fails to respond or has only a transient response to volume resuscitation, the physician should be suspicious of: (1) ongoing blood loss, (2) under-appreciation of the degree of original blood loss, or (3) non-hemorrhagic causes of shock such as pericardial tamponade, tension pneumothorax, or spinal cord injury.

Circulatory failure in the face of ongoing blood loss is the most common scenario, with blood loss occurring into one of the three functional cavities of the body: the chest, the abdomen, or the pelvis. In addition, ongoing blood loss can occur externally from a severed blood vessel or laceration, or internally into an extremity; this is seen most commonly with a fractured femur.

Diagnosis of cavitary hemorrhage is made by physical examination and analysis of radiologic adjunctive tests.[15,16] Hemorrhage from a chest injury can be diagnosed by physical examination, examination of chest tube drainage, and review of a chest X-ray. Hemorrhage from a solid organ in the abdomen can be made by physical examination of the distended, hypo-resonant abdomen. Adjuncts to the physical examination of the abdomen include diagnostic peritoneal lavage (DPL), focused abdominal ultrasound for trauma (FAST), or computed tomography (CT) scan, although the last should be avoided in an unstable patient. With DPL, a catheter is placed directly into the abdomen; if free blood is aspirated then the likelihood is high of solid organ injury as the cause of

hemodynamic instability. Likewise, performing ultrasound of the abdominal cavity to look specifically for free intra-abdominal fluid has been shown to be highly sensitive in identifying those patients with solid organ injury that is contributing to their instability. Hemorrhage from the retroperitoneal pelvic cavity can be the source of significant bleeding following pelvic fracture. A plain pelvic X-ray can eliminate the pelvis as the source of bleeding, although the presence of a fracture does not ensure that this fracture is the source of bleeding. External bleeding is obvious with a good physical examination. Close examination of long bone integrity, coupled with plain X-ray, can readily rule out hemorrhage into the extremity as a cause of hemodynamic instability.

Once the site of hemorrhage has been ascertained, control of that hemorrhage is necessary. Treatment of hemorrhage in the patient with multiple injuries is directed at rapid control of the points of bleeding, regardless of site, in order to move on to the next life-threatening injury. If external bleeding is present, direct compression is the controlling procedure of choice, followed by tourniquet if applicable, followed by surgical intervention if necessary to control hemorrhage. Blind clamping of bleeding vessels in a wound should be avoided. Long bone fractures should be stabilized promptly with external traction devices, which reduce further bleeding.

If hemorrhaging has resulted in loss of more than 1,000–1,500 cc from one of the chest cavities, or persists at greater than 200–300 cc per hour, a thoracotomy should be performed and bleeding controlled.[17] Delay of definitive repair of major injuries in the chest needs to be considered in the light of the remaining potentially life-threatening injuries awaiting treatment or discovery.[18]

A grossly positive DPL or FAST with free fluid in the face of hemodynamic instability warrants performing an expeditious exploratory laparotomy.[19,20] At that time, the main focus should be on controlling hemorrhage. For example, this might necessitate a splenectomy in the face of splenic injury or packing of a hepatic injury. Once the bleeding is controlled, a quick examination for injuries resulting in persistent contamination of the abdominal cavity must be performed and this soilage controlled. If the patient is at significant risk for other life-threatening injuries (i.e., head injury or thoracic aortic injury), complex abdominal reconstruction procedures should be avoided and the abdomen should be temporarily closed.

If a pelvic fracture is thought to be the source of hemorrhage, the first line of therapy is use of an external stabilization device such as a sheet wrap technique or pelvic binder,[21] which closes down the volume of the pelvis and stabilizes the pelvis from persistent movement. Most pelvic bleeding is venous and amenable to this type of stabilization. If instability persists despite external compression wrapping, the patient should undergo an angiogram to identify and embolize ongoing arterial hemorrhaging. Recently, surgical exploration and pelvic packing has been suggested to be an effective alternative to embolization as a first step.[22]

Once hemorrhage has been controlled the patient must be evaluated expeditiously for injuries that might cause death or serious disability in the next 4 to 6 h.

Head Injury

The most important controllable determinants of secondary brain injury are hypotension and hypoxia.[23] These are the rationales for controlling airway, breathing, and circulation before direct management of even obvious head injury. However, once the patient's blood pressure has been stabilized into the normal range, the patient must be evaluated for possible serious head injury. The timing of a head CT is governed by the "4-h" rule[24] and the probability that surgically treatable intracranial pathology is present. The likelihood of serious brain injury requiring surgical intervention is related to both the patient's level of consciousness on arrival and the presence or absence of lateralizing neurologic signs.[25] Patients with a GCS higher than 12 and no evidence of lateralizing signs are at low risk for having a surgically treatable intracranial lesion, and, therefore, work-up for other life- threatening injuries should be pursued first. Ultimately, any patient with a loss of consciousness, amnesia, or a GCS lower than 15 should undergo a head CT to rule out an intracranial injury.[26] In the patient who has a GCS lower than 9 or lateralizing signs regardless of the GCS, the risk of a surgically treatable lesion increases significantly. Therefore, once hemorrhage has been controlled, this patient should undergo a head CT to eliminate the possibility of a surgically correctable lesion. If the patient is comatose, a CT scan of the cervical spine should also be obtained in order to identify an occult cervical spine fracture.

If a surgically treatable lesion, such as a subdural or epidural hematoma, is identified, the patient should proceed directly to the operating room for treatment. If there is no surgically treatable lesion by CT scan, but clinical evidence for a severe head injury, the placement of a device to monitor intracranial pressure should be considered.[27]

Aortic Injury

Following elimination or treatment of life-threatening head injury, priorities should be shifted to determine whether the thoracic aorta might have sustained injury. These injuries are associated with rapid deceleration mechanisms seen most frequently in motor vehicle crashes or falls. A high index of suspicion is necessary to identify patients without overt signs of aortic disruption.[28] A plain anterior posterior (AP) chest radiograph (CXR) can provide clues to the presence of a thoracic aortic injury. These include, among others, a widened or indistinct mediastinum at the level of the aortic arch, a left pleural fluid collection, and deviation of the nasogastric tube. However, a clinically worrisome percentage of patients do not have any signs of injury on CXR. Helical CT scans of the chest have replaced aortic arteriograms as the diagnostic tool of choice in most trauma centers.[29] In the face of an abnormal

CXR or a high index of suspicion based on mechanism of injury, a thoracic CT scan is performed. In most cases, aortic injury can be visualized on thoracic CT scan with aortic reconstruction, and the patient may proceed with to the operating room for definitive repair without a formal arteriogram. Repair of the aortic injury should be done through a left lateral thoracotomy with cardiopulmonary bypass pump to maintain perfusion to the aorta below the injury.[30] Use of this technique has significantly reduced the incidence of post-repair paraplegia. Because this technique requires systemic anticoagulation, definitive repair or control of other injuries (e.g., an injured spleen) should be performed in conjunction with the aortic repair. Advances in endoluminal stenting have allowed for a non-operative approach to selected aortic and other major vascular injuries, sometimes eliminating the need for more extensive surgical approaches.[31,32]

Pelvic Fracture

If a pelvic fracture was not addressed previously because of hemodynamic instability, it should be done at this time. External stabilization should be performed to promote healing and provide continued stabilization until internal stabilization or percutaneous stabilization of fractures is achieved. This should be done in conjunction with the repair of extremity fractures. Evaluation of the bladder and rectum is indicated when there is major deformity or fragmentation.

Extremity Injury

Following elimination of any potential life-threatening injuries, attention should be directed at stabilizing fractures and revascularizing extremities if necessary.

Soft Tissue and Non-life or Non-limb-Threatening Injuries

Finally, attention can be directed toward evaluating and initially managing soft-tissue and other non-life-threatening or non-limb-threatening injuries. These include maxillofacial injuries that are often not surgically repaired until swelling has been reduced.

Stages of Resuscitation

The resuscitation can be broken down into a series of stages.[33]

Phase I: Damage Control

Phase I refers to the initial management in the emergency room, the initial diagnostic studies, and initial surgical intervention. The critical concept associated with this phase is control of hemorrhaging, either definitively by splenectomy or temporarily by abdominal packing and temporary abdominal closure for a complex hepatic, duodenal, or pancreatic injury. The main focus should be on stopping the hemorrhage and controlling contamination of body cavities with enteric contents, pancreatic or bilious fluids, or urine. Definitive repairs should be delayed. This technique is used in patients with significant metabolic acidosis, hypothermia, or coagulopathy or in those in whom these conditions are beginning to develop.

Phase II: SICU Resuscitation

The SICU is the resuscitation area after the damage-control phase is complete. The main focus of SICU care should be to complete the fluid resuscitation to correct the metabolic acidosis, warm the patient, and correct any coagulopathy with blood products, when indicated. Further diagnostic studies may be performed during this phase to identify other injuries,[34,35] but these should ideally be performed at the bedside until the patient is completely resuscitated. This phase may last from 24 to 72 h. If the patient fails to respond to the SICU resuscitation and exhibits continued signs of blood loss, hypothermia, or coagulopathy, there may be a continued source of surgical bleeding requiring early re-exploration.

Phase III: Completion Workup/Re-exploration

Once the patient's hypothermia, acidosis, coagulopathy, and hemodynamic status has improved, a complete radiographic work-up outside the SICU may be performed and the patient may be returned to the operating room for definitive repair of injuries.

Specific Organ System Injuries: ICU Implications

Central Nervous System Injuries

Traumatic brain injury is addressed elsewhere in this volume as well as other sources.[27] The key concept in managing these injuries is that patients with traumatic brain injury have a poorer outcome if hypoxia and/or hypotension from other injuries co-exist with the brain injury. Prevention of secondary brain injury requires aggressive treatment of the causes of hypoxia (airway and breathing) and hypotension (circulation). Therefore, controlling the hemorrhage must be accomplished before or simultaneously with managing intracranial injuries.

Maxillofacial Trauma

There are three main issues related to maxillofacial trauma relevant to the SICU. First, the airway must be controlled. In patients with massive facial injury characterized by bleeding and soft-tissue swelling, airway management often requires the most skilled and experienced specialists. A surgical airway should be considered early in the evaluation

and management. Intubating these patients early is prudent, as opposed to expectant management, because the swelling that eventually causes airway compromise precludes standard endotracheal approaches. Nasotracheal intubation should be avoided because it may precipitate bleeding from maxillofacial fractures. Second, all patients with major maxillofacial trauma, especially from a blunt mechanism, should be suspected of having intracranial pathology and should undergo a head CT. Finally, cervical spine pathology must be suspected and appropriate precautions taken during intubation to prevent neck extension.

Despite the airway being controlled, bleeding may continue.[36,37] Managing bleeding in the nasopharyngeal spaces with packs or Foley balloons is usually successful. In rare situations, an arteriogram is required to embolize a lesion. Hemorrhaging from the main carotid artery and its trunks requires surgical control in most cases. SICU management is focused on protecting the airway and correcting hemorrhagic shock.

Spinal Column Injuries

Cervical spine injuries are addressed elsewhere in this volume. The main concerns in the SICU are to protect an "at risk" neck until it can be determined if an injury has occurred. This is best done with a hard collar. Special attention should be directed at skin care beneath the collar. When patients require a collar for longer than 24 h, a well-padded hard collar should be used to prevent the development of decubiti.[38,39] When a patient remains comatose in the SICU, a variety of strategies have been proposed to complete the evaluation of the cervical spine. It is clear that in patients with sufficient mechanism and coma, plain cervical films alone are insufficient to diagnose cervical injury.[40,41] Most current algorithms include helical CT of the cervical spine to evaluate for an injury. Controversy continues regarding the need for further testing beyond a normal CT scan in the comatose patient.[42] Additional studies advocated include MRI,[39,43,44] passive flexion-extension radiographs,[45] and active fluoroscopy.[46–48]

Patients involved in high-impact mechanisms of injury (e.g., high falls, motor vehicle crashes) are at a significant risk for thoracolumbar spine fractures. All patients at risk should remain on log-roll precautions on a firm bed. They may be removed from the backboard. AP and lateral plane films of the spine and/or a CT scan should be performed to rule out any fractures or ligamentous disruption.[49]

Chest Injuries

Chest injuries can be divided based on the mechanism of the injury (blunt vs. penetrating) and by anatomic classification (involving the chest wall, lungs, heart, and great vessels).[17] Penetrating chest wall injuries can result in bleeding from intercostal vessels that can be life threatening. A sucking chest wound can result in a collapsed lung. Blunt chest wall injuries can lead to respiratory compromise if they are extensive enough to cause chest wall instability or significant pain. Aggressive pain management with an epidural anesthetic is the approach of choice, when clinically possible, and may obviate the need for intubation and mechanical ventilation. Surgical stabilization of rib fractures has been described and may be of some value in patients who have marked chest wall instability, which is the sole reason for respiratory failure. However, rib fractures are often accompanied by parenchymal lung injuries, which can progress and result in significant hypoxia that requires mechanical ventilation. These lung injuries occur more commonly in blunt chest trauma with a pulmonary contusion, but can occur with blast injuries from penetrating objects. Penetrating cardiac injuries should be dealt with before SICU admission. Pericardial tamponade can be the presenting sign in the SICU if the diagnosis was missed. Elevated central venous pressure with hypotension repeatedly responsive to fluid boluses suggests cardiac tamponade and mandates an echocardiogram. Blunt injuries to the heart range from wall motion abnormalities and arrhythmias to valvular and chamber rupture. Echocardiography is the diagnostic procedure of choice, and management is based on the findings. Diagnosis of great vessel injuries is dependent on clinical suspicion. SICU management of these patients is usually postoperative, but in certain clinical situations (e.g., concomitant severe head injury), surgical intervention may be delayed. In this case, aggressive management of hypertension with beta-blockade is required to reduce the extension of the injury.

Abdominal Injuries

The diagnosis and management of intra-abdominal injuries are beyond the scope of this chapter. Definitive management of intra-abdominal injuries should not present specific SICU issues different from the ones seen following other emergency abdominal surgery, including recognition of postoperative bleeding, intra-abdominal infection, and compromise of intestinal anastomoses.

The management of intra-abdominal injuries as might occur during damage control can lead to specific considerations in the SICU[50]. Under these circumstances, as outlined earlier, control of bleeding and continued soilage receives priority, and the abdomen is rapidly and often temporarily closed. Gauze packs often are left behind to tamponade bleeding liver or pelvic injuries. On rare occasions, vascular clamps or shunts are left in place or the bowel is stapled closed.

In the face of massive fluid resuscitation and mid-gut ischemia, edema may develop in both the permanently and temporarily closed abdomen.[51,52] In either case, the patient must be observed for signs of abdominal compartment syndrome, which is discussed in Chap. 45.

Pelvic Injuries

Management of pelvic fractures in the SICU is directed at maintaining pelvic compression, if instituted, and monitoring

for ongoing bleeding. If bleeding persists despite external fixation of appropriate injuries, the patient should undergo arteriogram and possible embolization[21] or surgical exploration and packing.[22] Recognition of urologic[53,54] and bowel injuries[55] is important in the presence of pelvic fractures, and delayed diagnosis of these injuries can result in unexplained sepsis in a SICU patient.

Extremity Injuries

SICU management of injury to the extremities focuses on frequent neurovascular examinations. Any change in the examination should warrant aggressive work-up. A high index of suspicion is required to identify arterial intimal injuries presenting as a delayed thrombosis or extremity compartment syndrome. Loss of or change in the pulse examination warrants performing an arteriogram. A physical examination that suggests extremity compartment syndrome should prompt compartment pressures to be measured with either a hand-held or ICU monitor transducer setup. Elevated pressures require fasciotomies to prevent long-term neurologic disability.[56–58]

Miscellaneous Considerations

Hypothermia/Acid-Base Disorders/Coagulation Disorders

Trauma patients often arrive at the hospital with some degree of *hypothermia*. Efforts at re-warming these patients should begin in the trauma room by increasing the ambient temperature, using passive warming devices, and infusing only warmed fluids and blood products. This effort should continue while the patient is undergoing diagnostic studies, operative intervention, and resuscitation in the SICU. *Acidosis* in the trauma patient almost always occurs as a result of hemorrhagic shock and should be treated with volume resuscitation and not bicarbonate infusion. *Coagulopathy* is usually associated with hypothermia, massive blood loss, head injury, or preexisting disease. In the presence of massive blood loss, replacement of coagulation factors should be anticipated before the development of coagulopathy.[59] The role of Factor VIIa in massive hemorrhage remains controversial but is an option.[60,61] Hypothermia, acidosis, and coagulopathy are critical factors to consider when contemplating embarking upon a damage-control approach for severe intra-abdominal injury. Intraoperatively, once any of these parameters becomes abnormal, the surgeon should consider *abbreviating* the surgical procedure and transferring the patient to the SICU. When the patient arrives in the SICU, the resuscitation should focus on correcting the three parameters. Once the patient is normothermic, the acidosis is corrected, and when the coagulopathies have resolved, the surgeon can consider returning to the operating room for definitive repairs.

Deep Venous Thrombosis/Pulmonary Embolism

Trauma patients admitted to the SICU can be at high risk for the formation of deep venous thrombosis (DVT) and consequent, pulmonary embolism.[62] A number of trauma-related risk factors have been identified, including severe head injury, spinal cord injury with paraplegia or quadriplegia, age over 55 years with isolated long bone fractures, pelvic fractures associated with long bone fractures, isolated complex pelvic fractures, and multiple long bone fractures. Patients with any of these injuries should be considered for increased surveillance for DVT, as well as prophylaxis. Most trauma protocols include daily physical examination of the lower extremities, as well as weekly venous duplex ultrasound in patients who are awake and twice weekly ultrasound in comatose or paralyzed patients. Duplex studies are not foolproof, however, and *tend to miss* pelvic venous sources of thrombi. The cornerstone of prophylaxis is early and frequent *ambulation*; however, this is not practical in the SICU patient. Therefore, prophylaxis should include sequential calf-compression stockings for all patients whose injuries allow their use, and plantar venous foot pumps on those patients with lower extremities that preclude the use of calf pumps. In addition to mechanical prophylaxis, there is evidence that low-molecular-weight heparin can be used safely in patients without hemorrhagic central nervous system injury, an active or potentially critically bleeding wound (liver or spleen injury), or requirements for reoperation. When a patient remains at significant risk for longer than 1 week, or has injuries that continue to preclude the use of heparin (e.g., hemorrhagic intracranial injury), serious consideration should be given to the placement of a prophylactic inferior vena cava filter.

Nutrition

The trauma patient requires high-caloric intake but is usually in reasonable nutritional condition before the trauma. Attempts should be made to use the enteral route whenever possible.[63] If feasible, a feeding jejunostomy tube should be placed at the time of any laparotomy. Alternatively, enteral feedings should be performed through a post-pyloric feeding tube or gastric tube.

Rehabilitation

The rehabilitation needs of the trauma patient are related to the magnitude of musculoskeletal injury, the presence of spinal cord and/or head injury, and the duration of time spent in the SICU. Early in the SICU stay, attention needs to be directed at preventing complications of *inactivity*, which may be exacerbated by neurologic impairment. Joint contractions should be prevented through early range-of-motion exercises across stable joints and the application of splints to prevent contractures. In patients with spinal cord injury, bowel dysfunction can be a major roadblock, and early use of stool softeners and suppositories can ensure regularity. This, in turn, allows enteral feeding to take place without problems. Early use of modern air mattresses has markedly reduced the occurrence of decubiti associated with the immobilization.

Rehabilitation of the patient with a head injury, including cognitive rehabilitation, usually occurs after discharge from the critical care unit. However, the psychosocial needs of the patient and the family should be adequately addressed while the patient is still in the SICU. This is especially true of patients with severe head injuries, or spinal cord injuries, or traumatic amputations.

Geriatric Trauma

Elderly trauma patients represent a higher percentage of the trauma admitted to surgical critical care units. This is driven primarily by demographics; as life expectancy increases the total number of patients in this cohort, a greater percentage of trauma patients are elderly. Better overall health in the older population and improved pre-hospital care contribute to the increased number of geriatric patients surviving what would have been a lethal accident.

Elderly patients present some unique physiologic and social issues.[64] These patients are far more likely to suffer complications secondary to their underlying comorbid conditions and are far more likely to die from these complications than younger patients.[65] Major physiologic changes that influence SICU care include those occurring in the cardiovascular, pulmonary, and renal systems. Early and aggressive *cardiovascular monitoring* in this patient population has been shown to improve outcome.[66,67] Attention to respiratory status, especially from aspiration, can reduce the rate of pneumonia, which is a major contributor to death. Finally, end-of-life, quality-of-life issues often become important in the clinical decisions associated with the care of the elderly. Aggressive treatment of the seriously injured geriatric patient may be contrary to the patient's own expressed wishes and these wishes should be sought out, preferably in a legal instrument or through discussions with family members.

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44
Burns

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It has been estimated that over 1.2 million people in the United States suffer burn injuries every year.[1] Most are treated as outpatients, yet nearly 60,000 require hospitalization. Approximately 5,000 of these patients die. Advances in resuscitation and monitoring techniques, wound management, nutritional support, and strict use of tissue culture-directed antibiotics have all contributed to decreases in morbidity, mortality, and long-term disability for these patients.

Initial Evaluation and Resuscitation

The initial evaluation of the burn patient should follow the same basic principles as the evaluation of any patient who has suffered traumatic injury. The ABCs of resuscitation, as taught in the American College of Surgeons Advanced Trauma Life Support Course,[2] provide the foundation for prompt recognition of life-threatening injuries, stabilization, and resuscitation from shock.

The first step in the resuscitation of a burn patient is the establishment of a patent airway. Patients suffering burns while confined in an enclosed space, such as a burning building or automobile, must be evaluated for the presence of upper airway thermal injury, smoke inhalation injury, and carbon monoxide (CO) poisoning. Signs and symptoms of upper airway thermal injury include hoarseness, soot in the oropharynx and hypopharynx, singeing of the face and facial hair, and stridor. The upper airway should be inspected and, if any airway compromise is encountered, the patient should be quickly intubated. The airway inspection may be aided by the use of fiber-optic laryngoscope with the endotracheal tube positioned over the scope. If soot or vocal cord swelling is observed, the endotracheal tube may be left in proper position as the scope is removed. If there is a chance that the patient may lose airway patency, endotracheal intubation should be performed. This maneuver may be performed easily during the early stages of resuscitation but may become impossible with ongoing vocal cord swelling.

Smoke inhalation injury, which actually constitutes a chemical burn of the lower airways and lungs from noxious products of combustion in inhaled smoke, is heralded by carbonaceous sputum as well as many of the signs and symptoms of upper airway thermal injury. Direct airway injury results in sloughing of the tracheobronchial mucosa, impaired mucociliary clearance, and distal bronchial tree occlusion. This type of damage can induce an inflammatory cascade, which begins with neutrophil chemotaxis and oxygen free radical release and ends in microvascular permeability and pulmonary edema, culminating in pneumonia, acute lung injury, and acute respiratory distress syndrome. Treatment should consist of mechanical ventilatory support using well-described lung-protective strategies[3] and positive end-expiratory pressure. An alternative ventilation strategy that has received particular attention in the smoke inhalation injury population is high-frequency percussive ventilation (HFPV) using the VDR ventilator (Percussionaire Corp., Sandpoint, ID). Proponents point out that HFPV confers a unique mucokinetic effect that facilitates clearance of secretions. Early retrospective studies suggested that HFPV can decrease nosocomial pneumonia rates in children[4] and adults as well as improve survival in adults when compared to conventional (pre-ARDSNET) ventilation.[5] A recently reported nonrandomized,

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single center study found a significant decrease in overall mortality when patients with smoke inhalation injury were treated with HFPV.[6] To date, no randomized, prospective, multicenter study comparing HFPV with conventional low-volume ventilation has been reported; and use of the VDR ventilator is limited by its complexity and lack of availability. Smoke inhalation injury in association with a cutaneous thermal injury greatly increases the incidence of both nosocomial pneumonia and mortality.[7,8]

CO poisoning is the cause of death in most fires. A normal product of combustion, CO, is transported very rapidly across the alveolar membrane, where it competitively displaces oxygen from hemoglobin. An arterial carboxyhemoglobin level above 15% indicates significant exposure. Signs and symptoms of toxicity correlate with an increasing level, and range from nausea and headache (15–25%) to stupor (30–40%) and finally coma and death (40–60%). The use of 90–100% oxygen reduces the half-life of CO from 4 h to 40 min. There are reports of the efficacy of hyperbaric oxygen treatment for CO toxicity.[9] However, to date no randomized, blinded studies have been published demonstrating its superiority over inspired 100% oxygen in patients who have suffered smoke inhalation injury. Delay in transporting the burn patient to an organized burn unit in favor of hyperbaric oxygen treatment should be avoided.

Another common product of combustion is hydrocyanide (CN). Like CO, CN is rapidly transported across the alveolus, where it binds to the cytochrome system and inhibits oxidative phosphorylation and adenosine triphosphate production. Treatment consists of administering 20 cc of 3% sodium nitrate followed by 50 cc of 25% sodium thiosulfate.

A major breakthrough in the management of severe burns was the work performed by Cope and Moore[10] and Baxter and Shires.[11,12] Their classic articles on fluid distribution in and resuscitation of burn victims have been the foundation upon which modern fluid therapy is based. From those reports comes the Parkland formula recommendation of 2 to 4 cc Ringer's lactate solution per kilogram body weight per percent total body surface area burned. One-half of this calculated amount is administered over the first 8 h and the remaining calculated volume is administered over the next 16 h. However, this calculation should be used only as a guide to initial resuscitation fluid administration rates, and the patient's response to these measures must be closely monitored. Traditionally, urine output has been taught as the gold standard for measuring resuscitation response. However, urine output alone cannot accurately measure the adequacy of resuscitation.[13] Other parameters that must be measured as baseline indicators of response are blood pressure, pulse pressure, pulse, arterial oxygenation, and pH. In larger burns with major fluid shifts, the use of a Swan-Ganz catheter should be considered.[14]

A great deal of investigation has been directed at determining proper endpoints of resuscitation. In a report by Rutherford et al.,[15] base deficit was shown to be a sensitive measure of degree and duration of inadequate perfusion and, therefore, adequacy of resuscitation. Before that report, Abramson et al.[16] showed the importance of reversal of anaerobic metabolism, as measured by serum lactate clearance, on survival following trauma. However, burn patients were excluded from both studies. Several reports on burn resuscitation end points were published in 1997. In a report by Barton et al.,[17] patients with a mean burn size of 45% were resuscitated using the Parkland formula with additional fluid boluses and dobutamine infusions. Those investigators found that cardiovascular function in burn patients responded to volume loading and inotropic support just as in patients suffering shock due to other reasons. Jeng et al.[18] studied serum lactate and base deficit as measures of burn resuscitation and concluded, "Serum lactate and base deficit might just be the more precise physiologic yardsticks that are required to advance the state of resuscitation from burn shock." An additional report by the same author suggested that serum lactate was predictive of mortality, but neither lactate nor base deficit were reliable indicators as endpoints for resuscitation from burn shock.[19] In a report published by Kaups et al.,[20] base deficit was shown to be superior to the Parkland formula for calculating fluid requirements, with a base deficit of −6 or less being a marker of increased mortality. However, this observation has not been borne out in other published studies.[21,22] Clearly, more work must be performed in this area to define proper resuscitation end points.

Wound Management

The initial management of the burn wound involves stopping the burning process. This is accomplished simply by removing all burned clothing and cooling the burned areas in cool (20°C) water. However, the effect of this cooling is lost after about 30 min. Indeed, cooling large burns with this method for prolonged periods of time results in heat loss and the adverse effects of hypothermia. Patients should never be cooled with ice or dry ice.

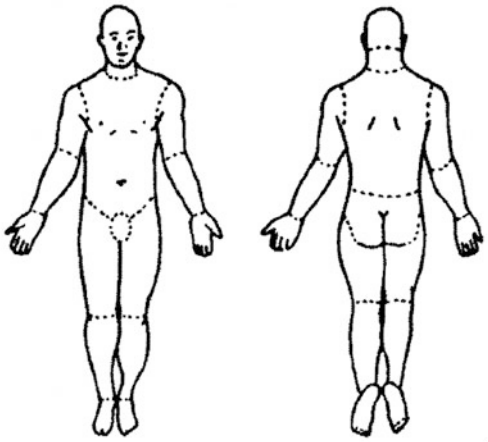
The extent and depth of the burn wound must be estimated to determine further care. While superficial (first-degree) burns are painful, they require little treatment other than symptomatic management with nonsteroidal anti-inflammatory drugs. When calculating the surface area, only burns of partial thickness (second degree) or deeper are included. This is best accomplished through the use of a Lund–Browder chart (see Fig. 44.1). However, if unavailable, the physician can estimate the size of the burn because the palmer surface of the patient's hand represents about 1% of the patient's body surface. When size estimation is complete, the patient is weighed and the initial intravenous (IV) fluid rate is calculated. The elapsed time from infliction of the burn to the initiation of fluid resuscitation, along with the total amount of fluid the patient may have received before the initiation of resuscitation, must both be considered when performing the initial calculation.

BURN ESTIMATE AND DIAGRAM
AGE VS AREA

Initial Evaluation

Cause of burn _____
Date of burn _____
Time of burn _____
Age _____
Sex _____
Weight _____
Date of admission _____
Signature _____
Date _____

Burn Diagram



Area	Birth 1 yr	1-4 yrs	5-9 yrs	10-14 yrs	15 yrs	Adult	2°	3°	Total	Donor Areas
Head	19	17	13	11	9	7				
Neck	2	2	2	2	2	2				
Ant. Trunk	13	13	13	13	13	13				
Post. Trunk	13	13	13	13	13	13				
R. Buttock	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2				
L. Buttock	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2				
Genitalia	1	1	1	1	1	1				
R.U. Arm	4	4	4	4	4	4				
L.U. Arm	4	4	4	4	4	4				
R.L. Arm	3	3	3	3	3	3				
L.L. Arm	3	3	3	3	3	3				
R. Hand	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2				
L. Hand	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2				
R. Thigh	5 1/2	6 1/2	8	8 1/2	9	9 1/2				
R. Leg	5	5	5 1/2	6	6 1/2	7				
L. Leg	5	5	5 1/2	6	6 1/2	7				
R. Foot	3 1/2	3 1/2	3 1/2	3 1/2	3 1/2	3 1/2				
L. Foot	3 1/2	3 1/2	3 1/2	3 1/2	3 1/2	3 1/2				
						Total				

FIG. 44.1. Lund-Browder chart.

Superficial second-degree burns are debrided of blisters and washed with a mild, non-deodorant soap. These burns are then covered by either a topical agent, such as 1% silver sulfadiazine (see Table 44.1) or a barrier dressing such as Biobrane™.[22] If Biobrane™ is chosen, it can be held in place with wound closure strips. It must be inspected carefully for the first few days following application for underlying fluid collections. If observed, they may be drained by opening the bubble over the collections. If underlying infection develops, the barrier should be removed and topical agents applied.

Systemic antibiotics are not indicated as a prophylactic measure. They should be reserved for use in cases of

Table 44.1. Topical agents.

Agent	Actions	Indications/Considerations	Considerations
Silver sulfadiazine	Broad spectrum, painless, minimal eschar penetration	Any size or depth of burn for prophylaxis or infection control	May cause leucopenia or skin allergy; creates pseudoeschar on wound
Mafenide acetate	Broad spectrum, effective against Pseudomonas, penetrates eschar, may be painful	Any size or depth of burn, use on burns of the nose or ears	Carbonic anhydrase inhibitor, may cause skin allergy. Available as cream or 5% solution; fewer side effects with solution
Acticoat™Aquacel Ag Silver Seal	Broad spectrum, effective against yeast	Any size or depth of burn for prophylaxis or infection control	Silver is not absorbed systemically; keep moist; dressing may remain intact for up to 7 days before changing
Bacitracin/polysporin ointment	Limited anti-bacterial coverage, no eschar penetration	Superficial burns reistance; often used on superficial burns of the face	Watch for bacterial resistance
Gentamycin ointment	Broad spectrum, painless, good eschar penetration	Gram-negative organisms resistant o other agents	Watch for bacterial resistance; renal and ototoxicity when used in large amounts
Povidone-iodine ointment	Broad spectrum, patients may complain of pain	Infected granulation tissue, organisms resistant to other topicals	May impair wound healing
Collagenase	Enzymatic debridement of eschar, no anti-bacterial properties; may mix with polysporin powder	Enzymatic debridement when surgical debridement may not be possible	Should not be used with compound containing metal ions such as povidone-iodine or silver

Table 44.2. Biological dressings and devices.[a]

Agent	Actions	Indications	Considerations
Pigskin	Frozen porcine split-thickness grafts (xenograft)	Temporary coverage of partial-thickness burns and granulation	Must be kept frozen. Aldehyde cross-linked version (E-Z Derm™) need not be frozen and has an extended shelf life
Cadaver skin	Frozen or fresh human split thickness grafts (allograft)	Temporary coverage of partial- or excised full-thickness burns, grafts, or granulation	Must eventually be replaced with autograft; rejection may occur as nutritional status improves
Biobrane™	Porcine collagen-coated nylon mesh	Clean partial-thickness burns (scalds), donor sites, autografts; may be used as a stent[13]	Immediate pain relief when applied; watch for underlying fluid collections
Transcyte™	Human newborn fibroblasts cultered onto Biobrane™	Temporary coverage of partial-thickness burns	Must be stored at −20°C
Integra™	Biodegradable lattice of bovine collagen and glucosamino-glycan with a silicon membrane serving as a temporary "epidermis"	Neodermis for full-thickness excisions; silicone layer is eventually surgically replaced with epidermal autograft	No inherent anti-bacterial properties, being used along seams; shearing forces may loosen silicone layer prematurely
Alloderm™	Cryopreserved, acellular, human dermis	Permanent neodermis for full-thickness excisions decreases scarring and contracture	Freeze dried; rehydrate in operating room; use for major joints and contracture releases

[a]Many of these products are available in different sizes. Final price depends on size and volume of product purchased.

systemic infection, and then should be culture-directed with as narrow a spectrum as possible. Wound biopsies should be taken on at least a weekly basis and sent for quantitative culture, and sensitivities to common topical agents also should be reported. Research into the use of prophylactic antifungals is currently being conducted, but no final results have yet been reported.

Full-thickness (third-degree) burns require skin grafting in most cases. Even grafting of deep partial-thickness burns should be considered in cases in which hospitalization and return to productivity would be enhanced. The timing of this surgical procedure comes after the full resuscitation of the patient. If the wound cannot undergo a grafting procedure by the third post-burn day, then wound cultures should be taken to assure colony counts of less than 10^5 organisms per gram of tissue. The ambient air temperature in the operating room should be increased to 85 °F for patients with large burns and those who are totally exposed during the procedure. The planned procedure should not require more than 2 h to complete. Blood products for transfusion must be readily available before the start of debridement of a large burn and warmed during administration.

Several technologic advances have been made in the areas of wound management (see Table 44.2).

Pain Management

Arguably, burns are the most painful injury a patient can experience. Control of pain is important, not only for humanitarian reasons, but also to decrease the patient's stress and inefficient use of calories.

Full-thickness burns, in which all elements of skin including nerves have been destroyed, are generally painless before grafting. However, partial-thickness burns are quite painful. Pain control must be initiated before any manipulation of the wound. Generally, morphine or fentanyl is used for manipulations such as dressing changes. Smaller burns may be managed with intramuscular injections and/or oral pain medications. Larger burns, however, should be treated with IV injections for a more reliable dose titration. Patients who are taking oral medications may find an increase in their pain threshold through the use of methadone. The initial dose of 5 mg is administered every 8 or 12 h, and is usually mixed in orange juice. Dosing and frequency may be adjusted depending upon the patient's response. Several authors have reported on the use of ketamine for the management of burn pain.[24–26]

Pain management of burns in pediatric patients can be challenging. Brown et al.[27] at the Shriners Burns Institute in Cincinnati have reported that haloperidol is safe and effective for use with pediatric patients. Humphries et al.,[28] who used the Ramsay scale as a measurement, found oral ketamine to be superior to narcotics and sedatives in this clinical setting.

There is little consensus regarding pain management among the various studies. Indeed, it has been reported that health care providers consistently undertreat pain from burn wounds.[29] In response to this, guideline-based approaches to pain management have been proposed by Ulmer[30] and Sheridan et al.[31]

Metabolic Response and Nutrition

Cope et al.[32] were the first to demonstrate that the hypermetabolic response to burns depends on the size and extent of the burn. Since that time, we have come to better understand the phases of this process. The hypermetabolic response in the patient with a body surface burn over 10–15% of the body is rarely significant. However, in larger burns it may increase to 2.5 times the normal rate.

The increase in metabolism typically starts about 24 h after the burn occurred, and peaks between 1 and 2 weeks. The patient exhibits tachycardia, tachypnea, and fever. The fever is believed to be the result of a hypothalamic response to circulating interleukin-6. The increased body temperature is dependent on the size of the burn wound and may not respond to antipyretics.[33] Other clinical signs include increased oxygen consumption and carbon dioxide (CO2) production, decreased systemic vascular resistance, and increased nitrogen excretion. Similar to fever, nitrogen excretion is dependent on the size of the burn. Waxman reported that nitrogen is lost from the wound at a rate of 0.1 × body surface area × percent burn per 24 h.[34]

When the burn wound is closed, the patient's metabolic rate returns to normal.[35,36] Until that time, the nutritional needs of the patient must be intensely supported. Appropriate nutritional support is accomplished by assessing the patient's nutritional status, assessing the caloric and nitrogen requirements of the patient, formulating a plan and approach to each component, determining the modes to accomplish the nutritional goals, and monitoring the nutritional plan and any complications.[37] Early excision and coverage with adequate nutritional support has been shown to abate catabolic effects as well as infectious complications.[38,39]

The use of anthropomorphic measurements, plasma protein levels, and immune competence are of no real value in assessing the nutritional state and requirements of the burn patient. In 1919, Harris and Benedict described their formula for estimating basal energy expenditures (BEE) in humans. Since then, other formulas, including the Curreri and Galveston formulas have been devised (see Table 44.3). Today, many centers rely on indirect calorimetry to estimate caloric requirements. Despite the numerous formulas and methods, it does not appear necessary or prudent to provide more than two times the patient's BEE.

Calories are provided as 30–40% fat, and the remainder of the diet is carbohydrates. Fat intake is important to prevent free fatty acid deficiency and binding of fat-soluble vitamins. Glucose is metabolized at 4–7 mg per minute. Providing more than this only increases oxygen use and CO_2 production.

Nitrogen is usually administered in the range of 20–25 g or approximately 3 g/kg of desirable body weight per day.

TABLE 44.3. Energy requirement formulas.

Harris–Benedict equation
Males: $BEE = 66.0 + (13.7 \times W) + (5 \times H) - (6.8 \times A) \times AF \times IF$
Females: $BEE = 65.5 + (9.6 \times W) + (1.7 \times H) - (4.7 \times A) \times AF \times IF$
Where W = weight in kilograms
H = height in centimetersV
A = age in years
AF = activity factor
IF = injury factor
Curreri Formula
Adults:
Energy requirement = 25 cal/W + 40 cal/% BSA
Children:
Energy requirement = 60 cal/W + 35 ca% BSA
Where W = weight in kilograms
% BSA = percent of body surface area burned
Galveston Formula (children)
Energy requirement = 1800 kcal/m^2 + 2200 kcal/m^2 of burn
U.S. Army Institute of Surgical Research Formula
Energy requirements = $\{BMR \times [0.89142 + (0.01335 \times TBSA)]\} \times 24 \times AF$
Where BMR = basal metabolic rate
TBSA = total body surface area
AF = activity factor
BMR (males) = $54.33782 - (1.19961 \times A) + (0.02548 \times A^2) - (0.00018 \times A^3)$
BMR (females) = $54.74942 - (1.54884 \times A) + (0.0358 \times A^2) - (0.00026 \times A^3)$
Where A = age in years

Multivitamins, particularly vitamin A for epithelial integrity, vitamin C for collagen synthesis, and vitamins E and B for wound repair, are commonly administered. Zinc is also recommended because of its role in wound healing.[40]

In addition to increased nutritional support for the hypermetabolic, catabolic state, the efficacy of modulating these states has been studied extensively. Oxandrolone, a testosterone analog, has been shown to decrease hospital stay in severely burned patients,[41] postulated to be because of, in part, its anabolic effects of increasing lean body mass in burn patients.[42] Insulin has been shown to increase skeletal muscle synthesis in severely burned patients, even at submaximal doses.[43] Beta blockade with propranolol has also been shown to decrease energy expenditure and increase net muscle protein balance.[44,45]

Several aspects of the effects of glutamine supplementation have been recently studied. Severely burned patients experienced decreased hospital stay.[46] In addition, decreases in gram-negative bacteremia, particularly *Pseudomonas* species, and ICU stays have been described.[47,48] The exact mechanism of improved infectious outcomes has yet to be elucidated, but is believed to involve the enhancement of gut integrity and immune function.[47,48]

For many years, post-burn ileus – common with burns over 25% of the total body surface area – was believed to be a contraindication to early enteral feeding. However, it is now known that post-burn ileus does not affect the small bowel. Early administration of 75% of the estimated caloric needs can be accomplished within the first 6 h after the burn and may lead to a reduction of the hypermetabolic state. The enteral route is preferred for nutritional support. Stopping enteral feeding in the immediate preoperative and operative period is unnecessary, although commonly requested by anesthesia colleagues.[49,50]

Complications

The most common complications associated with burns are respiratory failure, infection, and graft failure. However, there are other early and late complications of burn injury that should be kept in mind.

Vascular compromise may result directly from thermal, electrical, or chemical injury. This direct injury affects the outer adventitial layer first and then the media. When vessels are weakened, rupture can occur. However, a more common cause of vessel rupture following burn injury is infection of the wound, which can lead to necrosis of the vessel wall. Burns that cause intimal damage produce a thrombogenic surface.[51]

During resuscitation of the patient with full-thickness burns of the trunk or circumferential full-thickness burns of any part of an extremity, consideration must be given to escharotomy (incision into the full-thickness eschar that relieves the underlying pressure resulting from fluid shift into the extravascular space). Because escharotomies are performed through full-thickness insensate skin, this procedure can be done without anesthesia, although light sedation may be administered. Escharotomy traditionally is performed using a scalpel, but it also can be performed with cutting electrocautery.

As mentioned previously, patients with burns over 20% of body surface area usually have gastric and colonic ileus. Another gastrointestinal complication is ulceration of the upper gastrointestinal tract. Described by Curling[52] as acute ulceration of the duodenum, this complication bearing his name is now assigned to any erosive disease of the gastroduodenal mucosa. Significant burn injury leads to acute mucosal disease in 8% of untreated patients.[53] Of these patients, 22% have hemorrhages and 6% have perforations.[54] The importance of prevention is clear. Measures include close monitoring of gastric pH and the use of antacids or H_2 blockers, proper nutritional support, and early enteral feeding.

Heterotopic ossification occurs with frequencies reported between 1 and 14%.[55,56] The pathogenesis is not fully understood. Factors such as burn size greater than 20% and immobility have been implicated. Munster and colleagues[56] reported that even though full-thickness burns are more susceptible, heterotopic ossification has been reported in partial-thickness burns as well.[57] Preventive measures include early ambulation and active and passive joint motion.

Contraction is a normal part of wound healing and determines ultimate functional outcome and cosmetic appearance. Return to pre-burn function and the best cosmetic result possible are the two most important goals of the surgeon after patient survival. Therefore, control of wound contraction and scar formation are crucial. McDonald and Deitch[58] reported that poor scar outcome was associated with several factors including dark skin pigmentation, younger patient age, deeper depth of the burn, absence of dermis, and delayed grafting 14 days after the burn. Grafts placed on the head and neck tend to have a worse outcome than grafts placed on the trunk and extremities. As with all complications, prevention is preferred over treatment. The presence of dermal elements decreases heavy scarring and contracture rates. Therefore, thicker grafts containing more dermis tend to scar less. However, thicker grafts are associated with their own complications and they may not be practical depending on the size of the burn and the area being grafted. Several products now available for the treatment of burns attempt to replace dermal elements (Table 44.2). The use of these products has been shown to decrease scarring and maintain function, while at the same time providing acceptable cosmetic results.[58] Compression garments used in the scar maturation period decrease scarring by pressure-induced realignment of collagen fibers and reduction of collagen synthesis.[60] These garments are ideally worn 24 h a day for 12 to 18 months after the burn occurs; they are removed only for bathing. The mainstay of prevention, however, remains early graft coverage of the wound to avoid septic complications and granulation buildup, as well as early ambulation and movement of joints.

The operative approach to scar revision is beyond the scope of this chapter, and the reader is referred to surgical texts and atlases on the subject.

Squamous or basal-cell malignancies that form with the wound, known as Marjolin's ulcer, are characterized by thickened scars that break down repeatedly over a period of several years. These malignancies generally do not appear until 10 years or more following the burn. Even though they are low grade on histologic examination, by the time the patient presents and a definite diagnosis is made through biopsy, roughly one-third of patients have regional nodal metastasis and the overall prognosis is poor.

The occurrence of abdominal compartment syndrome, first described in the late 1800s, seems to have generated renewed interest among trauma and burn surgeons. The syndrome is characterized by high peak airway pressure, oliguria, and intra-abdominal pressures of greater than 25 mm Hg as measured transvesically with a Foley catheter and transducer. Abdominal decompression is the only treatment and may be accomplished either by laparotomy[61] or placement of a temporary peritoneal dialysis catheter.[62]

Chemical Burns

Injury from acids or alkalis is caused by desiccation of tissues and denaturation of proteins. As a rule, alkali burns tend to be deeper than those caused by acids, but the alkalis are usually not systemically absorbed.

The description of chemical burns is the same as that of thermal burns. However, it is important to remember that deep chemical burns may appear deceptively superficial on initial presentation.

As with any burn injury, an important first step in management is to stop the burning process. All clothing must be removed. If the chemical is dry, as much of it as possible should be brushed off. This is followed by copious wound irrigation. If the chemical is wet, irrigation of the wound is begun. The earlier wound irrigation is begun, the better the outcome.[63,64] The irrigation should be continued for a minimum of 30 min.[2] Exceptions to this principle are hydrochloric acid, which should be naturalized with soda lime (avoid saline irrigation) and lithium metal, which may react violently with water. The size estimation and fluid resuscitation guidelines are the same for chemical as for thermal burns.

Electrical Injury

Electrical injuries happen less often than thermal burns, but they are much more difficult to manage and are associated with a higher morbidity and mortality rate. As current passes through the body, it meets resistance from the tissues. The amount of resistance is inversely proportional to the relative amount of water found in the tissue. Those tissues that have relatively little water content (i.e., bone) have more resistance to the current. According to Joules Law, the amount of heat produced by the passage of current is proportional to the resistance. Clinically, the more superficial tissues may appear normal, but the underlying bone and adjacent muscle are destroyed. In these situations, usually encountered with high-voltage injury, amputation of the involved extremities is commonly part of the initial debridement and wound management.

Because the amount of tissue destruction is not obvious with electrical injury, the amount of fluid needed for initial resuscitation is twice the amount predicted by the application of the Parkland formula. In addition, the destruction of muscle produces myoglobin, which is released into the systemic circulation and excreted by the kidneys. In the normal acid environment of the urine, the myoglobin precipitates in the tubules and causes acute tubular necrosis and renal failure. To avoid this complication, fluid administration is increased over what is calculated with resuscitation formulas, and 25 g of mannitol is administered followed by 12.5 g every 2 h until the urine clears the myoglobin pigment. Additionally, sodium bicarbonate is administered to raise the urine pH to 7 while maintaining blood pH below 7.5. Renal doses of dopamine may also help increase renal blood flow and urine output.[65]

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45
The Abdominal Compartment Syndrome

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A compartment syndrome exists when increased pressure in a closed anatomic space threatens the viability of surrounding tissue. When this occurs in the abdominal cavity, the impact on end-organ function within and outside the cavity can be devastating. The abdominal compartment syndrome (ACS) is not a disease, but a clinic syndrome that has many causes and develops within many disease processes. Unlike many commonly encountered disease processes, which remain within the purview of a given discipline, intra-abdominal hypertension (IAH) and the ACS readily cross the usual barriers and may occur in any patient population regardless of age, illness, or injury. As a result, no one specific specialty can represent the wide variety of physicians, nurses, respiratory therapists, and other allied healthcare personnel who might encounter patients with IAH and/or ACS in their daily practice. The IAH is a graded phenomenon that can be acute or chronic, primary or secondary, and localized or generalized in character. The ACS on the contrary is not graded but rather considered as an "all or none" phenomenon. Recent animal and human data suggest that the adverse effects of elevated intra-abdominal pressure (IAP) can occur at lower levels than previously thought and even before the development of clinically overt ACS. This chapter will present a concise overview of the historic background, epidemiologic data, definitions, pathophysiologic implications, and treatment options for ACS.

Historical Background

The effects of elevated IAP have been known since 1863, when Marey of Paris highlighted that "the effects that respiration produces on the thorax are the inverse of those present in the abdomen."[1] In 1890, Heinricius demonstrated that IAPs between 27 and 46 cmH_2O were fatal to animals because of impairment of respiration, decreased cardiac diastolic distension, and hypotension. It was not until 1911 that Emerson conducted numerous experiments in dogs showing that the contraction of the diaphragm is the chief factor in the rise of IAP during inspiration, that elevated IAP increases systemic vascular resistance, and that excessive IAP can cause death from cardiac failure even before asphyxia develops. He concluded that "the distension of the abdomen with gas or fluid results in cardiac compromise because of an overloading of the resistance in the splanchnic area" and that "removal of ascitic fluid results in relief of the labouring heart."

In 1876, Wendt first described the association of IAH and renal dysfunction. After a long era of over 75 years with only scattered attempts to shed new light on IAP, Bradley and Bradley showed a decreased glomerular filtration rate and renal plasma flow with increased IAP. The term abdominal compartment syndrome (ACS) was first used by Fietsam et al. in the late 1980s to describe the pathophysiologic alterations resulting from IAH secondary to aortic aneurysm surgery. They wrote: "in four

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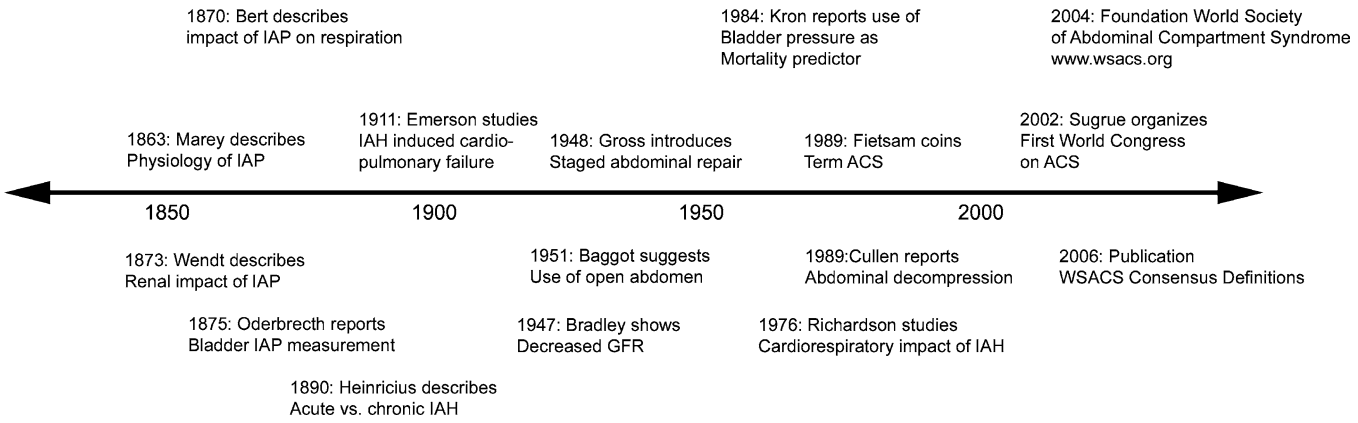


FIG. 45.1.The timeline of intra-abdominal pressure, intra-abdominal hypertension and abdominal compartment syndrome.

patients with ruptured abdominal aortic aneurysms increased IAP developed after repair. It was manifested by increased ventilatory pressure, increased central venous pressure, and decreased urinary output. This set of findings constitutes an abdominal compartment syndrome caused by massive interstitial and retroperitoneal swelling… four patients received more than 25 liters of fluid resuscitation… Opening the abdominal incision was associated with dramatic improvements…"[2] Hence, the first definition of ACS was finally coined (Fig. 45.1).

Definitions

The World Society of Abdominal Compartment Syndrome (WSACS – www.wsacs.org) has been founded to serve as a peer-reviewed forum and educational resource for all healthcare providers, as well as industry, which have an interest in IAH and ACS. The mission of the society is to foster education and promote research, and thereby improve the survival of patients with IAH and ACS. Recently, the first consensus definitions report of the WSACS has been published.[3]

Intra-abdominal Pressure (IAP)

Since the abdomen and its contents can be considered as relatively noncompressive and primarily fluid in character, behaving in accordance with Pascal's law, the IAP measured at one point may be assumed to represent the IAP throughout the abdomen.[4,5] IAP is therefore defined as the steady-state pressure concealed within the abdominal cavity. IAP increases with inspiration (diaphragmatic contraction) and decreases with expiration (diaphragmatic relaxation).

Definition 1. The intra-abdominal pressure (IAP) is the steady-state pressure concealed within the abdominal cavity

Abdominal Perfusion Pressure (APP)

Analogous to the widely accepted and clinically utilized concept of cerebral perfusion pressure, calculated as mean arterial pressure (MAP) minus intracranial pressure (ICP), abdominal perfusion pressure (APP), calculated as MAP minus IAP, has been proposed as a more accurate predictor of visceral perfusion and a potential endpoint for resuscitation.[6–9] APP, by considering both arterial inflow (MAP) and restrictions to venous outflow (IAP), has been demonstrated to be statistically superior to either parameter alone in predicting patient survival from IAH and ACS.[9] A target APP of at least 60 mmHg has been shown to correlate with improved survival from IAH and ACS.

Definition 2. $APP = MAP - IAP$

Filtration Gradient

Inadequate renal perfusion pressure (RPP) and renal filtration gradient (FG) have been proposed as key factors in the development of IAP-induced renal failure.[9,10] Changes in IAP will have a greater impact upon renal function and urine production than will changes in MAP. As a result, oliguria is one of the first visible signs of IAH.[11]

Definition 3. $FG = GFP - PTP = MAP - 2 \times IAP$

IAP Measurement

In an attempt to standardize and improve the accuracy and reproducibility of IAP measurements, the following definitions are proposed:

Definition 4. IAP should be expressed in mmHg and measured at end-expiration in the complete supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the mid-axillary line.

Definition 5. The reference standard for intermittent IAP measurement is via the bladder with a maximal instillation volume of 25 mL of sterile saline.

Normal and Pathologic IAP Values

In the strictest sense, normal IAP ranges from 0 to 5 mmHg.[12] Certain physiologic conditions, however, such as morbid

obesity or pregnancy, may be associated with chronic IAP elevations of 10–15 mmHg to which the patient has adapted with an absence of significant pathophysiology. In contrast, children commonly demonstrate low IAP values.[13] The clinical importance of any IAP must be assessed in view of the baseline steady-state IAP for the individual patient.

Definition 6. Normal IAP is approximately 5–7 mmHg in critically ill *adults.*

Intra-Abdominal Hypertension (IAH)

Pathological IAP is a continuum ranging from mild IAP elevations without clinically significant adverse effects to substantial increases in IAP with grave consequences for virtually all organ systems in the body.[1]

Definition 7. IAH is defined by a sustained or repeated pathologic elevation of IAP ≥ 12 mmHg.

The more severe the degree of IAH, the more urgent is the need for decompression of the abdomen (either medically or surgically) with resolution of the damaging pressure.

Definition 8. IAH is graded as follows:

- *Grade I:* IAP 12–15 mmHg
- *Grade II:* IAP 16–20 mmHg
- *Grade III:* IAP 21–25 mmHg
- *Grade IV:* IAP > 25 mmHg

Abdominal Compartment Syndrome (ACS)

Intra-abdominal hypertension clearly represents a continuum with IAP varying from patient to patient and from moment to moment according to underlying etiologic factors, cardiac filling status, presence of organ failure, and preexisting comorbidities. This initial generally accepted definition was called the TRIAD of ACS: (1) a pathologic state caused by an acute increase in IAP above 20–25 mmHg that (2) adversely affects end-organ function or can cause serious wound complications, and in which (3) abdominal decompression has beneficial effects.[14,15] Currently, the ACS refers to the cardiovascular, pulmonary, renal, splanchnic, abdominal wall/wound, and intracranial disturbances resulting from elevated IAP, regardless of etiology. Although the critical IAP that defines ACS is subject to debate, of greater importance than any one absolute IAP value is the development of organ dysfunction and failure.[16]

Definition 9. ACS is defined as a sustained IAP > 20 mmHg (with or without an APP < 60 mmHg) that is associated with new organ dysfunction/failure.

Classification of IAH/ACS

Primary ACS (formerly termed surgical, postoperative, or abdominal ACS) is characterized by the presence of acute or subacute IAH of relatively brief duration occurring as a result of an intra-abdominal process such as abdominal trauma, ruptured abdominal aortic aneurysm, hemoperitoneum, acute pancreatitis, secondary peritonitis, retroperitoneal hemorrhage, or liver transplantation. It is most commonly encountered in the traumatically injured or postoperative patient.

Definition 10. Primary ACS is a condition associated with injury or disease in the abdominopelvic region that frequently requires early surgical or interventional radiological intervention.

Secondary ACS (formerly termed medical or extra-abdominal ACS) is characterized by the presence of subacute or chronic IAH that develops as a result of an extra-abdominal etiology such as sepsis, capillary leak, major burns, or other conditions requiring massive fluid resuscitation.[17–23] It is most commonly encountered in the medical or burn patient.[18,24–26]

Definition 11. Secondary ACS refers to conditions that do not originate from the abdominopelvic region.

Recurrent ACS (formerly termed tertiary ACS) represents a redevelopment of ACS symptoms following resolution of an earlier episode of either primary or secondary ACS. It is most commonly associated with the development of acute IAH in a patient who is recovering from IAH/ACS and therefore represents a "second-hit" phenomenon. It may occur despite the presence of an open abdomen (known as the "open abdomen compartment syndrome") or as a new ACS episode following definitive closure of the abdominal wall.[27] Recurrent ACS, due to the patient's current or recent critical illness, is associated with significant morbidity and mortality.[28]

Definition 12. Recurrent ACS refers to the condition in which ACS redevelops following previous surgical or medical treatment of primary or secondary ACS.

Occasionally, patients may demonstrate signs and symptoms consistent with both primary and secondary ACS. Examples might include a patient who develops sepsis with fluid overload after initial surgical stabilization for trauma.[23,26] This overlap of clinical conditions and potential etiologies has added to the confusion regarding the definition of ACS. Nevertheless, the majority of IAH/ACS patients may be assigned to one of these three classes.

Recognition of ACS

Clinical Awareness

Despite this increasing frequency in critically ill patients and an escalation of medical literature on the subject, there still appears to be an under-recognition of the syndrome. The results of several surveys[29] on physicians' knowledge of IAH and ACS showed that there is still a general lack of clinical awareness and many intensive care units (ICUs) never measure the IAP. When it is measured, the intravesical route is used exclusively. No consensus exists on optimal timing of measurement or when decompressive laparotomy should be performed, and there is a great variation between surgeons, intensivists, and pediatricians.[30]

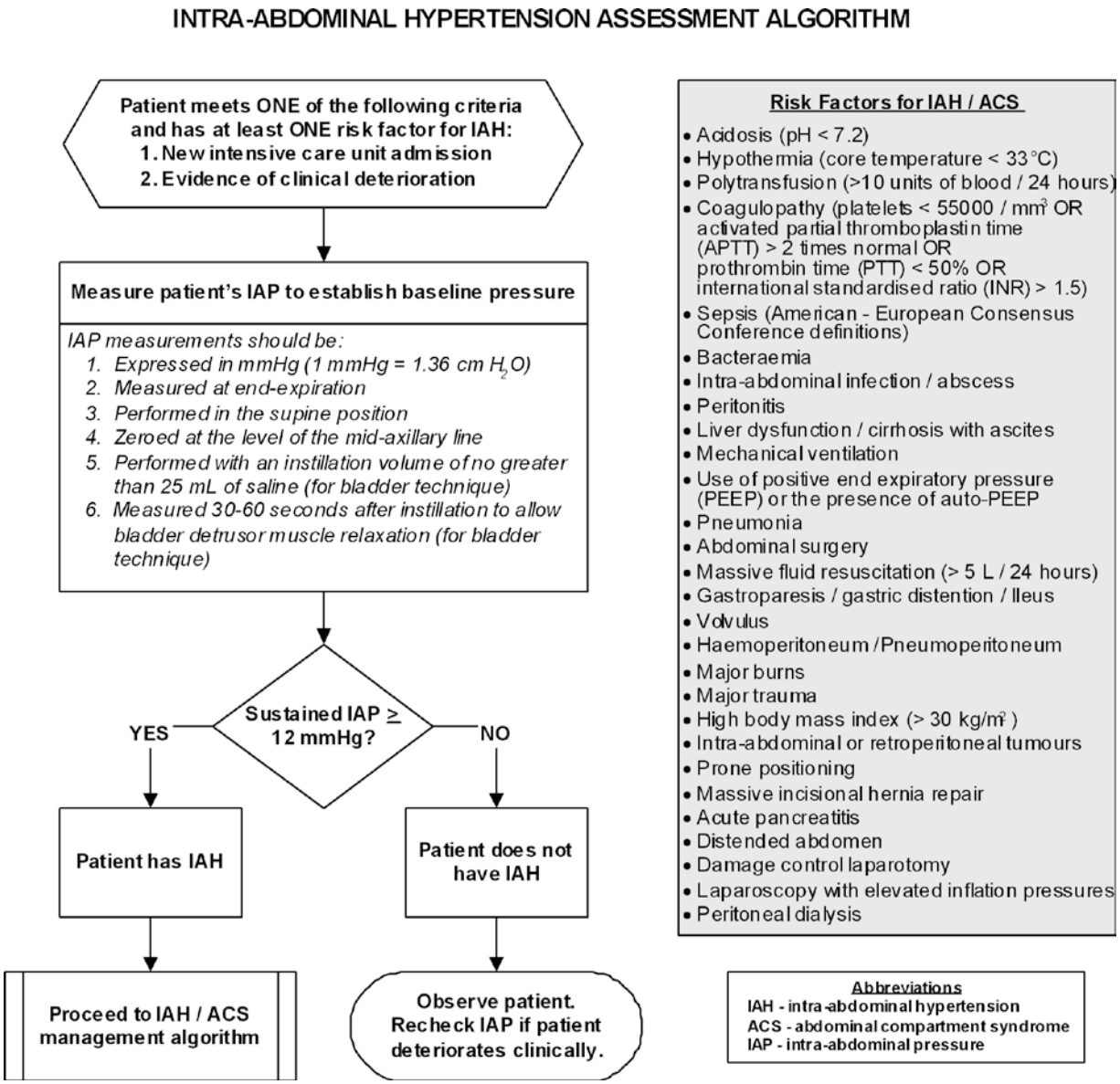


Fig. 45.2. Intra-abdominal hypertension assessment algorithm.

Etiology

The ACS can be diagnosed when there is increased IAP with evidence of end-organ dysfunction. While multiple causes of acute cardiopulmonary, renal, hepatosplanchnic, or neurologic deterioration exist in the ICU, it is important that we recognize the IAP as being an independent risk factor for this organ function deterioration. Hence, the timely recognition of the underlying risk factors and predisposing conditions that lead to IAH and ACS is extremely important. Indications for IAP monitoring should be based on the presence/absence of these risk factors (Fig. 45.2). Many conditions are reported in association with IAH/ACS, and they can be classified into four categories : first, conditions that decrease abdominal wall compliance; second, conditions that increase intraluminal contents; third, conditions related to abdominal collections of fluid, air, or blood; and finally, conditions related to capillary leak and fluid resuscitation. Table 45.1 lists some of the clinical conditions related to these four categories. Table 45.2 gives an overview of other recommendations as suggested by the WSACS, and an algorithm for the assessment of IAH is proposed in Fig. 45.2.[31]

Diagnosis

Clinical and Radiologic Examination

A direct correlation between the abdominal perimeter and IAP has not been found. Clinically significant IAH may be present in the absence of abdominal distension, yet chronic abdominal

TABLE 45.1. Etiologic risk factors and predisposing conditions for IAH.

Related to diminished abdominal wall compliance
- Mechanical ventilation, especially fighting with the ventilator and the use of accessory muscles[167,168]
- Use of positive end-expiratory pressure (PEEP) or the presence of auto-PEEP[142,169,170]
- Basal pleuropneumonia
- High body mass index[50,113,114,166,171]
- Pneumoperitoneum
- Abdominal (vascular) surgery, especially with tight abdominal closures[2,90,165,172,173]
- Pneumatic anti-shock garments[174,175]
- Prone and other body positioning[71]
- Abdominal wall bleeding or rectus sheath hematomas[176,177]
- Correction of large hernias, gastroschisis or omphalocoele[100,178]
- Burns with abdominal eschars[104]

Related to increased intra-abdominal contents
- Gastroparesis/gastric distention/Ileus/Colonic pseudo-obstruction[128,165,179]
- Abdominal tumor[180,181]
- Retroperitoneal/abdominal wall hematoma[177,182]

Related to abdominal collections of fluid, air or blood
- Liver dysfunction with ascites[165,183]
- Abdominal infection (pancreatitis, peritonitis, abscess, etc.)[151,180,184–188]
- Hemoperitoneum[165]
- Pneumoperitoneum[189–192]

Related to capillary leak and fluid resuscitation
- Acidosis (pH below 7.2)[165]
- Hypothermia (core temperature below 33 °C)[193,194]
- Polytransfusion/trauma (>10 units of packed red cells/24 h)[23,165,166,195]
- Coagulopathy (platelet count below 50,000/mm^3, or an activated partial thromboplastin time (APTT) more than 2 times normal, or a prothrombin time (PTT) below 50%, or an international standardized ratio (INR) more than 1.5)[84,165]
- Sepsis (as defined by the American – European Consensus Conference definitions)[165,196–199]
- Bacteremia
- Massive fluid resuscitation (>5 L of colloid or crystalloid/24 h with capillary leak and positive fluid balance)[6,20,21,91,165,166,200–204]
- Major burns[107,147,205,206]

The combination of acidosis, hypothermia and coagulopathy has been forwarded in the literature as the deadly triad.[193,194]

distension such as those seen in pregnancy, obesity, cirrhosis, or ovarian tumors can result in an increased abdominal perimeter without a concomitant increase in IAP. Other studies have shown that clinical IAP estimation is also far from accurate, with a sensitivity and positive predictive value of around 40–60%.[32,33]

Radiologic investigation including plain films of the chest and abdomen, abdominal ultrasound and computed tomography (CT) scan are all also insensitive to the presence of increased IAP.

Measurement of Intra-Abdominal Pressure

The key to recognizing ACS in a critically ill patient is the demonstration of elevated IAP: "measuring is knowing!"[31] The pressure within the abdominal cavity is normally slightly atmospheric in spontaneously breathing subjects. IAP can be directly measured with an intraperitoneal catheter attached to a pressure transducer. During CO_2 insufflation in laparoscopic surgery, IAP is measured directly via the Verres needle.

Different indirect methods for estimating IAP are used clinically because direct measurements are considered by some to be too invasive.[4,34] These techniques include rectal, uteral, gastric, inferior vena caval, and urinary bladder pressure measurement. Only gastric and bladder pressures are used clinically. Over the years, bladder pressure has been forwarded as the gold-standard indirect method (Fig. 45.3). The bladder technique has achieved the most widespread adoption worldwide because of its simplicity and minimal cost.[4,5] However, considerable variation is noted between the different techniques used, and recent data suggest to instill minimal volumes (10–25 ml) into the bladder for priming.[35,36]

Recently, new measurement kits including a FoleyManometer (Holtech Medical, Copenhagen, Denmark, at www.holtechmedical.com), AbViser-valve (Wolfe Tory Medical, Salt Lake City, Utah, USA, at www.wolfetory.com), and a balloon-tipped stomach catheter (Spiegelberg, Hamburg, Germany, at www.spiegelberg.de and Pulsion Medical Systems, Munich, Germany, at www.pulsion.com) have become commercially available.[5]

Several methods for continuous IAP measurement via the stomach, peritoneal cavity, and bladder have also been validated.[34,37–39] Although these techniques seem promising, further studies need to be done before their general use can be recommended.

Pathophysiologic Implications

IAH affects multiple organ systems in a graded fashion. In order to better understand the clinical presentation and management of disorders of IAH, one must understand the physiologic derangements within each organ system separately.[31] It is beyond the scope of this book chapter to give a concise and complete review of the pathophysiologic implications of raised IAP on end-organ function within and outside the abdominal cavity.[24,25] Figure 45.4 schematically shows the systemic effects of ACS. We will only discuss some key messages related to each organ that will affect daily clinical practice.

Neurologic Function

Acute IAH causes an increase in intracranial pressure (ICP) because of augmentation in pleural pressure. Cerebral perfusion pressure (CPP) will decrease because of a functional obstruction of cerebral venous outflow in combination with a reduced systemic blood pressure as a result of decreased preload.[8,40,41] Laboratory data, utilizing mainly a pneumoperitoneum model, demonstrated a mechanical effect of high IAP increasing ICP and decreasing CPP.[42–46] This effect requires for its realization the pressure transmission from the abdomen

TABLE 45.2. Consensus recommendations.

Recommendation	Term	Description
1	Risk factors for IAH	Patients admitted to the ICU should at least once (preferably on admission) be screened for possible risk factors for the development of IAH or ACS
2	Indication for IAP monitoring	If one or more risk factor is present, a baseline IAP measurement should be obtained for future reference
3	Epidemiology	Studies examining the prevalence and incidence of IAH/ACS should be based on the consensus definitions and classifications
4	Epidemiology	Epidemiologic data should be given for mean, median, and maximal IAP values on admission and during the study stay
5	Treatment	Treatment for IAH/ACS is based on three principles: 1. specific medical procedures to reduce IAP and the consequences of ACS 2. general (intensive care) support of the critically ill patient 3. optimization after (surgical) decompression to perhaps counteract some of the specific adverse effects associated with decompression
6	Medical treatment	The medical treatment options should be targeted to specific goals and can be divided into five groups: 1. Improvement of abdominal wall compliance 2. Evacuation of intraluminal contents 3. Evacuation of peri-intestinal and abdominal fluids 4. Correction of capillary leak and positive fluid balance 5. Specific treatment
7	Temporary abdominal closure (TAC)	It is not obligatory to use a vacuum-assisted fascial closure (VAFC) as first-time TAC since it is quite expensive and about one-third of the patients can have their fascia closed at the second laparotomy. If used, a homemade VAFC is preferred initially
8	IAP measurement	Future studies need to examine the ideal frequency for IAP measurement as well as the diurnal and nocturnal variations during continuous IAP monitoring
9	IAP and APP thresholds	Studies looking at IAP and APP thresholds should be based on the analysis of receiver operating characteristics (ROC) and the area under the ROC-curve
10	ROC curves	A good area under the ROC curve should be at least 0.75; and the best threshold needs to be identified with a sensitivity and/or specificity of at least, or close to 75%
11	IAP validation	Studies examining new devices to measure IAP should always compare the new IAP measurement method with some form of gold standard
12	IAP validation	The validation of the new technique should not be limited to the analysis of correlation, but it should also include a Bland and Altman analysis
13	Bias	The bias or the difference between 2 IAP methods should be close to 0 mmHg (range −1 to +1 mmHg). (Recommendation 13)
14	Limits of agreement	The maximal allowed limits of agreement (LA) when comparing 2 IAP methods should be within a range of 4 mmHg (LA = bias ± 4 mmHg)

IAP intra-abdominal pressure; *APP* abdominal perfusion pressure; *IAH* intra-abdominal hypertension; *ACS* abdominal compartment syndrome; *LA* limits of agreement; *ROC* receiver operating characteristics; *TAC* temporary abdominal closure; *VAFC* vacuum-assisted fascial closure.

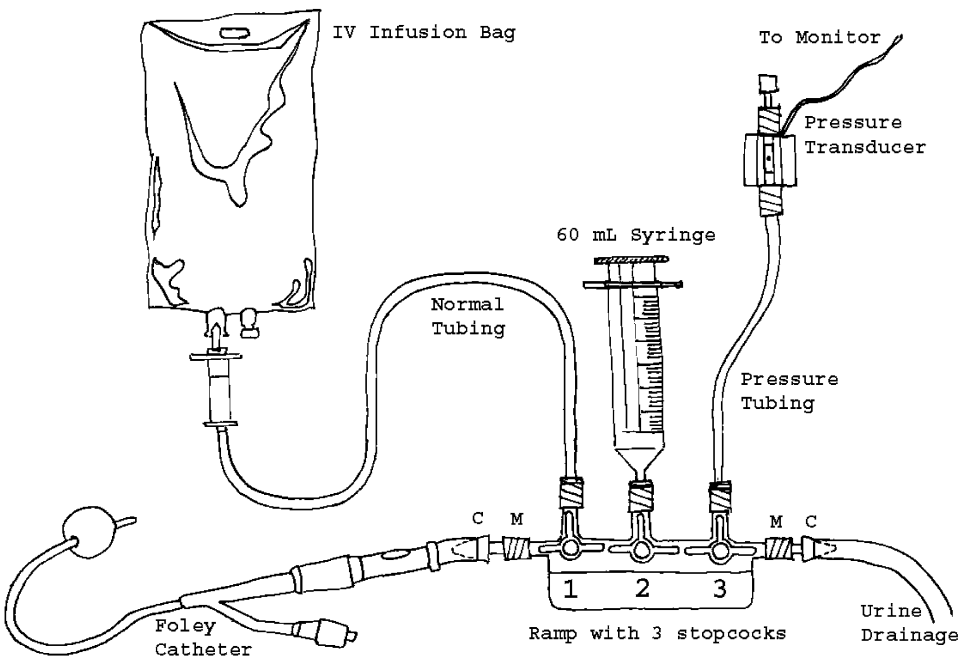
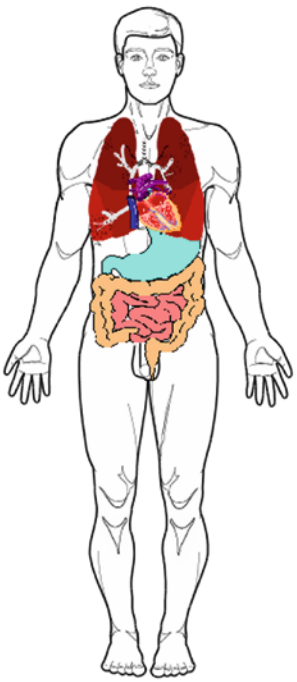


FIG. 45.3. Using a patent Foley catheter with clamped drainage tube, 10–25 mL sterile water are infused into the bladder via three three-way stopcocks placed in series between the Foley catheter and the urine drainage tubing. The bladder pressure measured with a transducer correlates well with directly measured intra-abdominal pressure.



CENTRAL NERVOUS SYSTEM
Intracranial pressure↑
Cerebral perfusion pressure↓
Idiopathic intracranial hypertension in morbid obesity

CARDIOVASCULAR SYSTEM[1]
Difficult preload assessment
Pulmonary artery occlusion pressure ↑
Central venous pressure ↑
Transmural filling pressure =↘
Intra thoracic blood volume index =↘
Global end-diastolic blood volume index =↘
Extravascular lung water =↗
Stroke volume variation ↗
Pulse pressure variation ↗
Right ventricular end-diastolic volume =↘
Cardiac output ↓
Venous return ↓
Systemic vascular resistance ↑
Venous thrombosis ↑
Pulmonary embolism ↑
Heart rate ↗=
Mean arterial pressure ↗=↘
Pulmonary artery pressure ↑
Left ventricular compliance ↓
Left ventricular regional wall motion ↓

HEPATIC SYSTEM
Hepatic arterial flow ↓
Portal venous blood flow ↓
Portocollateral flow ↑
Lactate clearance ↓
Glucose metabolism ↓
Mitochondrial function ↓
Cytochrome p450 function ↓
Plasma disappearance rate
Indocyanine green ↓

GASTROINTESTINAL SYSTEM
Abdominal perfusion pressure ↓
Celiac blood flow ↓
Superior mesenteric artery blood flow ↓
Blood flow to intra-abdominal organs ↓
Mucosal blood flow ↓
Mesenteric vein compression ↑
Intramucosal pH ↓
Regional CO2 ↑
CO2 gap ↑
Success enteral feeding ↓
Intestinal permeability ↑
Bacterial translocation ↑
Multiple organ failure ↑
Gastrointestinal ulcer (re)bleeding ↑
Variceal wall stress ↑
Variceal (re)bleeding ↑
Peritoneal adhesions ↑

RESPIRATORY SYSTEM,
Intrathoracic pressure ↑
Plueral pressure ↑
Functional residual capacity ↓
All lung volumes ↓
(~restrictive disease)
Auto-PEEP ↑
Peak airway pressure ↑
Plateau airway pressure ↑
Dynamic compliance ↓
Static respiratory system compliance ↓
Static chest wall compliance ↓
Static lung compliance =
Hypercarbia ↑
PaO2 ↓ and PaO2/FiO2 ↓
Dead-space ventilation ↑
Intrapulmonary shunt ↑
Lower inflection point ↓
Upper inflection point ↑
Extravascular lung water=↗
Prolonged ventilation
Difficult weaning
Activated lung neutrophils ↑
Pulmonary inflammatory infiltration ↑
Alveolar edema ↑
Compression atelectasis ↑

RENAL SYSTEM
Renal perfusion pressure ↓
Filtration gradient ↓
Renal blood flow ↓
Diuresis ↓
Tubular dysfunction ↑
Glomerular filtration rate ↓
Renal vascular resistance ↑
Renal vein compression ↑
Compression ureters ↑
Anti-diuretic hormone ↑
Adrenal blood flow=
Abdominal wall complications in CAPD ↑

ABDOMINAL WALL
Compliance ↓
Rectus sheath blood flow ↓
Wound complications ↑
Incisional hernia ↑

ENDOCRINE SYSTEM
Release pro-inflammatory cytokines ↑ (IL-1b, TNF-a, IL-6)

[1] Cardiovascular effects are exacerbated in case of hypovolemia, hemorrhage, ischemia and high PEEP ventilation

FIG. 45.4. The systemic effects of ACS.

to the thorax through an intact rib cage. The increased IAP causes an increase in intrathoracic pressure that results in a decrease in cardiac output (CO).

The effects of IAH and ACS on the Central Nervous System (CNS) have not been extensively studied to date, and remain a challenging area for laboratory and clinical investigators.

Because of the interactions between intra-abdominal, intrathoracic, and intracranial pressures, accurate monitoring of IAP in head trauma victims with associated intra-abdominal lesions is worthwhile.

The presence of increased IAP can be an additional "extracranial" cause of intracranial hypertension in patients with abdominal trauma without overt craniocerebral lesions.

Laparoscopy in the acute post-traumatic phase is more foe than friend, and a recent head injury should be considered an absolute contraindication for laparoscopic procedures.[47–52]

Cardiovascular Function

When IAP rises above 10 mmHg, CO drops because of an increase in afterload (Fig. 45.5). Systemic vascular resistance

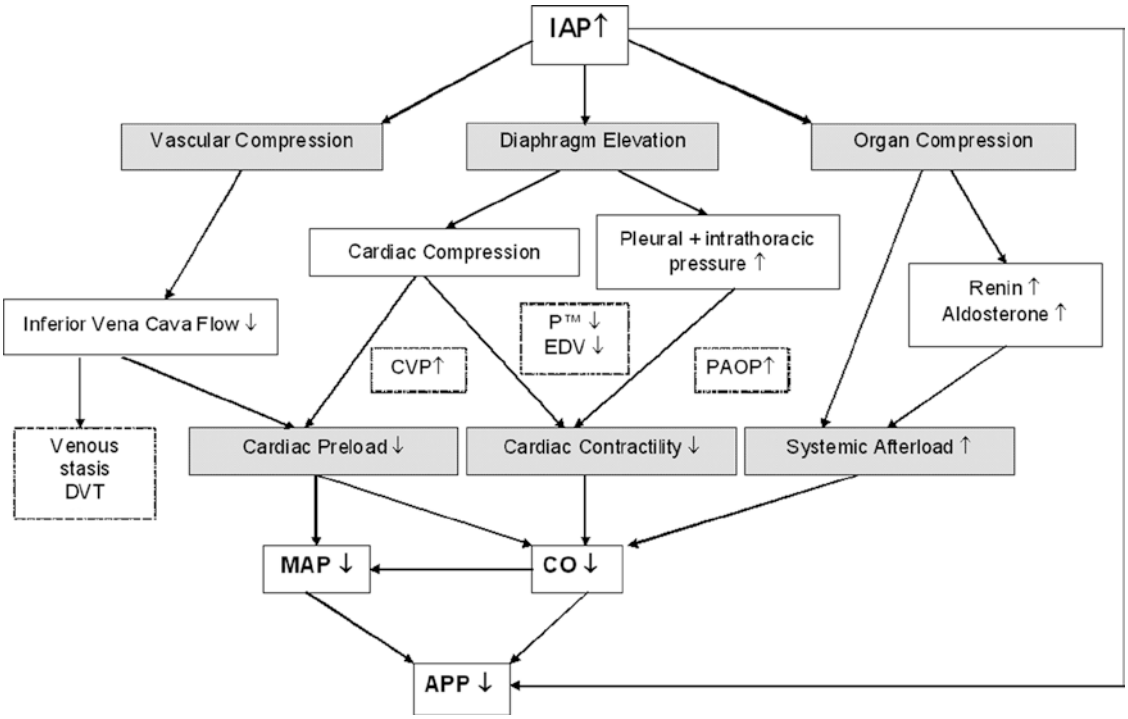


FIG. 45.5. Cardiovascular effects of IAH.

(SVR) increases due to mechanical compression of vasculary beds and a reduction in preload (because of drop in stroke volume and a reduction of venous return).[53–56] Mean arterial blood pressure may initially rise due to shunting of blood away from the abdominal cavity but thereafter normalizes or decreases. Heart rate usually rises, as well as filling pressures.[9,57]

Cardiovascular dysfunction and failure (low CO, high SVR) are common in IAH or ACS. Accurate assessment and optimization of preload, contractility, and afterload are essential to restore end-organ perfusion and function. Our understanding of traditional hemodynamic monitoring techniques and parameters, however, must be reevaluated in IAH/ACS since pressure-based estimates of intravascular volume, like pulmonary artery occlusion pressure (PAOP) and central venous pressure (CVP), can be misleading.

The clinician must be aware of the interactions between intrathoracic pressure (ITP), IAP, positive end-expiratory pressure (PEEP), and intracardiac filling pressures; misinterpretation of the patient's minute-to-minute cardiac status may result in the institution of inappropriate and potentially detrimental therapy. Transmural (TM) filling pressures calculated as the end-expiration value (ee) minus the intrathoracic pressure (ITP) might better reflect preload:

$$CVP^{TM} = CVPee - ITP$$

$$PAOP^{TM} = PAOPee - ITP$$

A quick estimate of transmural filling pressures can also be obtained by subtracting half of the IAP from the end-expiratory filling pressure:

$$CVP^{TM} = CVPee - ITP/2$$

$$PAOP^{TM} = PAOPee - ITP/2$$

The surviving sepsis campaign guidelines targeting initial and ongoing resuscitation toward a CVP of 8–12 mmHg[58] should be interpreted with caution in case of IAH/ACS to avoid unnecessary over- and under-resuscitation.

Volumetric estimates of preload status – such as right ventricular end diastolic volume index (RVEDVI), global end-diastolic volume index (GEDVI), or intrathoracic blood volume index (ITBVI) – are especially useful in such patients with changing ventricular compliance and elevated ITP related to IAH.[56,59–62] Functional hemodynamic parameters such as SVV, PPV, or SPV should be used to assess volume responsiveness.[63] Application of a goal-directed resuscitation strategy may improve cardiac function and reverse end-organ failure.

Respiratory Function

The interactions between the abdominal and the thoracic compartment pose a specific challenge to the physicians working in the ICU and the emergency and operating room.[64] Both compartments are linked via the diaphragm; and on average a 50% transmission of IAP to the intrathoracic pressure has been noted in previous animal and human studies (range 25–80%).[56] Patients with primary ACS will often develop a secondary acute respiratory distress syndrome (ARDS) and will require a different ventilatory strategy and more specific treatment than a patient with primary ARDS.[65,66] The major problem lies in

the diminished total respiratory system compliance resulting in a low functional residual capacity (FRC) and low lung volumes mimicking a form of restrictive lung disease. Together with the alterations caused by secondary ARDS, this will lead to the so-called "baby-lungs." Some key-issues to remember are:

- IAH decreases total respiratory system compliance by a decrease in chest wall compliance, while lung compliance remains unchanged.[67,68]
- Best PEEP should be set to counteract IAP while at in the same time avoiding over-inflation of already well-aerated lung regions:

$$\text{Best PEEP} = \text{IAP}$$

The ARDS consensus definitions should take into account PEEP and IAP values.

During lung-protective ventilation, the plateau pressures should be limited to transmural plateau pressures below 35 cmH_2O instead of the classical alveolar plateau pressures measured by the ventilator:

$$\text{Pplat}^{TM} = \text{Pplat} - \text{IAP}/2$$

The PAOP criterion in ARDS consensus definitions is futile in case of IAH and should be adapted since most patients with IAH and secondary ARDS will have filling pressures above the 18 mmHg definition cutoff.

The presence of IAH dramatically increases lung edema, especially in cases of direct lung injury or capillary leak; with this concept in mind, monitoring of extravascular lung water index (EVLWI) seems warranted.[69] The combination of capillary leak, positive fluid balance, and raised IAP places the patient at an exponential danger for lung edema. Body position adversely affects IAP, and putting an obese patient in the upright position can cause ACS.[70] Conversely, permitting the abdomen to hang freely during prone positioning and placing a patient in an anti-Trendelenburg position may improve respiratory mechanics.[71]

The use of muscle relaxants should be balanced against the beneficial effect on abdominal muscle tone resulting in decrease in IAP and improvement of APP. However, the more cranial position of the diaphragm during paralysis (especially in conditions of IAH or ACS) may worsen lung mechanics, resulting in atelectasis and infection.[72]

The presence of IAH will lead to pulmonary hypertension via increased intrathoracic pressures with direct compression on lung vessels and via the diminished left and right ventricular compliance. In this case, the administration of inhaled nitric oxide (NO) or ilomedine (prostacyclin) may be justified.

Renal Function

Intra-abdominal hypertension (IAH) has been associated with renal impairment for over 150 years.[1] It is only recently, however, that a clinically recognized relationship has been found.[10,73] One of the most dramatic sequelae of increased IAP is the effect on renal function and urine output. An increasing number of large clinical studies have identified that IAH (≥15 mmHg) is independently associated with renal impairment and increased mortality.[11,74] The etiology of these changes is not well established and may be multifactorial: reduced renal perfusion, reduced cardiac output, and increased systemic vascular resistance, and alterations in humeral and neurogenic factors.

Renal function may be improved by paracentesis of the ascitic fluid and reduction in the IAP.[75] Prompt reduction of IAP has a dramatic effect on urine output in patients with primary and secondary IAH after trauma. Within the capsule of the kidney itself, local hematoma formation may have an adverse affect on tissue perfusion, causing a local renal compartment syndrome.[76,77]

Elevated IAP significantly decreases renal artery blood flow and compresses the renal vein leading to renal dysfunction and failure.[78] Oliguria develops at an IAP of 15 mmHg and anuria at 30 mmHg in the presence of normovolemia, and at lower levels of IAP in the patient with hypovolemia or sepsis.[79,80] Renal perfusion pressure (RPP) and renal filtration gradient (FG) have been proposed as key factors in the development of IAP-induced renal failure. Thus, changes in IAP have a greater impact upon renal function and urine production than changes in MAP. It should not be surprising, therefore, that decreased renal function, as evidenced by the development of oliguria, is one of the first visible signs of IAH. Conversely, it behooves us as clinicians to be cognizant of the fact that an elevated IAP is often the first sign of impending ACS.

Liver Function

The liver appears to be particularly susceptible to injury in the presence of elevated IAP. Animal and human studies have shown impairment of hepatic cell function and liver perfusion even with only moderately elevated intra-abdominal pressure.[81,82] Furthermore, acute liver failure, decompensated chronic liver disease, and liver transplantation are frequently complicated by IAH and ACS.[83,84] Significant IAH correlates with extra-hepatic organ dysfunction and mortality in patients undergoing liver transplantation. Thus, close monitoring and early recognition of IAH, followed by aggressive treatment of IAH and ACS, may confer an outcome benefit in patients with liver disease.

The plasma disappearance rate (PDR) for indocyanine green (ICG) correlates not only with liver function and perfusion but also with IAP.[85] Since cytochrome P 450 function may be altered in case of IAH/ACS, medication doses should be adapted accordingly.

Within the capsule of the liver itself, local hematoma formation may have an adverse affect on tissue perfusion, causing a local hepatic compartment syndrome.

With increasing IAP, there is decreased hepatic arterial flow, decreased venous portal flow and increase in the porta-collateral circulation, resulting in decreased lactate clearance, altered glucose metabolism, and altered mitochondrial function.

Splanchnic Perfusion

Intra-abdominal hypertension has profound effects on splanchnic organs, causing diminished perfusion, mucosal acidosis, and setting the stage for multiple organ failure.[86] If uncorrected, IAH will result in abdominal compartment syndrome and increase morbidity and mortality. The pathologic changes are more pronounced after sequential insults of ischemia-reperfusion and IAH. It appears that IAH and ACS may serve as the second insult in the two-hit phenomenon of the causation of multiple-organ dysfunction syndrome.[87,88]

- IAP inversely correlates with intramucosal pH (pHi).[89–91]
- IAP inversely correlates with ICG-PDR.[85]
- IAH triggers a vicious cycle leading to intestinal edema, ischemia, bacterial translocation, and, finally, MODS.[92–94]
- Maintenance of adequate perfusion pressure (APP > 65 mmHg) is mandatory.[6]

In the future, we will be looking at the back pressure at the venous side, making pressure-flow relations even more important.

Abdominal Wall Abnormalities

Increased IAP has been shown to reduce abdominal wall blood flow by the direct, compressive effects leading to local ischemia and edema.[95] This can decrease abdominal wall compliance and exacerbate IAH.[68] Abdominal wall muscle and fascial ischemia may contribute to infectious and noninfectious wound complications (e.g., dehiscence, herniation, necrotizing fasciitis) often seen in this patient population.

Multiple Organ Failure

Recent clinical studies have demonstrated a temporal relationship between ACS and subsequent multiple organ failure (MOF).[17,86,96] In animals, ACS provokes cytokine release and neutrophil migration resulting in remote organ failure. In humans, ACS results in splanchnic hypoperfusion that may occur in the absence of hypotension or decreased cardiac output. This ischemia and reperfusion injury to the gut serves as a second insult in a two-hit model of MOF where the lymph flow conducts gut-derived pro-inflammatory cytokines to remote organs.

With the advent of new studies, the interplay among IAP, intramucosal pHi, and increased gut permeability (as demonstrated by bacterial translocation) becomes clearer. The association between increased gut permeability and the development of MOF and death has also been recently demonstrated. The question still remains whether increased IAP is the cause or an epi-phenomenon in the emergence of MOF. Nonbelievers will point toward IAP as a mere side effect of the resuscitative efforts in trauma, septic, or burn patients, whereas believers will point toward the direct negative effects of increased IAP on organ perfusion increasing intestinal and capillary permeability, and requiring ongoing resuscitation that will eventually lead to a vicious cycle.

Importance of Iap in Other Clinical Conditions

IAH and Lymphatic Drainage

From recently published data,[97] we hypothesize the following events occurring during sepsis:

- Induction of sepsis causes capillary alveolar barrier damage, with a subsequent increase in the water content in the pulmonary interstitium.
- The pulmonary lymphatic flow progressively increases, in order to maintain the water homeostasis of the pulmonary interstitium, with a subsequent increase in the lymphatic thoracic pressure.
- Sepsis increases the permeability of the endothelium in the lungs but also in the splanchnic bed, with a consequent similar increase in the lymphatic flow.
- When the full drainage capacity of the lymphatics is reached, the amount of edema in the pulmonary and splanchnic interstitium increases dramatically.
- This favors development of alveolar edema in the lung and peritoneal edema in the abdomen, with consequent increase in IAP.
- The alveolar edema and increased IAP (critical value = 20 cmH_2O) further compress lymphatic vessels deteriorating their drainage capacity.
- Direct movement of fluids from the abdomen to the thorax and from the thorax to the abdomen via the diaphragm are partially impeded by the morphological network of lymphatics in the diaphragm.
- Positive pressure MV with PEEP reduces the drainage of lymph from the lungs because of decreased net translymphatic pressure gradient and increased IAP.
- This finally decreases the lymphatic pressure gradient in the splanchnic regions, with a further increase in water content and IAP, triggering the vicious cycle.

Although often ignored because of its complexity, the role of lymphatics is extremely important to determine the fluid balance in the lung and peripheral organs. Different pathology and management can influence the response of the lymphatics with dramatic effects on end-organ function.[98–100]

ACS in Burn Patients

Patients with large burns (50% of body surface or greater) or with associated inhalation injuries are at risk of developing IAH.[18] Patients with burns that are very large, greater than 70% total body surface area (TBSA), are at the risk of developing ACS, particularly if they have a concurrent inhalation injury. The development of IAH and ACS is related to the volume of crystalloid fluid infused during the burn resuscitation and does not require abdominal injury or operation or even the presence of abdominal wall burn eschar.[18,102–107]

Burn patients are also at risk for developing IAH and ACS during subsequent septic episodes.

A variety of management options exist for IAH including observation, sedation, pharmacologic paralysis, abdominal wall escharotomy, and percutaneous catheter decompression of the peritoneal cavity.[104,107] Options for the management of ACS include the standard decompressive laparotomy and, in some cases, percutaneous catheter decompression. Most patients who require intervention improve significantly. However, these patients have very large burns, often severe inhalation injuries, and frequently die later in their hospitalization from complications of their burns that are unrelated to their ACS.

- Burn patients are at great risk to develop large volume resuscitation-related secondary ACS.
- Burn patients who develop IAH mostly have more than 50% TBSA burns.
- Burn patients who develop ACS mostly have more than 75% TBSA burns and concurrent inhalation injury.

Paracentesis with continuous draining of ascites combined with albumin replacement might be of some benefit

ACS in Hematologic Patients

Recent studies have alluded to the increased incidence and consequences of IAH in hematological patients.[108] The causes are multifactorial:

- Growth-factor-induced capillary leak syndrome with concomitant large volume fluid resuscitation and third-space sequestration.
- Chemotherapy-induced ileus, colonic pseudo-obstruction (Ogilvie's syndrome), mucositis, or gastroenteritis.
- Sepsis and infectious complications aggravating intestinal and capillary permeability.
- Extramedullary hematopoiesis as seen with chronic myeloid leukemia resulting in hepatosplenomegaly, chronic IAH, and chronic (irreversible) pulmonary hypertension.
- The mechanisms of veno-occlusive disease seen after stem cell transplantation may be triggered by or related to increased IAP.

IAP During Pregnancy

In the second and the third trimester of pregnancy, the uterus occupies a major part of the abdominal cavity, and, in the supine position, dyspnea and a decrease in blood pressure ("supine hypotension syndrome") are common.[109] These symptoms are due to the restriction of the diaphragm and compression of the inferior vena cava. However, overall IAP is usually not elevated.[110] Furthermore, the symptoms are alleviated in the lateral, sitting, or standing positions. Owing to hormonal influence during pregnancy, the abdominal wall is slowly stretched, increasing its compliance, which reduces the potential for increase in IAP caused by the expanding uterus. However, if IAP increases due to other reasons (e.g., pneumoperitoneum at laparoscopy), perfusion of the uterus and the fetus might be severely compromised.[111]

ACS in Morbidly Obese Patients

Recent studies show that obese patients have higher baseline IAP values.[112] As with IAH in the critically ill, elevated IAP in the morbidly obese patient can have far-reaching effects on end-organ function. Disease processes common in morbidly obese patients – such as obesity hypoventilation syndrome, pseudotumor cerebri, gastroesophageal reflux, and stress urinary incontinence – are now being recognized as being caused by the increased IAP occurring with an elevated body mass index.[50,113,114] Furthermore, the increased incidence of poor fascial healing and incisional hernia rates have been related to the IAH-induced reductions in rectus sheath and abdominal wall blood flow.

- IAH-related complications of morbid obesity generally respond to weight loss.[52]
- The morbidly obese are at a greater risk of developing ACS because of preexisting baseline IAH and organ dysfunction.
- Clinicians should have a low threshold for monitoring IAP in obese patients because of the so-called "silent IAH."
- IAH and ACS are no longer regarded as solely a disease of the critically ill.

Clinical Management and Medical Treatment

The management of patients with IAH is based on three principles[115,116]:

1. Specific procedures to reduce IAP and the consequences of ACS
2. General support (intensive care) of the critically ill patient
3. Optimization after surgical decompression to counteract some of the specific adverse effects associated with decompression

Before surgical decompression is considered, less-invasive medical management should be optimized. Different treatment strategies have been suggested to decrease IAP.[7] These include the use of paracentesis, gastric suctioning, rectal enemas, gastroprokinetics (cisapride, metoclopramide, domperidone, erythromycin), colonoprokinetics (Prostygmine), furosemide either alone or in combination with human albumin 20%, continuous venovenous hemofiltration with aggressive ultrafiltration, continuous negative abdominal pressure, and, finally, sedation and curarization. An algorithm for the clinical management of IAH and ACS is proposed in Fig. 45.6 while Table 45.3 gives an overview of the different medical treatment options available.

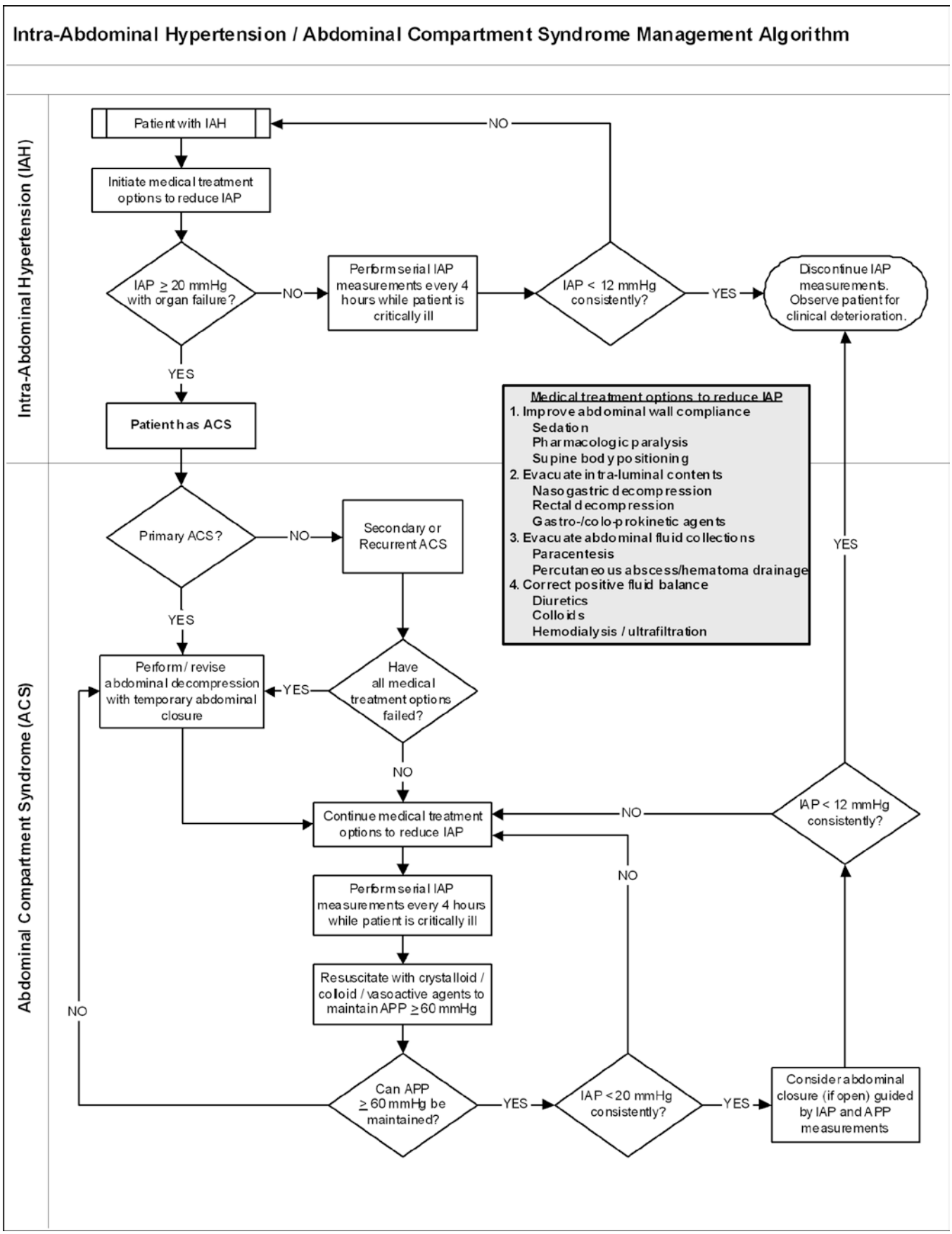


FIG. 45.6. Intra-abdominal hypertension and abdominal compartment syndrome management algorithm.

Table 45.3. Medical treatment options for IAH and ACS.

1. Improvement of abdominal wall compliance
   - Sedation
   - Neuromuscular blockade
2. Evacuation of intraluminal contents
   - Gastric tube and suctioning
   - Gastroprokinetics (erythromycin, cisapride, metoclopramide)
   - Rectal tube and enemas
   - Colonoprokinetics (neostygmine, Prostygmine bolus or infusion)
   - Endoscopic decompression of large bowel
3. Evacuation of peri-intestinal and abdominal fluids
   - Ascites evacuation
   - Percutaneous drainage of collections
4. Correction of capillary leak and positive fluid balance
   - Albumin in combination with diuretics (furosemide)
   - Dialysis or ultrafiltration
5. Specific therapeutic interventions
   - Continuous negative abdominal pressure (CNAP)
   - Negative external abdominal pressure (NEXAP)
   - Targeted abdominal perfusion pressure (APP)
   - (experimental: Octreotide and melatonin in secondary abdominal compartment syndrome)

Improvement of Abdominal Wall Compliance

The relation between abdominal contents and IAP is not linear but exponential. Depending on the compliance of the abdominal wall, the curve will be shifted to the left. In septic patients, abdominal wall compliance changes over time and is dependent upon the baseline IAP. Recent studies have shown that the application of sedation can help to control IAH by increasing abdominal wall compliance. The administration of muscle relaxants has been shown to decrease IAP, a phenomenon known for a long time in the operating room.[8,72,117–119] Fentanyl, on the contrary, may acutely increase IAP by stimulation of active phasic expiratory activity.[120] In obese patients, weight loss resulted in a subsequent decrease in IAP.[52] Body positioning and the use of skin pressure decreasing interfaces will also affect IAP.[71,85,121]

Evacuation of Intra-Luminal Contents

Ileus is common in most critically ill patients and, in particular, in those who have had abdominal surgery, peritonitis, major trauma, massive fluid resuscitation, electrolyte abnormalities, and the administration of narcotics and sedative hypnotics.

In view of the abdominal pressure volume relationship, any alteration in one of its contents will decrease IAP, especially in a condition of ACS with low abdominal wall compliance. Therefore, noninvasive evacuation of abdominal contents should be attempted by means of gastric tube placement and suctioning, rectal tube and enemas, and possibly endoscopic decompression.[122–125]

This treatment can be accomplished in conjunction with gastro- and or colonoprokinetics such as erythromycin (200 mg IV every 6 h), metoclopramide (10 mg IV every 8 h), neostygmine or Prostygmine (2 mg diluted in up to 50 ml IV given slowly by infusion).[126–131]

Evacuation of Abdominal Fluid Collections

Drainage of tense ascites by insertion of a small tube or single-lumen catheter may result in a decrease in IAP.[26,75,132–134] In patients with liver cirrhosis and esophageal varices, paracentesis can help to decrease variceal wall tension as well as the risk for rupture and bleeding.[135] Paracentesis is also the treatment of choice in burn patients with secondary ACS.[107,136,137] With hematomas, blood collections, or a local abscess, CT-guided fine-needle aspiration has recently been described in the setting of IAH and ACS.

Since no low-morbidity procedure is available to decompress ACS, Voss developed a percutaneous procedure to increase abdominal capacity and to decrease IAP, based on the principles of abdominal wall components separation.[138] This minimally invasive procedure was feasible and effective in a porcine model of ACS. In burn patients, a similar procedure had the same beneficial effects.[107]

Correction of Capillary Leak and Positive Fluid Balance

In the initial phase, hemorrhage or fluid loss should be compensated in order to prevent splanchnic hypoperfusion.[139–141] The combination of hypovolemia and PEEP seems to aggravate the pathophysiologic effects of IAH.[142–145] Low-dose infusion of dobutamine, but not dopamine, also corrects the intestinal mucosal perfusion impairment induced by moderate increases in intra-abdominal pressure.[146] Because of the nature of the illness and injury associated with ACS, these patients retain large volumes of sodium and water after the initial resuscitation. Because of the capillary leak, this will exacerbate tissue edema and third spacing. In the early stages, diuretic therapy in combination with albumin can be considered to mobilize the edema, but only if the patient is hemodynamically stable. In some cases, it is preferable to give colloids or albumin instead of crystalloids.[147,148] In burn patients, the coadministration of ascorbic acid results in reduced fluid requirements.[149,150] However, many patients will develop oliguria and anuria as the renal blood flow is reduced. In these cases, the institution of renal replacement therapy should not be delayed.[151–153]

Specific Treatments

Recently, the application of continuous negative abdominal pressure by means of a cuirass has been studied in animals and humans, showing a decrease in IAP and increase in end-expiratory lung volumes.[42,46,154–156]

Gattinoni recently demonstrated that the application of external negative abdominal pressure (NEXAP) was able to decrease IAP in 30 ICU patients; however, baseline IAP values were quite low.[155]

In a similar manner to targeting cerebral perfusion pressure (CePP = MAP − ICP) or coronary perfusion pressure (CoPP = DBP − PAOP), it may be appropriate to target

abdominal perfusion pressure (APP), where APP = MAP – IAP, to a level that reduces the risk of worsened splanchnic perfusion and subsequent organ dysfunction, although this needs to be clinically validated.[6,7,56] Traditional resuscitative endpoints include titrating fluids toward a central venous pressure (CVP)[58] of 8 to 12 mmHgand a MAP[157] of 65 mmHg. In the case of IAH or ACS, this strategy may lead either to under-resuscitation or unnecessary over-resuscitation.

Octreotide is a long-acting somatostatin analog that has been studied primarily in animals. It has shown to have the ability to control neutrophil infiltration and improve the reperfusion-induced oxidative damage after decompression of intra-abdominal hypertension.[158]

Melatonin, a secretory product of the pineal gland known to have free radical scavenging and antioxidative properties, has recently been shown to reduce lipid peroxidation in cell membranes, a process that promotes cell death as the functional integrity of these structures is damaged.[159] Melatonin also has anti-inflammatory effects and inhibits the activation of neutrophils by free radicals. In rats, melatonin reduces reperfusion-induced oxidative organ damage.

Surgical Treatment

Abdominal Decompression

Although decompression remains the only definite management for ACS, the timing of this procedure still remains controversial. During the intervention, specific anesthetic challenges need to be solved, and after decompression the patient is at risk for ischemia-reperfusion injury, venous stasis, and fatal pulmonary embolism.[160] Maintaining adequate preload and abdominal perfusion pressure are the keys to success.[141] Open abdomen treatment (or laparostomy) was initially intended for patients with diffuse intra-abdominal infections, and often used in combination with a planned re-laparotomy approach. Owing to the increased awareness of the deleterious effects of intra-abdominal hypertension, open abdomen treatment – either prophylactic or therapeutic – is more common in the ICU.[17,161]

Several methods for temporary abdominal closure (TAC) are [AU6] available as below:*Moist gauze* closure was once the preferred method of covering the abdomen, but this is no longer used as it carries a substantial risk of creating intestinal fistulas (Fig. 45.7).

Towel clip closure is often used as an initial method of TAC after damage control surgery, because of the speed of closure (Fig. 45.8). After re-exploration, it can be replaced by one of the following techniques:

In the *Bogota bag* method, a plastic sheet is cut from a sterile 3 L irrigation bag and sewn to the skin or fascia (Fig. 45.9). This system is inexpensive and offers an advantage in that the bowel and abdominal contents can be easily inspected and accessed. However, fluid losses are difficult to control, which makes it a real challenge for the nursing staff.

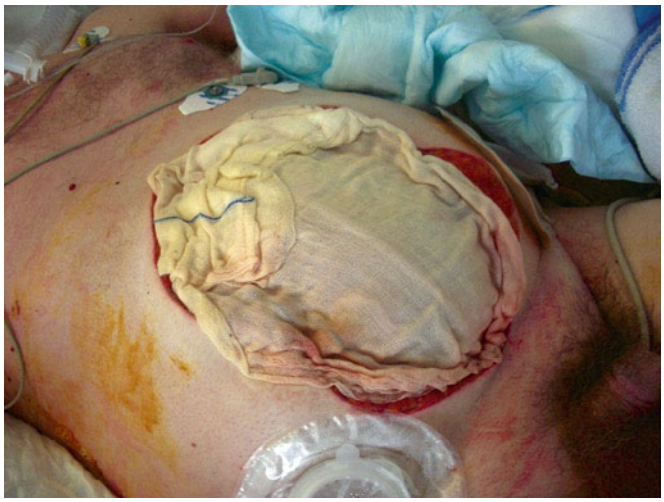


FIG. 45.7. Temporary abdominal closure: moist gauze.

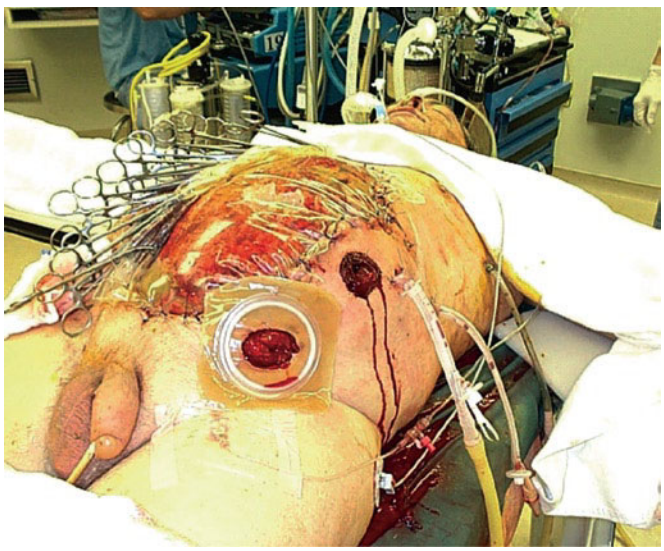


FIG. 45.8. Temporary abdominal closure: towel clip closure.

Removable prosthetic materials are those used initially in the open abdomen treatment of intra-abdominal sepsis, and can be used for TAC in other circumstances as well (Fig. 45.10). Examples are the zippers and the Wittman patch (which uses a Velcro closure system), etc.

In the *Vacuum-assisted fascial closure* (VAFC) systems (Fig. 45.11), different packing techniques that use suction or vacuum to control the fluid draining from the open abdomen have been described (the vacuum pack technique and modified sandwich vacuum pack technique, or Vacuum- Assisted Closure system). These are simple solutions for the management of open abdomen and provide easy control and quantification of fluid losses.

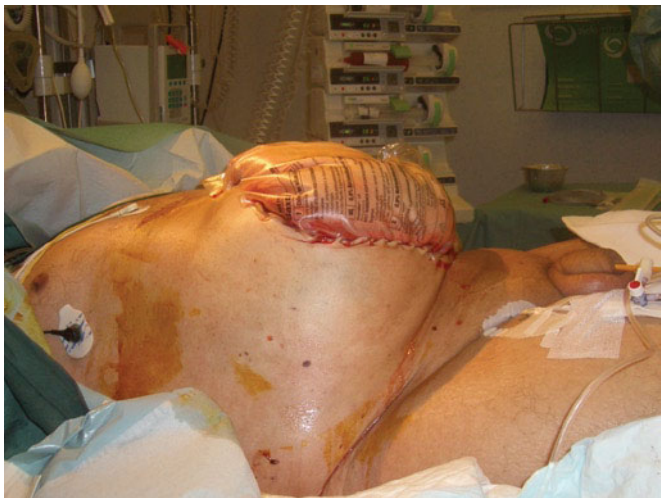


FIG. 45.9. Temporary abdominal closure in a patient with abdominal compartment syndrome with a so-called "Bogota bag."

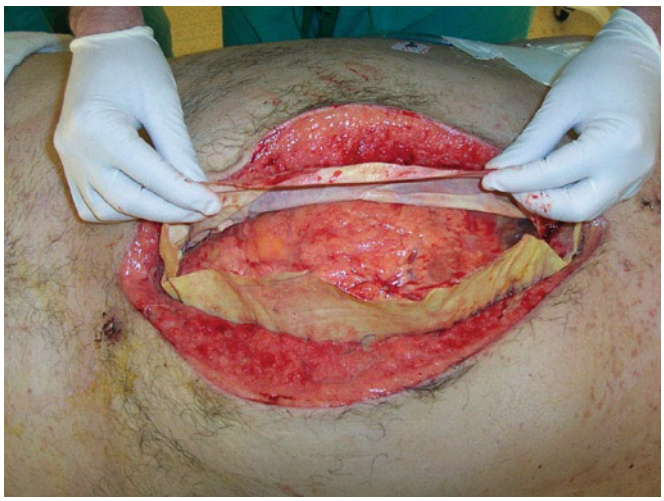


Fig. 45.10. Temporary abdominal closure: Wittman patch.

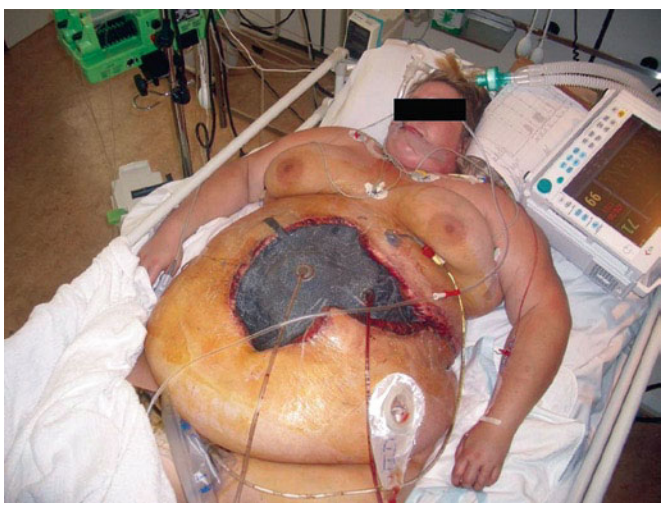


FIG. 45.11. Temporary abdominal closure: Vacuum-assisted fascial closure.

Planned Re-laparotomy vs. On-Demand Laparotomy

In some patients, one surgical procedure will not suffice to treat the intra-abdominal problem. The most common examples are intra-abdominal infection and intestinal ischemia. The IAP will guide the physician in choosing the best treatment options (Fig. 45.6).

Planned Re-laparotomy

A surgical intervention is planned after an initial procedure, often because of massive contamination or ischemic bowel, irrespective of the patient's condition.

On-Demand Laparotomy

A surgical procedure is only performed when a postoperative problem is suspected on clinical grounds, such as an enteral leak or abdominal abscess.

Conclusions

First suggested in 1863 by Marey, ACS, is a constellation of the physiologic sequelae of increased IAP, termed IAH. Recent observations suggest an increasing frequency of this complication in all types of patients, neonates to the elderly; and in diverse clinical conditions, surgical to nonsurgical. Even chronic elevations of IAP seem to affect the various organ systems in the body. The presence of IAH and ACS are significant causes of organ failure, increased resource utilization, decreased economic productivity, and increased mortality among a wide variety of patient populations.[24]

Despite its obvious clinical implications, attention is not paid to IAP and IAH. ACS still is not uniformly appreciated or diagnosed. Only a few medical and surgical intensivists believe in the concept of IAH and actively attempt its prevention and treatment [30]. The result, as is strongly substantiated by retrospective and prospective data, is a successful reduction in organ failures and mortality.

The literature on IAH and ACS has exponentially increased in the last decade. Several unanswered questions, however, cloud our understanding of the pathophysiology of elevated IAP. What is the ideal method of measuring IAP? What level of IAP is critical that needs abdominal decompression? Is it a level at which the classic manifestations of ACS become evident? Or is it a level at which subtle changes in physiology predates the development of ACS? Which is more important: IAP or abdominal perfusion pressure (APP)?

Considerable progress has been made over the past decade, but there is significant work yet to be done. We must study and learn from the past and, at the same time, proactively "invent" the future. As aptly described by Dr. Ivatury,[162] IAH/ACS is "…a clinical entity that had been ignored for far too long… the mystery of IAH and ACS continues to unfold, transgressing

the boundaries of acute and chronic illness and medical and surgical specialties." The future of IAH and ACS is in our hands, and the results of recent multicenter studies confirm the importance of IAH and ACS on patient outcome.[163–166]

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46
Rhabdomyolysis

Flávio E. Nácul and John M. O'Donnell

Rhabdomyolysis is a potentially life-threatening syndrome resulting from the destruction or disintegration of striated muscle with leakage of muscle enzymes, myoglobin, potassium, phosphate, uric acid, and other intracellular constituents into the bloodstream.

Accounts of rhabdomyolysis can be found as far back as the Old Testament, which reported a condition with characteristics similar to those of rhabdomyolysis that affected the Jews during their exodus from Egypt, following abundant consumption of quail. This condition was assumed to have been caused by intoxication with hemlock herbs that quails consume during their spring migration.[1] The earliest modern report of rhabdomyolysis appears in the German literature, which describes the classic triad of muscle pain, weakness, and dark urine in German soldiers who were buried in and rescued from trenches during World War I.[2] More recently, Bywaters and Beall first associated crush injuries with dark urine, shock, and renal failure in patients who were bombing casualties during World War II.[3] In 1943, Bywaters and Stead used an animal model to identify the offending agent as myoglobin.[4] Since that time, rhabdomyolysis has become recognized as a common cause of acute kidney injury (AKI), with the estimated risk of AKI following rhabdomyolysis ranging from 4 to 33%.[5,6]

Etiology

The causes of rhabdomyolysis can be broadly divided into traumatic and nontraumatic (Table 46.1). Single episodes are most commonly caused by physical factors such as trauma, infections, or drugs. A history of recurrent episodes or a family history suggests a genetically determined metabolic myopathy. Cocaine abuse, exercise, and prolonged immobilization were identified as the most frequent causes of rhabdomyolysis in patients admitted to the emergency department of a large urban hospital in the United States.[7]

Selected Causes

Cocaine

In a growing number of cases, cocaine use has been implicated in the development of rhabdomyolysis and acute renal failure. The mechanism of cocaine-associated rhabdomyolysis is unclear, but it potentially includes ischemia caused by vasoconstriction, direct toxicity, hyperpyrexia, and increased muscle activity from agitation or seizure.[8]

Exercise

Strenuous exercise, including marathon running, can cause rhabdomyolysis, especially in runners who have not trained sufficiently or in individuals who are exercising under extremely hot or humid conditions. Potassium is essential for vasodilation of the muscles' microvasculature; in hypokalemic patients, because exercise would not be accompanied by sufficient muscle blood flow, rhabdomyolysis could occur as a result of ischemia.[9–11]

Injuries

Many cases of severe rhabdomyolysis seen in the surgical intensive care unit are the result of trauma. Traumatic rhabdomyolysis, is mainly the result of traffic or occupational accidents, but may occur, for example, secondary to the collapse of a multistory building.

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Table 46.1. Causes of rhabdomyolysis.

Traumatic causes
Direct muscle injury
Exertional injury
Extreme physical exercise
Seizures
Ischemia-reperfusion injury
Vascular injury repair
Compartment syndromes
Thermal injury
Electrical injury
Recumbence injury
Operative-positioning injury
Nontraumatic causes
Infections
Viral
Influenza
Human immunodeficiency virus
Coxsackievirus
Epstein–Barr virus
Bacterial
Legionella
Streptococcus sp.
Francisella tularensis
Metabolic disorders
Diabetes
Hypothyroidism
Electrolyte imbalances
Medications
Amphotericin B
Monoaminooxidase inhibitors
Toxins
Drugs of abuse
Ethylene glycol
Organic solvents
Heavy metals
Insect bites
Genetic disorders
Metabolic disorders
Autoimmune diseases
Polymyositis
Dermatomyositis

Crush Syndrome is caused by prolonged mechanical compression of skeletal muscle, resulting in hypoperfusion and hypoxia of the muscle.

Operative-Positioning Injury

Rhabdomyolysis has been reported from surgical positioning, including those in prone, supine, lithotomy, and lateral decubitus positions. It is more common in patients with elevated body mass index who undergo surgeries lasting longer than 4 h. Elevations in the serum creatinine kinase (CK) concentration or reports of buttock, hip, or shoulder pain in the postoperative period should raise the possibility of rhabdomyolysis and prompt clinical investigation. Routine preoperative and postoperative measurements of the serum CK and serum creatinine levels to aid detection is recommended following high-risk procedures.[12]

Statins

HMG-CoA reductase inhibitors, including simvastatin, are among the most frequently prescribed classes of medications in the United States, with more than 15 million Americans taking these drugs. Relatively rare adverse effects related to the known toxic effects of these drugs are more common than generally realized. Clinically significant statin-induced rhabdomyolysis is an uncommon but life-threatening adverse effect. Reports of myopathy and rhabdomyolysis with statins are a reminder to prescribers to measure creatine kinase levels in patients presenting with muscle pain or weakness.[13]

Propofol

Propofol (2,6-diisopropylphenol) is a potent intravenous hypnotic agent that is widely used in adults and children for sedation and for the induction and maintenance of anesthesia. Propofol has gained popularity for its rapid onset and rapid recovery even after prolonged use. Over the past decade, however, increasing numbers of reports have described a potentially fatal adverse effect called propofol-related infusion syndrome (PRIS). This is characterized by metabolic acidosis, rhabdomyolysis of both skeletal and cardiac muscle, arrhythmias, myocardial failure, renal failure, hepatomegaly, and death. There is an association between PRIS and propofol infusions at doses higher than 4 mg $kg^{(-1)}h^{(-1)}$ for longer than 48 h. Some research suggests that the syndrome may be caused by either a direct mitochondrial respiratory chain inhibition or an impaired mitochondrial fatty-acid metabolism mediated by propofol anesthesia.[14,15]

Malignant Hyperthermia

Malignant hyperthermia is a fulminant life-threatening disease characterized by hypermetabolism, muscle rigidity, muscle injury, and increased sympathetic nervous system activity. Trigger agents for malignant hyperthermia include all potent inhalational agents and depolarizing muscle relaxants. Malignant hyperthermia should be suspected when the patient presents with unexplained tachycardia, increased end-tidal CO2, decreased oxygen saturation (SpO2), and increased body temperature associated with muscle rigidity, cardiac arrhythmias, metabolic acidosis, hyperkalemia, increased CK, and myoglobinuria. Treatment includes supportive measures and the administration of dantrolene.[16]

Pathophysiology

Although the mechanism of muscle injury in traumatic rhabdomyolysis is self-evident, the precise mechanisms of muscle injury in nontraumatic rhabdomyolysis are not as clear.

In rhabdomyolysis there is a decrease in the function of sodium-potassium adenosine triphosphatase that results in the inability of the myocyte to extrude sodium from the cytoplasm. This results in sarcoplasmatic influx of water, which

produces cell swelling; the influx of calcium in exchange for sodium; the activation of vasoactive molecules and proteases; and the development of free oxygen radicals. The result is a myolytic reaction and cell death.

Myoglobin, potassium, lactic acid, phosphate, uric acid, sulfate, and other substances are released into the bloodstream. The injured muscle sequesters calcium and solute, lowering serum calcium and reducing intravascular volume. Lewis and Dalakas[17] provided evidence that as much as 12 L of fluid may extravasate into the lower extremities after extensive muscle injury, resulting in severe extracellular fluid (ECF) volume contraction.

There are three main mechanisms by which rhabdomyolysis can lead to renal failure:

1. The myoglobin released into plasma is readily filteredby the glomerulus, which transiently appears in the urine as pigment casts. Volume depletion, along with release of acid components from injured muscle, causes a drop in urine pH. The low urine pH causes myoglobin to precipitate and obstruct the distal nephron. Tubular obstruction may also be caused by hyperuricemia and the deposition of urate in the tubules.
2. Myoglobin has a direct toxic effect, producing a free-radical-mediated renal injury, especially in the proximal tubule. Myoglobin is filtered in the glomerulus and reabsorbed into the proximal tubular cell where the porphyrin ring is metabolized, yielding free iron. Because very large quantities of myoglobin are present in the proximal tubular cell, overwhelming its capacity to convert the free iron into ferritin, the free-iron concentration increases and generates free radicals, leading to oxidant stress to the renal cell.[18]
3. Pathological release of myoglobin into the bloodstream causes increases in vascular resistance of vital organs such as the kidney, which may contribute to the development of renal dysfunction.[19]

Tissue thromboplastin concentrations increase and can lead to disseminated intravascular coagulation (DIC), which is an almost universal finding in patients with severe rhabdomyolysis. In most cases, DIC is diagnosed mainly by abnormalities found through laboratory testing rather than by overt clinical bleeding or thrombosis.

Diagnosis

Although careful history and physical examination serve as the foundation for making an early diagnosis, rhabdomyolysis should be suspected when a patient presents with an acute increase in serum concentrations of CK to more than five times the upper limit after myocardial infarction has been excluded as a cause.

History and Physical Examination

A high index of suspicion must be maintained in the appropriate clinical setting. Cooperative patients may complain of muscle pain, weakness in their extremities, and dark urine. Physical examination may reflect signs of significant volume depletion. The skin overlying the involved areas is occasionally bruised or hemorrhagic, and the muscle groups are often swollen, tender, and firm to palpation.

Laboratory Data

The levels of CK rise within 12 h of the injury, peak within a few days, then diminish by 50% every 48 h. In patients with severe rhabdomyolysis (CK>5,000 U/L), the serum CK levels might predict the development of acute kidney injury. Brown et al. studied 2,083 trauma intensive care unit admissions and showed that a CK level of 5,000 U/L was the lowest abnormal level associated with renal failure.[20] Ward et al.[21] found that patients with a peak serum CK concentration >16,000 U/L had the highest risk of developing acute renal failure, whereas Veenstra et al.[22] found that patients with a peak CK concentration of >15,000 U/L had significantly higher rates of acute renal failure. Although the true value of CK as an accurate prognostic tool has not been determined, a serum CK level of 10,000 U/L is suggested as the threshold for identifying those patients who are at risk and require treatment. Levels of CK should be monitored daily to document the extent of injury and its resolution.

Rhabdomyolysis is confirmed by a positive urine or serum test for myoglobin. Myoglobin is filtered by the kidney and appears in the urine when the plasma concentration exceeds 1,500 ng/mL (normal <85 ng/mL). When the urine concentration of myoglobin exceeds 250 µg/mL (normal <5 ng/mL), corresponding to the destruction of more than 100 g of muscle, it produces a tea- or cola-colored urine. Urinary myoglobin provokes a typical reddish-brown (port wine) color (Table 46.2). Myoglobinuria can be inferred by a positive dipstick for heme, in the absence of red blood cells on microscopic examination of urine. Red discoloration of the urine when erythrocytes cannot be detected by microscopy must be a result of hemoglobinuria or myoglobinuria, unless the color of the urine is caused by drugs or metabolites (Table 46.2).[23] Myoglobin has a short half-life and is rapidly cleared by renal excretion and metabolism to bilirubin. Serum myoglobin levels may return to normal within 6–8 h. Because overall degradation and removal of CK is slower, the concentration of CK remains elevated much longer than the concentration of myoglobin. Consequently, the CK level is more reliable than the myoglobin level in assessing the presence of rhabdomyolysis.[24]

TABLE 46.2. Characteristics of urine and plasma in rhabdomyolysis, hemolysis, and hematuria.

Characteristics	Rhabdomyolysis	Hemolysis	Hematuria
Red discoloration plasma	–	+	–
Positive benzidine dipstick	+	+	+
Presence of erythrocytes by urine microscopy	–	–	+
Elevated CK concentration in the blood	+	–	–

Urinary benzidine dipstick does not differentiate between myoglobin, hemoglobin, and red blood cells; *CK* creatinine kinase. (Reprinted from Vanholder R, Sever MS, Erek E, Lameire N. Rhabdomyolysis. J Am Soc Nephrol. 2000;11:1553–1561; with permission.)

A classic pattern of changes in serum electrolytes occurs in rhabdomyolysis and includes an increase in the plasma concentrations of potassium and phosphate as these components are released from the cells and a decrease in calcium as calcium moves into the cells and then gradually increases.

Aldolase, lactate dehydrogenase (LDH), and serum glutamic-oxaloacetic transaminase (SGOT) are nonspecific enzyme markers that are elevated in patients with rhabdomyolysis.

Electrocardiogram

Electrocardiogram may reveal the presence of acute hyperkalemia, including peaked T waves, prolongation of the PR and QRS intervals, and loss of the P wave.

Magnetic Resonance Imaging

Although imaging studies generally play no role in the initial diagnosis of rhabdomyolysis, a magnetic resonance imaging (MRI) with gadolinium enhancement has been found to be more sensitive than either computed tomography or ultrasound imaging in detecting muscle edema and inflammation if an area of muscle potentially undergoing rhabdomyolysis is not apparent from patient history or physical examination. An MRI is the method of choice to evaluate the distribution and extent of the affected muscles, especially when fasciotomy is considered for treatment.[25,26]

Complications

The complications of rhabdomyolysis can be classified as early or late. Early complications develop in the first 24–48 h and include electrolyte abnormalities, such as severe hyperkalemia secondary to massive muscle breakdown, causing cardiac arrhythmia. Hypocalcemia is another early complication that can be potentiated by the large amount of phosphate released from the muscle cells. Late complications develop after 24–48 h and include AKI, DIC, reversible hepatic dysfunction, and metastatic calcification. Reversible hepatic dysfunction has been reported and is characterized by elevated liver enzymes, the values of which peak within 72 h of hospitalization and last for about 2 weeks. The pathogenesis of these abnormalities is not well defined and may be multifactorial. Hyperpyrexia, hypotension, and proteases released from injured muscle may each or all be contributory.[27] Calcium-phosphate complexes deposit in tissues secondary to tissue-accumulation of calcium, and hyperphosphatemia also may occur.

Management

Volume Resuscitation

The treatment of rhabdomyolysis is primarily directed at preserving renal function. Because up to 12 L of fluid may be sequestered in the necrotic muscle tissue, volume resuscitation is the most important component in the early treatment of patients with suspected rhabdomyolysis. Intravenous hydration with 1–1.5 L of normal saline must be initiated as early as possible and followed by a continuous infusion at 200–700 mL/h with careful monitoring of central venous pressure as well as sodium and calcium concentrations. Once the patient is hemodynamically stable, intravenous fluid can be switched to 0.45 normal saline to reduce the administration of sodium and chloride. Lactated Ringer's solution should be avoided as it contains potassium. Urine output should be monitored with a Foley catheter in place until myoglobinuria has ceased. The volume administered may be much greater than the urinary output; the difference between intake and output is a result of the accumulation in the damaged muscles.

Alkalinization of the Urine

The alkalinization of urine to a pH greater than 6.5 theoretically prevents renal toxicity by decreasing renal precipitation of myoglobin. Because no large randomized prospective trials have been performed, this intervention remains controversial. Although there is no globally accepted regimen for the administration of sodium bicarbonate, it is a common practice; a sample protocol is presented in Table 46.3. Acetazolamide, a carbonic anhydrase inhibitor, may be useful if serum pH is >7.5 after bicarbonate therapy or if aciduria persists despite alkalemia. Acetazolamide will correct metabolic alkalosis and increase the urine pH.[2] The administration of sodium bicarbonate and acetazolamide can produce a mild alkalemia that theoretically may enhance metastatic calcification.

Diuresis

The use of mannitol is controversial as it is mostly supported by experimental animal and retrospective clinical studies. If oliguria persists despite adequate volume resuscitation, mannitol therapy should be used. By maintaining the glomerular filtration rate and promoting brisk diuresis, the amount of myoglobin that precipitates in the renal tubules is decreased. Mannitol can also be useful in decreasing compartmental pressure and preventing the development of a compartment syndrome.[28] Mannitol is administered as a bolus dose of 1 mg/kg followed by intermittent dosing every 4–6 h. Because mannitol can cause volume overload and a hyperosmotic state, it should be used with caution in patients with marginal cardiac function and established acute renal failure. Mannitol can also cause abnormalities in serum osmolarity and electrolytes, so frequent monitoring of both is recommended. Loop diuretics should be avoided because they have a theoretical disadvantage of acidifying the urine.

TABLE 46.3. Sample protocol for alkalinization of urine volume.

1. Administer a bolus of 100 mEq sodium bicarbonate intravenously
2. Infuse about 50 mEq/h of sodium bicarbonate intravenously
3. Monitor the urine and plasma pH frequently in order to keep the plasma pH<7.5 and the urine pH>6.5; if the urine remains acidotic with a plasma pH>7.5, a carbonic anhydrase inhibitor can be added to the regimen

Management of Metabolic Abnormalities

Correction of the other metabolic abnormalities is no different from correction of the same abnormalities when they occur in other settings. Potassium levels generally peak 12–36 h after injury and elevations are treated vigorously with standard hyperkalemic therapy. Hyperphosphatemia usually responds to aggressive volume resuscitation. Hypocalcemia is generally not treated except when it is associated with acute signs and symptoms or with a danger of hyperkalemic arrhythmias. Any calcium administered likely sequesters in the injured muscle and increases the risk of heterotopic ossification. Nephrotoxic drugs should be avoided.

Treatment of AKI

Despite optimal treatment, some patients develop AKI and renal replacement therapy may be necessary. Myoglobinuric AKI generally is self-limiting and starts to improve within 10–14 days of treatment if the release of myoglobin into the bloodstream has ceased.

Treatment of Compartment Syndrome

Patients often present with painful swollen extremities and should be monitored for the development of an extremity compartment syndrome.[29] The compartment syndrome examination is geared toward the classic description of pain out of proportion, pallor of the extremities, paralysis, paresthesias, and pulselessness (the five *P*s). If compartment syndrome is suspected, muscle compartment pressures should be measured directly. Normal compartment pressures range from 0 to 15 mmHg. Pressures measuring in excess of 30 mmHg usually require surgical assessment.[2]

The Role of Free-Radical Scavengers and Antioxidants

Several experimental therapies are under investigation for treating patients with severe rhabdomyolysis. Free-radical scavengers, antioxidants, platelets activating factor (PAF), receptor blockers, and the endothelin receptor antagonist bosentan may attenuate the development of myoglobinuric kidney injury.[29–31]

Treatment of the Local Injury

The nature of the injury and the clinical circumstances dictate the specific treatment, which can include fasciotomy, debridement, and amputation. The surgical treatment of extremity injuries remains controversial; a full discussion is beyond the scope of this chapter.

Table 46.4. Sample volume-replacement protocol.

1. Administer bolus 1–1.5 L of normal saline (NS) intravenously
2. Provide continuous infusion of 0.5 NS at 200–700 cc/h
3. Monitor urine output hourly with a Foley catheter in place; desired urine output is approximately 200 cc/h
4. Monitor hemodynamic and cardiac changes through cardiovascular monitoring

Prognosis

Rhabdomyolysis has a good prognosis when treated early and aggressively. Full recovery of renal function is expected for most cases.[25]

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Postoperative Care of the Cardiac Surgical Patient

Ross F. DiMarco Jr.

The subspecialty of interventional cardiology began in 1977. Since then, the discipline of interventional cardiology has matured rapidly, particularly with regards to ischemic heart disease. As a result, more patients are undergoing percutaneous catheter interventional therapy for ischemic heart disease and fewer patients are undergoing surgical myocardial revascularization. Those patients referred for surgical revascularization are generally older and have more complex problems. Furthermore, as the population ages more patients are referred to surgery for valvular heart disease. The result of these changes is a population of surgical patients older and sicker than previously treated. These patients require even more specialized postoperative care and pose unique challenges in critical care management. The clinical challenges are accompanied by the need to provide care in a cost-conscious manner and in an atmosphere that is carefully scrutinized and benchmarked. Managing postoperative cardiac patients is more challenging now than in the past and it is extremely important that those physicians providing critical care for the postoperative cardiac surgical patient have a clear knowledge of their unique problems. This chapter is designed to provide a basic understanding of the physiologic derangements of this group of patients and to offer treatment strategies for their successful care.

Pathophysiologic Consequences

The open-heart patient requires specialized care because physiologic systems are disrupted by cardiopulmonary bypass (CPB). CPB results in a generalized inflammatory response caused by blood contact with the synthetic surfaces of the bypass circuit.[1] The interface between blood elements and the surfaces of the circuit causes a generalized inflammatory response. This inflammatory response results in a series of complex reactions that activate the complement, clotting, and fibrinolytic cascades causing bleeding, microemboli, fluid retention, and an altered hormonal response.[2–5]

CPB is a nonspecific activator of the inflammatory system.[6] After the discontinuation of CPB, generalized complement activation occurs with elevations of C3a and C5a anaphylatoxins.[7] The activation of these anaphylatoxins can result in pulmonary sequestration of leukocytes[7,8] and the production of superoxides. There then occurs further leukocyte activation and the generation of leukotactic factors that further increase the local inflammatory response.[9,10] Also, vasoactive amines from platelets are liberated in response to CPB or possibly from protamine administration, which can result in pulmonary hypertension and systemic hypotension.[11] Yet another result of the complement activation is an increase in vascular permeability that may predispose the patient to a capillary-leak syndrome with fluid sequestration in the third space, particularly the lung.[12] From a clinical perspective, the generalized inflammatory response results in postoperative pulmonary dysfunction, renal dysfunction, and a resetting of the hypothalamic thermoregulatory center.[9,12]

The inflammatory response caused by CPB also has direct negative cardiac effects. The inflammatory state caused by CPB involves platelet–endothelial cell interactions and vasospastic responses resulting in low-flow states in the coronary circulation.[13] The anaphylatoxin C5a is a potent molecule that is spasmogenic and has leukocyte-activating properties that cause degranulation and release of toxic oxygen free radicals. The complement-exposed leukocytes are attracted to adhere to the vascular endothelium and to aggregate, resulting in margination in blood vessels and leukoembolization. These inflammatory cells mediate injury by increasing their production and releasing oxygen free radicals or proteolytic enzymes.[14] It is this release of oxygen free radicals that is generally accepted as the cause for transient postoperative ventricular dysfunction that manifests itself about 2 h after cessation of CPB and is

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at its worse at 4–5 h after CPB.[15,16] Recovery of ventricular function begins in 8–10 h and full recovery usually occurs by 24–48 h.[16] The systemic vascular resistance rises as ventricular function worsens. This is a compensatory mechanism in an effort to maintain systemic blood pressure and perfusion in the face of depressed ventricular contractility. The oxygen free radicals and the proteolytic enzymes released by the neutrophils also damage endothelial cells increasing capillary permeability resulting in capillary leak during this period.[17] The capillary leak may last from 1 to 2 days and is related to the duration of CPB. Hypothermia has multiple adverse effects on the postoperative open-heart patient. Regarding the circulatory status, it predisposes cardiac dysrhythmias, increases SVR, precipitates shivering and impairs coagulation.[18] It also indirectly decreases cardiac output by increasing vasoconstriction and causing bradycardia. As a consequence of the inflammatory state after CPB, the postoperative open-heart patient is in a unique physiologic state where rules applicable to other physiologic situations may not apply, and a failure to recognize this concept results in management errors. Concerns about the short- and long-term effects of CPB has generated the recent concept of off-pump coronary artery bypass surgery. While there seems to be growing evidence that this off-pump approach to the surgical management of ischemic heart disease is advantageous, there does remain some debate.[19] Despite the movement toward avoidance of CPB in selected patients with ischemic heart disease, the majority of these patients as well as virtually all patients with valvular heart disease are operated on using CPB. The CPB circuit is not the only factor responsible for this altered physiologic state. The time of ischemia and reperfusion, hypothermia, hypotension with nonpulsatile flow, altered coagulation, and the administration of blood and products are other factors contributing to the altered postoperative physiologic state.[20]

Management of the Postoperative Open-Heart Patient

Initial Management

The patient after open-heart surgery presents with multiple, rapidly changing clinical problems. Initially, these patients are unstable and their clinical status is extremely fluid and dynamic. Caring for the postoperative open-heart patient requires bedside presence and the knowledge of general fundamental concepts of patient care as well as concepts specific to this set of patients. The initial management of these patients as they return from the operating room is critical, for it may well set the tone for the rest of the recovery period. Clinical errors at this time can have far-reaching implications. The initial management should begin even before the patient arrives in the intensive care unit (ICU). It is vital to review the chart noting indications for surgery, preoperative hemodynamic data, comorbid conditions, medications, and allergies.

Upon the patient's arrival in the ICU, perform a careful systematic assessment of the patient. Begin the assessment by speaking directly to the surgical and anesthesia team. Ascertain what procedure was done in the operating room and inquire as to any intraoperative events that might impact the patient's postoperative course. Then, physically examine the patient as part of this initial evaluation. During the initial assessment, avoid focusing on any one issue and attempt to get a global picture of the patient's clinical status. At this time, the patient is completely dependent on support systems, and dysfunction of any one of these can lead to disaster.[21] The following points must be observed: heart rate and rhythm, blood pressure, temperature, right and left heart filling pressures, hemodynamic profile, pharmacologic support, ventilator status, chest drainage, neurologic status, laboratory results, EKG, and chest X-ray. A thorough knowledge of the specific monitoring and drug delivery lines is imperative as is knowledge of where the drains are placed. Once the initial assessment is complete, specific issues can be identified, prioritized, and addressed.

Basics of Cardiovascular Hemodynamic Management

The primary objective in managing the postoperative open-heart patient is achieving adequate hemodynamic performance by optimizing myocardial oxygen supply and demand.[22] Optimal tissue oxygenation is essential to avoid organ dysfunction and can be determined by calculating oxygen delivery and oxygen demand. Oxygen delivery is a function of oxygen-carrying capacity and cardiac output. Oxygen demand is a function of oxygen consumption.[23]

The most important concept in the optimization of myocardial oxygen supply and demand, and tissue oxygenation is an adequate cardiac output. *Cardiac output* is expressed as liters per minute and *cardiac index* as liters per minute per square meter. Normal cardiac index is between 2.0 and 4.4 L/min/m^2.[24] An uncomplicated recovery from cardiac surgery can be anticipated when the cardiac index is maintained greater than 2.0 and 2.2 L/min/m^2.[24,25] Cardiac output is a function of stroke volume and heart rate, where cardiac output (CO) is the product of heart rate (HR) and stroke volume (SV). An optimal heart rate is usually between 80 and 110 beats per minute.[26] This rate allows for optimal filling of the heart at an economic level of myocardial oxygen consumption. Stroke volume is determined by preload, afterload, and contractility, and can be influenced by cardiac rhythm. Stroke volume is the end-diastolic volume minus the end-systolic volume and in normal states is 70 ml

Preload refers to left ventricular end-diastolic sarcomere fiber length and is a function of end-diastolic ventricular volume (LVEDV). It can be directly measured by echocardiography and is indirectly measured by left heart filling pressures; i.e., pulmonary artery diastolic pressure (PADP), pulmonary capillary wedge pressure (PCWP), and left atrial pressure (LAP). The former are all reflections of the left ventricular end diastolic pressure (LVEDP). The compliance of the left

ventricle is determined by the relationship between filling volumes and pressures, or LVEDV/LVEDP. Stiff ventricles have low compliances and require higher filling pressures to achieve adequate volumes. This scenario is almost universal after cardiac surgery.

Afterload is a reference to left ventricular wall tension during systole. It is determined by intraventricular systolic pressure and ventricular wall thickness.[27] Since there is minimal change in left ventricular wall thickness during cardiac surgery, intraventricular systolic pressure has the most impact on afterload. Systolic blood pressure (SBP) as a function of systemic vascular resistance (SVR) is the major determinant of afterload. An elevated SBP resulting from peripheral vasoconstriction and an elevation of the SVR negatively influences both stroke volume and myocardial oxygen demand. Myocardial oxygen demand is elevated because a major determinant of myocardial oxygen consumption is ventricular wall tension.

Contractility is the intrinsic strength of myocardial contraction at a constant preload and afterload. It is best assessed by echocardiography, and can be inferred from an analysis of cardiac output and filling pressures.

While cardiac output is an important component of oxygen delivery, it is not the only factor. Oxygen delivery is a function of cardiac output, hemoglobin, and arterial oxygen saturation (SaO_2). Most of the oxygen delivered to tissues is bound to hemoglobin. Low hemoglobin is a major factor adversely affecting oxygen delivery; therefore, maintenance of optimal hemoglobin is essential. Conversely, efforts should be made to limit transfusions, if possible, to avoid transfusion-related illnesses, immunologic compromise, and cost. A strategy should be in place to guide transfusions and should be based on criteria providing adequate oxygen delivery. The optimal postoperative hemoglobin is probably 22–24%.[28,29] Red blood cell (RBC) transfusions should be considered in patients with hematocrits lower than 22–24% and those patients with poor LV function, marginal SaO_2, ischemic findings on electrocardiogram (ECG), hypotension, tachycardia, and effort-related symptoms. Similarly, the optimal oxygen saturation is 95–100%, and maintaining an SaO_2 greater than 95% does not enhance oxygen delivery.

Mixed venous oxygen saturation (SvO_2) is a measure of the adequacy of oxygen delivery to the tissues. It can be measured from blood drawn from the distal port of a Swan–Ganz catheter or continuously using a fiber-optic oximetric pulmonary artery catheter. A diminished SvO_2 generally indicates decreased tissue perfusion and/or increased oxygen extraction by tissues. SvO_2 is an indirect correlate of the cardiac output. In the absence of factors that increase oxygen utilization, a 10% decrease in SvO_2 is an indication of a low cardiac output and can be seen before any change in other hemodynamic parameters. Other causes of a diminished SvO_2 are shivering, elevated temperature, anemia, alteration in inspired oxygen, and altered alveolar gas exchange. These conditions cause a diminished SvO_2 in the presence of a normal cardiac output by causing increased oxygen utilization. SvO_2 measurement can be of particular help in assessing adequate oxygen delivery when thermodilution cardiac output is unreliable (e.g., tricuspid regurgitation, improperly placed Swan–Ganz catheter, malfunctioning Swan–Ganz catheter), when thermodilution cardiac output is unavailable because Swan–Ganz cannot be placed (e.g., mechanical prosthesis in the tricuspid position), or when the clinical situation is unstable requiring online, minute-to-minute cardiac evaluation.[22]

Another important aspect in the appropriate management of the postoperative patient is minimizing the myocardial oxygen demand (MVO_2).[30] The MVO_2 is influenced by afterload, preload, heart rate, and contractility. Reducing afterload will reduce oxygen demand. Increasing preload, heart rate, and contractility will improve cardiac output but will also increase MVO_2. Providing adequate myocardial oxygen supply is equally important to the postoperative patient. Myocardial oxygen supply is determined by coronary blood flow, duration of diastole, coronary perfusion pressure (systemic diastolic pressure minus LVEDP), hemoglobin level, and arterial oxygen saturation. Postoperatively, myocardial oxygen supply is optimized by avoidance of tachycardia, maintenance of adequate perfusion pressure (avoid hypotension and hypertension), avoiding ventricular distention and inappropriately elevated LVEDP, and by managing preload judiciously.

Low Cardiac Output in the Postoperative Period

The goal of postoperative management is the maintenance of a satisfactory cardiac output. Hemodynamically, the cardiac index (CI) should be greater than 2.2 L/min/m^2 at a pulmonary capillary wedge pressure (PCWP) of less than 20 mmHg or pulmonary artery diastolic pressure (PADP) of less than 22–27 mmHg with a heart rate less than 100 bpm. Clinically, the patient should be warm, well perfused, and with an appropriate urine output.[22] By definition, a CI greater than 2.2 L/min/m^2 is satisfactory, a CI of 2.0–2.2 L/min/m^2 is marginal, and a CI below 2.0 L/min/m^2 is unacceptable and calls for intervention. Ninety percent of all postoperative open-heart patients demonstrate a transient low cardiac output (LCO) related to the release of oxygen free radicals in response to the induced inflammatory state of cardiopulmonary bypass, or from ischemic/reperfusion injury as a result of cardioplegic arrest.[15,18,31,32] The ventricular function becomes depressed in 2 h and is at its worst at 4–5 h. Generally, there is significant recovery in about 8–10 h and full recovery by 24–48 h.[33] LCO is more common in patients with preoperative LV systolic dysfunction, diastolic dysfunction, prolonged cardiopulmonary bypass, and in women.[34,35]

Clinical Manifestations of Low Cardiac Output

As cardiac output deteriorates, compensatory mechanisms develop and are the result of sympathetic autonomic stimulation and endogenous catecholamine production. These compensatory mechanisms result in an increased heart rate, increased contractility, and increased arterial and venous tone (resulting in elevation of preload and afterload). These compensatory

mechanisms may increase the cardiac output but at the expense of myocardium oxygen utilization, and consequently the myocardium may become more depressed. As the myocardium becomes depressed, the left ventricular function worsens and the systemic vascular resistance (SVR) increases in an attempt to maintain systemic blood pressure. This elevation in the SVR is compounded by the vasoconstriction seen with hypothermia.

The early clinical manifestations of low cardiac output may be subtle. The only findings may be cool extremities accompanied by progressive tachycardia. As the compensatory mechanisms fail, more advanced clinical manifestations occur. Overt findings of poor peripheral perfusion such as pale, cool extremities and diaphoresis, pulmonary congestion and poor oxygenation, oliguria secondary to poor renal perfusion, and metabolic acidosis will be manifest. Early intervention is indicated at the onset of the early manifestations to avoid the complications of prolonged hypoperfusion and progression to the advanced manifestations.

Etiology of Low Cardiac Output

The etiology of LCO can be abnormal preload, afterload, contractility, or heart rate and rhythm or a combination of these. The most common causes of LCO after surgery are related to decreased left ventricular *preload* caused by hypovolemia and bleeding, vasodilatation, rewarming, drugs, cardiac tamponade, right ventricular dysfunction, positive pressure ventilation, and a tension pneumothorax. Increased *afterload* is usually the result of acute vasoconstriction most often related to vasoactive drug therapy. It can also be from preexisting hypertension, pain or awareness, fluid overload, or hypothermia. Decreased *contractility* is causative of LCO in patients with preexisting LV dysfunction in association with perioperative ischemia. Perioperative ischemia is usually a consequence of poor intraoperative myocardial protection, incomplete revascularization, coronary artery or conduit spasm, coronary artery "trash" syndrome, graft closure, acute anemia, hypoxia, or acidosis of any etiology. *Tachyarrhythmias* adversely affect cardiac output by decreasing cardiac filling time and subsequently decreasing stroke volume coronary perfusion time. Tachyarrhythmias also increase myocardial oxygen demand. *Bradyarrhythmias* depresses cardiac output, especially when left ventricular dysfunction limits the compensatory mechanism of an increasing stroke volume. Bradyarrhythmias are particularly deleterious in association with aortic insufficiency of any degree. When atrial fibrillation occurs, there is a loss of atrial contribution to cardiac output and subsequent fall in the cardiac output. Finally, any ventricular arrhythmia adversely affects the cardiac output.

Diastolic dysfunction causes LCO in a specific set of patients. It is often seen in small women with hypertension, patients with long-standing aortic stenosis, or patients with hyperdynamic left ventricles. All of these situations are associated with left ventricular hypertrophy, poor ventricular relaxation, and near-obliteration of the left ventricular cavity during systole.[36,37] Diastolic dysfunction presents with normal LV function and normal or elevated PCWP, but a LCO syndrome. These patients deteriorate quickly if sinus rhythm or atrial–ventricular synchrony is lost.

Miscellaneous noncardiac causes of LCO include anaphylaxis or anaphylactoid reaction, marked alterations in temperature, sepsis, adrenal insufficiency, and the various protamine reactions. When no obvious diastolic or systolic dysfunction is present, then consider *tamponade* from blood or clot within the confines of the mediastinum and pericardium.

Diagnosis of Low Cardiac Output

The diagnosis of low cardiac output begins with a *bedside physical examination.* The early clinical manifestations of LCO are apparent to the clinician with a heightened suspicion for their presence. The importance of a careful bedside assessment cannot be overstated. The examination should include the condition and appearance of skin and mucous membranes, breath sounds, murmurs, temperature of extremities, and a level of consciousness. The *EKG monitor* is a minimum level of monitoring after open-heart surgery. It is a screening device for ischemia and arrhythmias, both causes of LCO. All ischemic changes on monitors must be further assessed with a 12-lead EKG and it is prudent to confirm all but the most obvious arrhythmias with a 12-lead EKG. *Hemodynamic monitoring*, at a minimum, includes a central venous pressure (CVP) line and can be used to assess preload as well as right ventricular function. Clinical LCO and low CVP suggests inadequate preload as the cause of LCO. Clinical LCO and an elevated CVP are more complicated. This situation may be the result of right heart failure, volume overload, left heart failure, tamponade, or some preexisting problem such as severe chronic obstructive pulmonary disease (COPD). In this circumstance, the information from a Swan–Ganz catheter or transesophageal echocardiogram (TEE) can clarify the situation. Swan–Ganz catheters (pulmonary artery catheters) are used in all patients in some institutions and selectively in others. Oximetric Swan–Ganz catheters are optional and are used in highly selected situations when minute-to-minute cardiac assessments are necessary. Swan–Ganz catheters provide an assessment of right and left heart filling pressures, determine cardiac output, stroke volume, SVR, and SvO_2. The information acquired from these catheters confirm the diagnosis of clinical LCO and provide information as to the etiology. For example, low filling pressures suggest preload as the causative factor, whereas high filling pressures indicate a problem with contractility or afterload. A *Chest X-ray* is a valuable and essential tool in the postoperative period for multiple reasons, but it can also assess the lungs as a cause for low cardiac output. In particular, a chest X-ray can identify a pneumothorax, hemothorax, pleural effusion, adult respiratory distress syndrome, and the endotracheal tube position as potential causes of a low cardiac output. It also assesses the mediastinum for an enlarged mediastinal silhouette suggesting tamponade or incorrect position of intrathoracic monitoring lines.

Echocardiography has become a first-line tool in evaluating the postoperative patient suspected of having LCO. It can either be a transthoracic examination or a transesophageal examination. The surface echocardiography has limited value in the immediate postoperative period because of the presence of dressings and chest tubes, but can provide some information about LV function and recognize obvious tamponade. Transesophageal echocardiography is an extremely valuable tool in the postoperative period and can be carried out at the bedside. It provides excellent visualization of cardiac dynamics, the pericardial space, and the mediastinum. It is the best diagnostic modality for LV function, presence of tamponade, and the development of new valvular abnormalities. It is also good for right ventricular assessment.

Each of the previous diagnostic modalities has an important role in the assessment of the postoperative cardiac surgical patient with suspected LCO. Once the diagnosis of LCO is established and the etiology determined, appropriate treatment actions can be instituted.

Management of Low Cardiac Output

The management of low cardiac output begins by excluding tamponade as the cause. If there is no indication of tamponade, treat the correctable noncardiac abnormalities such as respiratory abnormalities, acid–base and electrolyte imbalances, and anemia. If LCO persists, direct therapy at treatable cardiac abnormalities such as ischemia with a nitroglycerine infusion and consider diagnostic catheterization with catheter or operative intervention if ischemia persists. Consider coronary spasm, but this is a difficult diagnosis. Suspect coronary spasm when the patient presents with hemodynamic instability and EKG changes, especially ST segment elevation. Coronary spasm usually responds to calcium channel blockers and is a particular threat in patients with arterial conduits as grafts. Arrhythmias can also cause LCO. Ideally, the patient should be in sinus rhythm at 70–90 bpm. In the presence of LCO, arrhythmia management should be aggressive and pacing support may be needed to maintain atrial–ventricular synchrony.

After the initial steps of correcting obvious noncardiac and cardiac abnormalities, the *volume status* should be assessed and preload optimized. It is helpful to know what filling pressures resulted in the best cardiac performance in the operating room or catheterization laboratory (cath lab) and adjust the volume accordingly. The cardiac performance should be followed closely as volume is administered, and if filling pressures increase without concomitant improvement of cardiac output, an inotrope will be needed. Be mindful that the injudicious use of volume administration will result in distention of the ventricle (right, left, or both) with a shift in the Frank–Starling curve. As the ventricular wall tension increases, the myocardial oxygen demand increases and contractility becomes impaired. If volume administration fails to improve filling pressures, there may be ongoing volume loss from hemorrhage, diuresis, capillary leak syndrome, or vasodilatation from drugs, warming, or previous comorbid conditions. Volume should be given in doses of 10% of estimated blood volume (blood volume is estimated as 0.065 × body weight in kg for adults). Orders for volume expansion should be written with a prescribed stop order when the optimal filling pressure is exceeded to prevent ventricular distension. The choice of the appropriate volume expander is important. If the hemoglobin is less than 9.5 g, give packed red blood cells (PRBCs); if the hemoglobin is 9.5–11.5 g, give PRBCs and a colloid of choice; and if the hemoglobin is 11.5 g or greater, give a colloid of choice or equivalent dose of crystalloid.[38]

Pharmacologic Management of Low Cardiac Output

Pharmacologic support is considered when the cardiac output fails to improve after optimizing preload, afterload, rate and rhythm, and metabolic abnormalities. The threshold for using vasoactive agents should be low in patients with a preoperative history of compromised ventricular function. The choice of the agent depends on multiple factors: the hemodynamic profile of the patient; associated medical conditions; treating physician's understanding of the agent; and, to a lesser extent, cost. Of these factors, the most important is the hemodynamic profile of the patient. Inotropic agents must be chosen based on the specific hemodynamic abnormality most responsible for the current LCO state. Often, the causative factors are multifaceted and dynamic, making flexibility and vigilance key. It is not unusual to need a combination of agents to successfully treat LCO. At the initiation of therapy for LCO, a bedside presence is mandatory to respond minute-to-minute to hemodynamic changes. An understanding of the basic mechanism of action and of the inotropic agents comprises the basis for agent selection.

In general, each category of agents exerts their effects differently. Catecholamines affect α-adrenergic and β-adrenergic receptors. They elevate the levels of intracellular cyclic AMP (cAMP) by β-adrenergic stimulation of adenylate cyclase. The phosphodiesterase (PDE) inhibitors, inamrinone and milrinone, elevate cAMP by inhibiting cAMP degradation. Elevation of cAMP augments calcium influx into myocardial cells and increases contractility. [34] The stimulation of α_1- and α_2-adrenergic receptors results in elevation of SVR and PVR. Cardiac α_1 receptors increase contractility and decrease heart rate. Stimulation of β_1 receptors results in increased contractility, heart rate, and conduction. In contrast, β_2 stimulation results in peripheral vasodilatation and bronchodilatation. The overall hemodynamic effect of these agents is dose-related. The need to use these agents in combination is often beneficial and necessary to achieve the desired hemodynamic effect and lessen undesired sequelae.[22]

When infusing vasoactive agents, several caveats are noteworthy. First, these agents have a lessened effect in an acid medium; therefore, it is important to maintain the patient in proper acid–base balance to achieve the full effect of the therapy. An increasing dose of the agent may be indicating a falling pH.

Secondly, the route of administration should always be through a central line and not peripherally. Thirdly, these agents should always be administered with a rate-controllable infusion pump. Finally, higher blood levels can be attained by infusing them directly into the left atrium to avoid partial deactivation or removal by the lungs. This method can also be employed to lessen the pulmonary vasoconstrictive effects and subsequent RV dysfunction of catecholamines such as epinephrine or norepinephrine. This method of infusion has its own inherent risks and should be reserved for extreme circumstances.[39]

Epinephrine is the catecholamine of choice for low cardiac output in many institutions. It has potent β_1 inotropic effects and increases cardiac output by increasing contractility and heart rate. Some of its effects are dose-related. At doses lower than 2 mcg/min (<0.03 mcg/kg/min), its β_2 effects result in mild vasodilatation and a decrease in the SVR while maintaining an adequate blood pressure. Doses greater than 2 mcg/min (>0.03 mcg/kg/min) produce α effects that cause vasoconstriction with an increased SVR potentially decreasing cardiac output further as well as increasing myocardial oxygen demand. Epinephrine may cause tachycardia, but often less than that with dopamine or dobutamine at comparable doses. It can be arrhythmogenic, usually causing ventricular ectopy. Hyperglycemia and metabolic acidosis are not infrequently associated with its use. While epinephrine can be used as a first-line agent in patients with ventricular arrhythmias or brittle diabetes mellitus, it must be done so with care. In some institutions, it is used as a second-line agent if dopamine and/or dobutamine are not tolerated or ineffective. Secondary uses for epinephrine include stimulation of heart rate in patients with bradycardia, bronchospasm, anaphylaxis, and general resuscitation for cardiac arrest. Epinephrine is the least expensive of the commonly used inotropes. Epinephrine is begun at 1 mcg/min and titrated to effect or to 4–6 mcg/min.

Dopamine is also a first-line agent for low cardiac output in some institutions. It is indicated for LCO with a low SVR and diminished systemic blood pressure. It also may be beneficial in the face of decreased urine output. Aside from its inotropic and chronotropic effects, an added effect is the selective "dopaminergic" effect that increases renal perfusion, glomerular filtration rate, and urine production by directly reducing renal afferent arteriolar tone and indirectly increasing efferent arteriolar tone. The hemodynamic effects of dopamine are largely dose-dependent. Despite its ability to increase urine production in some instances, it has never been shown to prevent acute renal failure.[40,41] At doses of 2–3 mcg/kg/min, the main effects are renal as described, although there can be a mild β_2 effect with a decrease in SVR and systemic blood pressure. At doses of 3–8 mcg/kg/min, β_1 effects are predominant increasing contractility. At this dose, there is also a chronotropic effect that increases heart rate and has the potential for arrhythmogenesis. Doses of dopamine of greater than 8 mcg/kg/min results in increasing inotropy, but also this dose causes a predominant α effect. This α effect occurs directly but also indirectly from the release of norepinephrine. The SVR increases as do the filling pressures and myocardial oxygen consumption leading to ventricular dysfunction. These adverse effects can be somewhat mitigated by the concomitant use of vasodilator therapy. Its use may be limited by profound tachycardia even at low doses and excessive urine production. Dopamine is begun as an infusion at 2.5 mcg/kg/min and titrated to 10–20 mcg/kg/min if needed. If a β_1 favorable response is not achieved at 10 mcg/kg/min, it is unlikely that higher doses will result in hemodynamic improvement.

Dobutamine has similar effectiveness as dopamine, but does not have its renal dopaminergic effect. Dobutamine may augment myocardial perfusion better than dopamine.[42] It is a positive inotrope with strong β_1 effect that increases contractility and also heart rate. Dobutamine has mild β_2 effect and decreases SVR; this effect is mild and may be offset by its mild α_1 vasoconstricting effect present in some specific circumstances.[43] Also, unlike dopamine, dobutamine reduces ventricular wall tension by reducing afterload and preload particularly in the presence of volume overload.[44,45] There appears to be augmentation of myocardial blood flow and an improvement of the myocardial oxygen supply and demand curve, but this positive effect may be lessened by tachycardia.[42] The usefulness of dobutamine may be limited by tachycardia that may be profound and may trigger atrial fibrillation. Because of its hypotension from the vasodilating effect, dobutamine should be used with caution in the hypotensive or hypovolemic patient and is contraindicated if tamponade is suspected. It is most commonly used for low cardiac output associated with a mildly elevated SVR and may have a synergistic effect when used with PDE inhibitors. It does have a moderate pulmonary vasodilatory effect and can improve RV dysfunction. It is more expensive than dopamine, yet only minimally more effective. Dobutamine is begun as an infusion at 5 mcg/kg/min and can be increased for effect up to 20 mcg/kg/min.

Inamrinone and *milrinone* are phosphodiesterase inhibitors known as "inodilators."[46] These agents produce positive inotropic effects and vasodilation independent of β_1 adrenergic stimulation. They improve biventricular output by increasing stroke volume index, left ventricular contractility, and producing pulmonary vasodilation. These agents also produce vasodilation in arteriolar and venous smooth muscle, thus reducing preload and afterload, and their use is associated with decreased myocardial oxygen consumption, despite a modest positive chronotropic effect. Inamrinone and milrinone decrease coronary vascular resistance, improve coronary perfusion, and improve the myocardial oxygen supply/demand ratio.[47] PDE inhibitors have an additive effect when used with catecholamines because of their differing sites of action.[48–50]

Catecholamines stimulate the production of cAMP whereas PDE inhibitors slow the hydrolysis of cAMP.[51] Inamrinone and milrinone are generally considered second-line agents in the treatment of LCO. They are usually employed when first-line

agents like dopamine or epinephrine are not providing adequate hemodynamic improvement or if side effects are limiting their effectiveness. However, there is evidence that administering these agents preemptively, prior to separation from cardiopulmonary bypass in patients with preoperative LV dysfunction, may eliminate the need for inotropic therapy subsequently.[52,53] Inamrinone and milrinone are particularly useful in patients with RV dysfunction secondary to pulmonary artery hypertension and elevated PVR. These agents are also useful in treating diastolic dysfunction as they have been shown to have relaxant or lusitropic properties. They also appear to have direct vasorelaxant effects on arterial graft conduits and may be useful in patients with evidence of internal mammary spasm or in the presence of radial artery grafts.[54,55] These drugs have a relatively long half-life of 2–4 h; consequently, the loading dose will be effective for several hours after administration but the patient should be reassessed at that time for any ongoing need for therapy. Since the PDE-inhibitors are effective vasodilators, the systemic blood pressure may require support, usually with α agonists. Vasopressin may be an alternative drug to support the systemic blood pressure while reducing the need for catecholamine pressors.[56] Inamrinone is associated with thrombocytopenia, but this is rare with milrinone. There does not appear to be any significant hemodynamic difference between inamrinone and milrinone, but milrinone has largely replaced inamrinone in clinical use because of the latter's thrombocytopenic effects.[57] Both are relatively expensive compared to other inotropic agents. Inamrinone is given as a loading dose of 0.75 mg/kg over 10 min (may need 1.5 mg/kg if bolus given while on cardiopulmonary bypass) followed by an infusion of 10–15 mcg/kg/min. Milrinone is given as a loading dose of 50 mcg/kg over 10 min, then an infusion dose of 0.375–0.75 mcg/kg/min.

Norepinephrine is another naturally occurring catecholamine. It has a pronounced effect on peripheral α receptors resulting in peripheral vasoconstriction, elevated SVR, and elevated systemic blood pressure. Norepinephrine also is a β_1 agonist increasing myocardial contractility and heart rate. The increased afterload, contractility, and heart rate result in an increase in myocardial oxygen consumption. The overall increase in myocardial oxygen consumption may have a deleterious effect on ischemic myocardium. The primary effect of norepinephrine is elevation of blood pressure and mild-to-moderate elevation of the cardiac output. It also has been shown to cause regional redistribution of blood flow with reduced renal, mesenteric, and peripheral perfusion. The primary indication for norepinephrine is a low cardiac output associated with a low SVR. It is a reasonable choice of pharmacologic support if the SVR is low and the cardiac output is 2.0–2.5 L/min/m^2. If the SVR is low and the cardiac output greater than 2.5 L/min/m^2, a pure α agonist may be used. If the SVR is low and the cardiac output is less than 2.0 L/min/m^2, another inotrope should be used in addition to or in place of norepinephrine.[31]

Norepinephrine can be used in combination with afterload reduction to titrate the systemic blood pressures to acceptable levels and to maintain a satisfactory systemic blood pressure. It can also be used in combination with epinephrine to augment the β_1 effect. The starting dose is 1 mcg/min (0.015 mcg/kg/min) and titrated to the desired systemic blood pressure. At doses greater than 20 mcg/min (0.2 mcg/kg/min), visceral and peripheral perfusion is reduced to such an extent the patient may become acidotic.

Isoproterenol is a β-adrenergic agonist. It has strong β_1 effect, some β_2 effect, and little α action. The β_1 effects increase cardiac output by its moderate increase in contractility and marked increase in heart rate. The β_2 effect reduces SVR. It has been shown to reduce pulmonary vascular resistance and may be effective in treating reactive pulmonary hypertension when right heart failure is contributing to low cardiac output. It can afterload reduce the right ventricle. Isoproterenol also has strong β_2 bronchodilator effect. The indications include right ventricular failure associated with elevated PVR and bronchospasm, and can be used to stimulate heart rate in patients with bradycardia and no functioning pacemaker wires. Its use is limited because it increases heart rate and myocardial oxygen demand. Since it is a nonselective β-adrenergic agonist, it will predispose to tachyarrhythmias, ventricular irritability, and ventricular dysrhythmias. As a result of the tachyarrhythmias, isoproterenol has been largely replaced by PDE inhibitors.[58]

Phenylephrine has no direct cardiac effects. It is a pure α-agonist that increases SVR. It does have some usefulness in the treatment of LCO resulting from myocardial ischemia secondary to global hypoperfusion. If systemic blood pressure is reduced as a consequence of vasodilatation, coronary perfusion may be compromised leading to myocardial ischemia and ventricular dysfunction. Phenylephrine directly stimulates α-adrenergic receptors leading to an elevation of the coronary perfusion pressure and resolution of global myocardial ischemia. Systemic vasodilatation is most often seen immediately following CPB or in the early hours of recovery as the patient rewarms. In these circumstances, phenylephrine may be helpful. Since it provides no direct cardiac benefits, its role is limited. Phenylephrine can cause vasoconstriction of an arterial conduit and should be used with caution in patients with arterial conduit grafts. Its main indication is to increase SVR in patients with low SVR and normal or elevated cardiac output. It can also be used as a temporizing measure in a hypotensive, hypovolemic patient until the volume status is corrected. The usual starting dose is 5 mcg/min and the usual dosing range is 0.05–1.5 mcg/kg/min.

Nesiritide is a recombinant B-type natriuretic peptide. It is identical to the endogenous B-type natriuretic peptide secreted by the ventricles in response to increased cardiac volume and pressure overload.[59] Nesiritide decreases sympathetic stimulation and inhibits the neurohumoral responses seen in heart failure. It exerts its effects by inhibiting the renin–angiotensin–aldosterone system to decrease aldosterone, norepinephrine, and endothelin levels resulting in natriuresis and diuresis. The net effect is a balanced reduction in preload and afterload, and

relaxation of smooth muscle.[60] It indirectly improves cardiac output with no increase in heart rate and no increase in myocardial oxygen demand. Nesiritide is lusitropic and dilates native coronary arteries and arterial conduits. It is not proarrhythmic. It has been shown to dilate afferent and efferent renal arterioles increasing glomerular filtration resulting in natriuresis and diuresis. Like PDE inhibitors, it can be used synergistically with catecholamines to reduce dosages and side effects. While nesiritide has demonstrated favorable clinical results in nonsurgical patients with decompensated heart failure and it has pharmacologic effects possibly beneficial to the postoperative cardiac surgical patient, experience with nesiritide in surgical patients is limited. Early results indicated that it may not be any better than milrinone.[61] One clinical trial did demonstrate a trend toward reduced length of stay without adverse effects.[62] Its main indication in the surgical patient is in conditions of diastolic dysfunction or LCO states associated with elevated pulmonary artery pressures. It is also useful in conditions of fluid overload and postoperative renal failure.[31] Nesiritide is given, a dose of a 2 mcg/kg over 1 min followed by an infusion of 0.01–0.03 mcg/kg/min.

Vasopressin is a peptide hormone synthesized in the hypothalamus and is released from the posterior pituitary upon stimulation by hyperosmolality, hypotension, and hypovolemia. It has two sites of action: kidney and blood vessels. The primary function of arginine vasopressin (AVP) is to regulate extracellular fluid volume by affecting renal tubular absorption of water. It acts on the renal collecting tubules by increasing water permeability and results in decreased urine formation. This is its antidiuretic function and is why it is commonly known as antidiuretic hormone (ADH). The antidiuretic effect increases blood volume and indirectly increases cardiac output and arterial blood pressure. A secondary function of AVP is vasoconstriction. It binds to vascular smooth muscle to cause vasoconstriction. AVP is a potent vasopressor even in patients with catecholamine-resistant hypotension. Loss of catecholamine pressor effect is a well-established phenomenon.[63] In acute shock states, vasopressin levels increase rapidly and then decrease in prolonged shock states leading to a relative deficiency of vasopressin.[64,65] The deficiency of vasopressin is thought to contribute to hypotension refractory to catecholamines, especially in sepsis.[65,66] Because vasopressin is a potent vasopressor, infusions of vasopressin leads to improved organ perfusion, increased mean arterial pressure, and improved neurological function.[63,65,67] Vasopressin is indicated for the management of severe vasodilatory shock. In patients with "vasoplegia," profound peripheral vasodilatation with preserved cardiac output, vasopressin may have a role. This condition is usually associated with patients on preoperative angiotensin-converting enzyme inhibitors or amiodarone. It may also be the consequence of leukocyte activation and release of proinflammatory mediators caused by the systemic inflammatory response to CPB.[68,69] Vasopressin is usually successful in reversing the low SVR when phenylephrine and norepinephrine are not.[68,70] Vasodilatory shock is not uncommon in patients with a ventricular assist devices (VAD) and may benefit from the vasoconstrictive actions of vasopressin.[71] Despite vasopressin's effect in vasodilatory shock, it remains a second-line agent because there is no current evidence to support the use of vasopressin as a first-line agent instead of catecholamines.[72] There is growing evidence that vasopressin may provide comparable or superior efficacy to epinephrine as a resuscitative agent for cardiac arrest and hemodynamic collapse when administered as a single bolus of 40 units intravenously.[73] The recommended infusion rate for vasopressin in the treatment of vasodilatory shock is 0.01–0.04 units/min. Doses greater that 0.04 units/min may lead to cardiac arrest.[64] Rapid rebound hypotension commonly occurs after vasopressin infusion is discontinued.[74] Potential adverse sequelae of vasopressin therapy include ischemic cutaneous necrosis, intestinal ischemia, and decreased hepatosplanchnic flow and cardiac output.[75]

Ionized calcium is critical for excitation–contraction coupling in cardiac muscle.[76] Hypocalcemia depresses ventricular contractility and peripheral vascular resistance; the net effect is LCO and low systemic blood pressure. The hemodynamic effects of *calcium chloride* are more profound if the patient is hypocalcemic. Serum ionized calcium levels are low postoperatively, particularly just prior to weaning from CPB, and a bolus of calcium is frequently given just prior to weaning from CPB. The effect of a bolus of calcium is increased contractility and increased SVR. It has little effect on the heart rate. It is more effective when the patient is hypocalcemic, but is also efficacious even if the patient is normocalcemic. Calcium chloride provides ionized calcium, which acts as a strong but very evanescent inotrope. A continuous infusion of calcium does not sustain its hemodynamic effect. Ionized calcium is necessary for the effective action of catecholamines. The main indication for calcium chloride is at the termination of cardiopulmonary bypass to augment systemic blood pressure during separation from bypass. It is also used as an emergency resuscitation agent to support hemodynamics until a more complete evaluation can be performed and more specific measures utilized. The dose is in increments of 0.5–1.0 g slow IV bolus.

Cardiopulmonary bypass and hypothermic arrest results in low levels of circulating thyroid hormone.[2,77,78] *Triiodothyronine* (T_3) has hemodynamic effects based on this reduction in the plasma-free level of T_3 following cardiopulmonary bypass. T_3 remains low for 24 h, but not low enough to cause symptoms of hypothyroidism. Augmenting the levels of T_3 can increase myocardial function and has been shown to increase cardiac output and lower SVR in patients with ventricular dysfunction.[79–81] T_3 exerts its positive inotropic effect by increasing aerobic metabolism and synthesis of high-energy phosphates. It directly stimulates calcium adenosine triphosphatase (ATPase) in the sarcolemma and sarcoplastic reticulum.[82] The enhancement of calcium transport decreases intracellular calcium aiding myocardial relaxation, myocardial compliance, and diastolic function.[2,77,82] T_3 also decreases

SVR.[83] Currently, there are conflicting results on the use of T_3 in the treatment of LCO. The current role for T_3 is salvage when cardiopulmonary bypass cannot be terminated despite maximum support including inotropic agents and intra-aortic balloon counterpulsation. There are no studies, to date, that show that T_3 favorably improves outcome in patients failing to separate from cardiopulmonary bypass even though hemodynamics have improved in patients with ventricular dysfunction.[84] The dosage is 0.05–0.8 mcg/kg as an IV bolus.

Mechanical Support for Low Cardiac Output

Pharmacologic support is the first-line therapy for LCO. *Mechanical support* should be considered for the management of LCO when there is need for more than two inotropic agents used at the upper range of their therapeutic efficacy, when there are complications from these agents, or when LCO progresses to cardiogenic shock. Other uses of mechanical support postoperatively include myocardial ischemia or the development of mitral regurgitation that cannot be managed medically. Finally, mechanical support is indicated for the patient experiencing acute deterioration and in need of a transplant. Available mechanical support devices are the intra-aortic balloon and circulatory assist devices such as left and/or right ventricular assist devices.

The *intra-aortic balloon pump* has been an effective tool for the management of LCO states, ongoing ischemia, valvular disease, and the complications of myocardial infarction since its development in 1968.[85] Intra-aortic balloon pump (IABP) counterpulsation provides hemodynamic support and control of ischemia before and after surgery.[86] It has been shown to be effective in improving the diastolic function of the left ventricle.[87] IABP counterpulsation is very effective in the management of low cardiac output states. Unlike most inotropic agents, it provides hemodynamic support to the failing heart by decreasing myocardial oxygen demand and improving coronary artery perfusion. IABP counterpulsation acts to improve the myocardial oxygen supply:demand ratio. It reduces the impedance of left ventricular ejection by rapidly deflating just before systole, thus unloading the LV, and in this way decreases myocardial oxygen demand. As it rapidly inflates just after aortic valve closure, it increases the diastolic coronary perfusion and improves myocardial oxygen supply. The survival rate of patients requiring postoperative IABP support is 60–70%.[88,89] The indications for IABP counterpulsation are perioperative ischemia, mechanical complications of myocardial infarction (such as acute mitral regurgitation, ventricular septal defect, and cardiogenic shock), postoperative low cardiac output states not responsive to moderate doses of inotropic agents, and for the acute deterioration of myocardial function to provide temporary support or a bridge to transplantation. IAPB counterpulsation is contraindicated in the presence of aortic insufficiency, aortic dissection, and severe aortic and peripheral vascular disease.

The IABP can be inserted percutaneously or surgically. The percutaneous approach is favored despite its somewhat higher prevalence of vascular complications.[90] Percutaneous insertion is preferred because of ease of insertion and removal. The IABP is inserted percutaneously using the Seldinger technique and is positioned fluoroscopically. The balloon tip marker should be positioned just distal to the origin of the left subclavian artery. The surgical insertion requires the exposure of the femoral artery and creation of a sidearm to the femoral artery with a vascular graft, followed by the insertion of the balloon through the graft. An alternative open surgical approach is exposure of the femoral artery and then direct cannulation with a vascular sheath using a guide wire. A hemostatic suture is placed in the femoral artery around the stem of the IABP. The IABP can be inserted by an open supra-inguinal approach in cases of severe femoral arterial disease, or the transthoracic approach via the ascending aorta in cases of severe aortoiliac peripheral disease. Triggering of the device is timed using EKG or arterial waveform. If EKG is used, the inflation is set at the peak of T wave, the end of systole. Deflation is set just before or on the P wave. Arterial waveform triggering is more reliable and a better timing technique when outside electrical impulses (i.e., pacemaker, electrocautery) may interfere with interpretation of the EKG signal. With arterial triggering, the inflation should occur at the dicrotic notch and deflation just before the onset of the aortic upstroke. Proper timing will show an arterial waveform with augmentation of the diastolic portion of the curve.

Support with the IABP is instituted at a 1:1 ratio with ventricular systole based either on EKG monitoring or the arterial pressure pulse tracing. There is often immediate hemodynamic improvement and the patient requires less inotropic support. When the required inotropic support reaches moderate levels (generally half the doses required prior to IABP support) consideration for weaning is possible. The IABP is weaned by reducing the assist ratio from 1:1 to 1:3 or less depending on the system. The weaning process can usually begin after 12–24 h of support and completed by 24–48 h. If the device was placed percutaneously, it can be removed similarly with firm pressure to the groin for 30 min. Since the arterial puncture site is several centimeters proximal to the skin insertion site, a common mistake is to direct the pressure at the skin insertion site instead of the arterial puncture site. When this error occurs, a large hematoma develops in the groin proximally. If a hematoma occurs or if the perfusion to the distal limb is compromised, immediate exploration is required.[91]

At times, there is a failure to achieve augmentation from the counterpulsation with the IABP. This can be the result of tachycardia and arrhythmias, inadequate balloon volume, and/or balloon rupture. Arrhythmias effect augmentation by disrupting the normal inflation and deflation patterns of the device. Rapid heart rates, usually atrial fibrillation with ventricular responses greater than 150 bpm, interfere with the balloon's ability to inflate and deflate. In this circumstance, augmentation can be achieved by changing the triggering ratio to 1:2 (one IABP cycle for every second cardiac cycle). Inadequate gas volume in the balloon can also result in an inability to

augment. Volume loss from the balloon can result from a gas leak or from failure of the balloon to unwrap. Either circumstance necessitates the removal of the balloon. Of more immediate concern is a balloon rupture. This is heralded by blood in the balloon tubing. The balloon must be removed immediately as helium and blood can create a rock-hard thrombus making surgical removal necessary.

Vascular complications are the most commonly encountered complications of IABP counterpulsation. The most catastrophic complication is an aortic or iliac artery dissection or rupture. Fortunately, this is an uncommon occurrence. Equally catastrophic is paraplegia from a periadventitial aortic hematoma or as the consequence of embolization of atherosclerotic debris to the spinal cord. Embolization or altered perfusion to visceral vessels can also occur with IABP counterpulsation. The most common vessels involved are the renal arteries. This usually occurs in the presence of significant atherosclerotic disease in the aorta. Altered perfusion of the kidneys and renal failure can happen if the balloon is situated below diaphragm.[92] The IABP can also restrict perfusion to the LIMA if it is advanced too far proximally into the subclavian artery.[93] Distal limb ischemia is the most common complication of the IABP. The occurrence rate is 5–10% and occurs more commonly with percutaneous placement, in women, and in patients with small femoral arteries. Heparin therapy is advisable if the IABP is in place more than 2–3 days after surgery. The management of compromised distal perfusion begins by knowing the preoperative vascular status of the patient as well as obtaining a baseline status of the distal extremities with physical examination and Doppler assessment as soon as possible after implantation of the IABP. Thereafter, the distal pulses or Doppler signals should be assessed hourly and recorded along with the vital signs of the patient. If the pulses or Doppler signals deteriorate, initially rule out peripheral vasoconstriction from hypothermia, low cardiac output, or as a result of vasopressor agents. If limb ischemia persists, remove the sheath from the femoral artery if the IABP was inserted percutaneously. If distal perfusion remains compromised, then remove the balloon and place it on the contralateral side if counterpulsation remains necessary. Femoral artery exploration is necessary if IABP removal does not improve the vascular integrity of the threatened limb. If the patient remains dependent on the IABP and the femoral artery approach is not feasible any longer, consider the transthoracic approach.

Thrombocytopenia can occur from the mechanical destruction of the platelets by the IABP. Thrombocytopenia may also be related to drug interactions (heparin, amrinone, etc.) When the IABP is implanted, a platelet count should be checked daily and if a downward trend develops, then every 8–12 h.

Circulatory Assist Devices

Circulatory assist devices were introduced by Cooley and his associates in 1969.[94] These devices, commonly referred to as ventricular assist devices (VADs), are used as a bridge to transplantation, a bridge to recovery, and for support after cardiac surgery. They are the ultimate therapy for low cardiac output. They are usually employed intraoperatively for failure to wean from cardiopulmonary, but can also be an option postoperatively if the patient fails to respond to vasoactive agents and the IABP. VADs should be considered if the patient does not respond to maximum medical therapy including the IABP.[95,96] The therapeutic strategy of VADs is to provide sufficient flow to support the systemic and/or pulmonary circulation while the myocardium recovers. Short-term devices are used if there is a reasonable chance for recovery, whereas long-term devices are considered if the chances of recovery are remote and the patient is a suitable candidate for transplantation. Prior to committing to circulatory assist, a thorough investigation for correctable causes of LCO must be made. Transesophageal echocardiography is helpful in evaluating ventricular wall motion and excluding other structural conditions related to the cardiac procedure. Preload and afterload should be optimized, appropriate inotropic therapy instituted, and placement of the IABP accomplished before considering circulatory assist.[91] Circulatory assist can be left or right heart bypass or combined biventricular bypass. The general indications for VAD implantation include a complete and adequate cardiac surgical procedure, the correction of all metabolic problems, the inability to wean from cardiopulmonary bypass, the inability to reverse deteriorating hemodynamic embarrassment despite maximum drug therapy and IABP, and a cardiac index less than 1.8–2 L/min/m^2.[22]

Left ventricular assist devices (LVADs) provide systemic perfusion while the left ventricle recovers. The indications for LVAD support include those general indications for VADs as well as a systolic BP less than 80 mmHg, left atrial pressure greater than 20 mmHg, SVR greater than 21 dyne s/cm^5, and urine output less than 20 mL/h.[97] LVADs require a left atrial cannula connected to an aortic cannula via a centrifugal pump. The LVAD flow is dependent on the intravascular volume and right ventricular function. The goal of management is a LVAD flow of 2.2 L/min/m^2. These devices reduce left ventricular wall stress by 80% and left ventricular myocardial oxygen demand by 40%. Monitoring mixed venous oxygen saturation can assess adequacy of tissue perfusion. After LVAD implantation, inotropic support should be discontinued to decrease myocardial oxygen demand. In some circumstances, an inotrope may be needed to support the right ventricle and vasoconstricting agents may be needed to maintain the SVR and a mean arterial pressure greater than 75 mmHg. Heparin therapy is necessary after postoperative bleeding stops and, particularly, when flow is decreased to less than 1.5 L/min. After 48 h of support, a TEE should be performed to assess the LV function. As the LVAD is weaned, a low-dose inotrope may be needed. Fifty percent of patients can be weaned successfully from LVAD and 25–30% survive to be discharged. Survival is improved in those patients with preserved right ventricles, no perioperative infarct, and a recovery of left ventricular function within 48–72 h. If ventricular function does not improve after 1 week of support, consideration should be made to

implant a long-term device as a bridge to transplantation if the patient is an appropriate candidate.[98]

Right ventricular assist devices (RVADs) provide support to the right ventricle (RV) and allow recovery much the same as do LVADs. The main contributing factor to right ventricular failure is an elevated pulmonary vascular resistance; however, it can also be the result of an RV infarction, or inadequate intraoperative protection. Indications for an RVAD include the general indications for VADs as well as a right atrial pressure greater than 20 mmHg, left atrial pressure less than 15 mmHg, and no tricuspid regurgitation. Right heart bypass is established by connecting the right atrial cannula to a pulmonary artery cannula via a centrifugal pump. Despite the presence of an RVAD, adequate systemic flows depend on intact left ventricular function.[99] Management goals are an RVAD flow of 2.2 L/min/m^2 and an increase in left atrial pressure to 15 mmHg while maintaining a right atrial pressure of 5–10 mmHg. Impaired RVAD support may be the result of hypovolemia or inadequate cannula drainage. During RVAD support, if the patient becomes hypotensive it may be the result of hypovolemia, left ventricular dysfunction, or a decreased systemic vascular resistance. A TEE to assess the left ventricular function may be appropriate at this time as well as the use of an inotrope or vasopressor. Interval TEE examinations may be used to assess the recovery of the right ventricle, and weaning criteria are the same as those for an LVAD.[22] From the standpoint of prognosis, generally patients requiring RVAD have a poor prognosis. Weaning is accomplished in only about 35% and survival to discharge in about 25%.[99]

Biventricular failure occurs in 10–15% of patients requiring postoperative circulatory assist. *Biventricular assist devices* (BiVADs) support both pulmonary and systemic circulation and can even be used in periods of ventricular fibrillation. The indications for BiVAD implantation are a right atrial pressure greater than 20–25 mmHg, left atrial pressure greater than 20 mmHg, no tricuspid regurgitation, and inability to maintain LVAD flow greater than 2.0 L/min/m^2 with a right atrial pressure greater than 20 mmHg. It is not an unusual circumstance for LVAD implantation to unmask right ventricular dysfunction and the need for an RVAD.[100] BiVADs are managed to create a sequential adjustment of RVAD and LVAD flow achieving a systemic flow rate of 2.2 L/min/m^2. The heparin requirements, the assessment of recovery, and device weaning are the same as for the LVAD and RVAD.[22] Weaning is accomplished in 35% of patients and survival to discharge in only 20%. This poor prognosis is a reflection of the adverse impact biventricular failure has on survival.[99]

To be optimally effective, circulatory assist devices as support for LCO require adequate pulmonary function and gas exchange. In circumstances of compromised cardiac and pulmonary function, cardiopulmonary function support is also required. Cardiopulmonary support (CPS) is accomplished with a portable centrifugal pump, membrane oxygenator, heat exchanger, and heparin-coated tubing. This system is generally referred to as *extracorporeal membrane oxygenation* (ECMO). Indications for ECMO or CPS are those of VADs in association with impaired oxygenation. ECMO can also be used for cath lab catastrophes or in support of high-risk angioplasty.[101,102] Only two cannulae are required for ECMO/CPS support, a venous drainage cannula and arterial perfusion cannula. If the sternum is open, the cannulation technique is the right atrium and aorta. The percutaneous cannulation can also be used using the common femoral artery and vein or the jugular vein. Since this system does not completely divert all the blood from the LV (pulmonary venous return to the LV persists), the LV is not completely decompressed, and a beating heart and competent aortic valve is necessary. An IABP is frequently concomitantly used to provide augmented pulsatile coronary perfusion.[103] The management of the patient on ECMO/CPS is complicated and labor intensive. It requires an experienced, committed, and well-trained staff. Preload must be optimized and the SVR may need support with α-agonist agents or vasopressin. Pulmonary artery hypertension must be controlled and may require using inhaled nitrous oxide. If renal failure occurs, consider early continuous venovenous hemofiltration. Ventilation with low tidal volumes is helpful.[22] Heparin-coated tubing may eliminate the need for full anticoagulation, but heparin anticoagulation is required to prevent excess fibrin formation in the oxygenator membrane. The activated clotting time (ACT) is maintained 160 s by continuous heparin infusion.[91] The results of ECMO/CPS depend on the degree of organ dysfunction at the time of initiation and the indication for its use. If it was instituted for cardiac arrest, the survival is 31%.[104] Of those patients placed on ECMO/CPS for postcardiotomy cardiogenic shock, 40–50% will die on support and only half of those who do not will survive the hospitalization. Patients who survived 30 days had a 63% 5-year survival.[105,106]

Currently, there are a variety of *mechanical assist drive devices* available for ventricular assist. Selection of the particular device depends on the length of support required. There are short-term devices and long-term devices.[107] The short-term devices are non-implantable and employed if recovery of ventricular function is expected. The long-term devices function as bridges to transplant and may be a long-term alternative to transplant. These devices are pulsatile, implantable, and provide total support of circulation. The selection of a long-term support device is rarely a consideration in the acute care management of the postoperative open-heart patient. However, a working understanding of the short-term devices may be required in the management of the postoperative patient with low cardiac output. The complications of these devices include mediastinal bleeding, mediastinal sepsis, thromboembolic events, renal failure, malignant ventricular arrhythmias, respiratory failure, refractory systemic vasodilatation, and immunocompromise.

Common Postoperative Hemodynamic Problems

Most patients return to the intensive care unit following open-heart surgery with an arterial line, Foley catheter, and usually a thermodilutional Swan–Ganz catheter. The hemodynamic

status of the patient can be determined by careful assessment of data provided by these monitoring devices. With information collected by these monitoring devices, an accurate and real-time profile of the patient's hemodynamic status can be calculated and appropriate therapeutic interventions prescribed. The following is a discussion of commonly encountered hemodynamic situations in the postoperative open-heart patient.

Hypotension with Normal Cardiac Output

This is a very common postoperative occurrence. It usually occurs with rewarming and responds well to volume expansion. If hypotension persists despite volume expansion, or if presenting hypotension is severe, consider temporizing with a vasopressor such as phenylephrine or norepinephrine. The systemic vascular resistance (SVR) and cardiac output/index must be followed closely when using either drug. The hemodynamic effects of *phenylephrine* are purely α-adrenergic and act to increase the systemic vascular resistance. It has no cardiac effects. The indirect cardiac effects include a decrease in cardiac output caused by an increasing afterload as well as a potential increase in the cardiac output by raising perfusion pressure in coronary arteries. Patients may become refractory to the therapeutic effects of phenylephrine after several hours and may require a change to norepinephrine. The starting dose of phenylephrine is 5 mcg/min and increase to effect up to 500 mcg/min, with the usual dosage range of 0.05–1.5 mcg/kg/min. If there is inadequate therapeutic response to phenylephrine, switching to *norepinephrine* may prove effective. Norepinephrine has powerful α-adrenergic properties and some weaker β-adrenergic effects. The α-adrenergic stimulation will increase the systemic blood pressure by increasing the SVR. The β-adrenergic effects will increase contractility and heart rate. Clinically, the α-adrenergic effects predominate and will increase myocardial oxygen demand and may cause a fall in cardiac output despite its β-adrenergic effect on contractility. The vasoconstrictive effects of norepinephrine may increase organ perfusion pressure but decrease absolute blood flow and result in visceral ischemia; this is an important potential adverse effect of this agent. The initial dose of norepinephrine is 1 mcg/min (0.015 mcg/kg/min) and titrate to effect. Recall that at doses greater than 20 mcg/min (0.2 mcg/kg/min), visceral and peripheral perfusion is reduced to such an extent the patient may become acidotic.

Hypertension and a Normal Cardiac Output

This is another common occurrence and is seen in patients with normal left ventricular function. It is related to an increased arterial resistance secondary to hypothermia and increased levels of circulating catecholamines, plasma renin–angiotensin, and vasopressin.[22,108,109] Postoperatively, systemic hypertension is more commonly seen in patients with normal left ventricular function, preoperative hypertension, preoperative use of β-blockers, and patients having aortic valve replacement.[110] The adverse sequelae of systemic hypertension include exacerbation of any latent myocardial ischemia by increasing afterload, stresses on suture lines, a predisposition to bleeding, and an increased potential for stroke and aortic dissection.[22,111] Hypertension may be the result of hyperdynamic cardiac function or peripheral vasoconstriction, or both; and a hemodynamic profile must be ascertained before initiating therapy so as to direct therapy at the appropriate cause. The usual criterion for pharmacologic treatment is a mean arterial pressure 10% above the upper level of the normal patient-specific mean arterial pressure (MAP), usually greater than 96 mmHg, or arbitrarily, a systolic blood pressure greater than 140 mmHg (MAP greater than 110 mmHg). In managing the postoperative hypertensive patient, a few caveats are important to keep in mind. First, a patient with a history of long-standing hypertension or critical carotid stenosis may require a higher perfusion pressure to maintain adequate cerebral and renal perfusion. Secondly, a patient with a tenuous aorta or thin-walled vein grafts may require a lower pressure to avoid suture line dehiscence and catastrophic hemorrhage.

The treatment goal in this scenario is to lower the SVR and reduce myocardial oxygen demand without adversely affecting coronary artery perfusion. The treatment of systemic hypertension in the early postoperative period is vasodilator therapy. This can be augmented with β-blocker therapy, calcium channel blocker therapy, angiotensin converting enzymes (ACE) inhibitor therapy, and sedation, depending on the clinical circumstances.

The vasodilator of choice for systemic hypertension postoperatively is *sodium nitroprusside* (SNP). SNP has a rapid onset of action and can produce rapid and excessive hypotension, but it has a short half-life. It is imperative that filling pressures are optimized before beginning SNP, or a hypotensive collapse will occur. SNP relaxes smooth muscle and as such decreases arterial resistance in the systemic and pulmonary circuit. It also relaxes venous capacitance vessels. It should be used with caution in the setting of myocardial ischemia as it can produce a coronary steal phenomenon. It has the potential for either short-term cyanide toxicity or thiocyanate toxicity with prolonged use.[112] SNP can also cause hypoxemia by opening intra-pulmonary shunts. The dosage is initiated at 0.1–0.25 mcg/kg/min and titrated to a maximum dose of 8 mcg/kg/min.

Nitroglycerine (NTG) is primarily a venous dilator that lowers blood pressure by reducing preload, filling pressures, stroke volume, and cardiac output. Since its primary action is on venous vessels, it usually maintains arterial diastolic pressure, but at high doses can produce arterial dilatation of varying degree and lower coronary artery perfusion pressure. NTG must be used with care if the patient is hypovolemic or the cardiac output is marginal, as reducing preload further will reduce cardiac output further and produce a reflex tachycardia. NTG works best in the hypertensive patient with active ischemia and high filling pressures.[113] The major adverse effect of NTG is methemoglobinemia and impaired oxygen

transport. The dosage begins at 0.1 mcg/kg/min and can be titrated up to 10 mcg/kg/min.

Hydralazine is a direct arterial vasodilator that can be used to unload the left ventricle and treat systemic hypertension. It produces arterial vasodilatation and usually a compensatory tachycardia. In the immediate postoperative period, it is used as a supplement to other agents and not as the primary drug for the management of hypertension. Hydralazine most commonly is used in the hemodynamically stable patient that remains hypertensive several days postoperatively but is unable to take oral medications. The dosage is 5–10 mg IV bolus every 4 h as needed.

Calcium channel blockers primarily produce antihypertensive effects by relaxing vascular smooth muscle. They are very effective for managing postoperative hypertension, but do have a variety of cardiovascular hemodynamic effects and conduction alterations specific to each particular agent. Calcium channel blockers are also used for the treatment of coronary spasm and rapid atrial tachycardias as well as for hypertension.

Nicardipine is a strong systemic and coronary vasodilator that does not cause coronary steal or tachycardia. It has little or no effect on the venous system and can be used without great concern for altering preload. The onset of action is rapid and has a relatively long half-life of 40 min. Nicardipine is not a negative inotrope and has no effect on AV conduction. The dosage is an initial IV bolus of 2.5 mg over 5 min and repeat every 10 min to a total dose of 12.5 mg, then begin an infusion of 2–4 mg/h.

Diltiazem also acts as a peripheral vasodilator that reduces SVR; however, it decreases cardiac output as a result of its negative inotropic and chronotropic (slows AV conduction) effect. Diltiazem is a good choice when hypertension is associated with coronary spasm because it is a potent coronary artery vasodilator. It is also a good option if hypertension is associated with atrial fibrillation and a rapid ventricular response. The dosage is 0.25 mg/kg IV bolus over 2 min and a repeat dose in 15 min of 0.35 mg/kg, then an infusion of 5–15 mg/h.

Verapamil is a peripheral vasodilator with moderate negative inotropic and chronotropic effects. Its indications for usage are similar to diltiazem. The dosage is 0.1 mg/kg IV bolus initially, then 2–5 mcg/kg/min infusion.

Nifedipine, like all calcium channel blockers, lowers blood pressure by reducing the SVR. It has potent vasodilatory actions. It causes a slight increase in heart rate and inotropy. When compared to SNP, an infusion of nifedipine has a more positive effect on cardiac output and a greater decrease in SVR. It has no effect on venous capacitance and preload.[114] Nifedipine is a potent coronary vasodilator and is an effective agent for managing suspected coronary spasm or arterial conduit spasm.[115] While an intravenous form is available, it is primarily given sublingually or orally at a dose of 10–30 mg every 4 h.

Amlodipine acts on the SVR as do all other calcium channel blockers and may result in an increased cardiac output as a result of decreasing afterload. It has no negative inotropic or chronotropic properties by virtue of its lack of effect on the SA and AV nodes. Amlodipine exerts its antihypertensive effect gradually over a 24-h span and is used mainly for the long-term management of hypertension. The dose of amlodipine is 2.5–10 mg daily.

β-*blockers* reduce pressure by negative inotropic and chronotropic actions. They reduce contractility, lower stroke volume and cardiac output, and lower heart rate. These agents are used to control hypertension associated with normal or hyperdynamic cardiac output, especially if the patient is tachycardic.

Esmolol is an ultrafast, short acting, cardioselective agent. Because it is so short acting, it is the β-blocker of choice for transient hypertension in a hemodynamically unstable patient. It should be used with caution in a patient with marginal cardiac output. The reduction in blood pressure is generally greater than the reduction in heart rate. It is cardioselective and can be used in a patient with bronchospasm. The dosage is an initial dose of 0.25–0.5 mg/kg over 1 min, followed by 50 mcg/kg/min over 4 min followed by a continuous infusion titrated to effect. If an adequate response is not obtained after the initial dose, another loading can be given followed by 100 mcg/kg/min over 4 min. There is little to be gained by cumulative doses of more than 200 mcg/kg/min.

Labetalol has α-adrenergic and β-adrenergic blocking effects as well as a direct vasodilatory effect. The α-adrenergic blocking effect prevents reflex vasoconstriction.[116] This agent is used when a longer-acting antihypertensive effect is needed because its duration of action is 6 h. Labetalol has a rapid onset of action resulting in a blood pressure response within 5 min. The dosage is 0.25 mg/kg IV bolus over 2 min, with subsequent dosing at 0.5 mg/kg every 15 min until desired effect is reached or a total dose of 300 mg is administered.

Metoprolol is a cardioselective β-blocker used mainly to control ischemia or to slow ventricular response in atrial fibrillation, but rarely can it be used to treat postoperative hypertension. The onset of action is 2 min and duration of action is about 5 h. The dosage is 5 mg IV bolus every 15 min until the desired effect is reached or a total dose of 15 mg.

Propranolol is a non-cardioselective agent with a long duration of action and has negative inotropic effect and as such is rarely used to treat postoperative hypertension. The dosage is in 0.5 mg increments given every 2–5 min until desired effect is reached or a total dose of 0.1 mg/kg.

Enalaprilat is an ACE inhibitor that reduces blood pressure by inhibiting the activation of the renin–angiotensin system. It causes a balanced arterial and venous dilatation and acts to reduce myocardial oxygen consumption by its action on preload and afterload. It generally does not cause a reflex tachycardia. Enalaprilat can be used alone or as a supplement in situations requiring high doses of nitroprusside or nicardipine. The onset of action is 15 min and usually has a 4-h duration of action. The dosage is 0.625–1.25 mg IV over 15 min every 6 h. It can be used as a continuous infusion of 1 mg/h with a doubling of the dose every 30 min until the desired effect is reached or a total dose of 10 mg.[117]

Fenoldopam mesylate is a dopamine receptor agonist that is a rapid-acting peripheral and renal vasodilator. It is indicated for the short-term management of severe hypertension. Fenoldopam mesylate causes a rapid fall in blood pressure and a reflex tachycardia. Other hemodynamic effects include increase in stroke volume index and cardiac index attributed to the fall in SVR. There is also an associated fall in pulmonary vascular resistance that may make its use beneficial in patients with pulmonary artery hypertension and RV failure. These properties make it an option for the management of postoperative hypertension in the cardiac surgical patient.[118] It also has a beneficial effect on the kidneys. It dilates renal afferent arterioles and increases renal blood flow. The dosage of fenoldopam mesylate is an initial infusion of 0.05–0.1 mcg/kg/min and increases at increments of 0.05 mcg/kg/min to the desired effect or a maximum of 0.8 mcg/kg/min. The renoprotective dose is 0.1 mcg/kg/min and is usually not associated with hypotension. While it has been shown to be effective in the management of postoperative hypertension in the cardiac surgical patient, it is not cost-effective and should be reserved for instances when other agents are ineffectual.

Low Cardiac Output and Normal Left Ventricular Function

The two most common causes of this scenario are right ventricular failure and diastolic dysfunction. *Right ventricular failure* is rarely an isolated clinical situation. When it is, it is the result of poor intraoperative protection or a right ventricular infarct. More commonly, it is associated with pulmonary artery hypertension, either preexisting or the result of infused vasoconstricting adrenergic agents, administration of blood products, a type III protamine reaction, hypoxemia, acidosis, or a tension pneumothorax. The hemodynamic hallmark of RV failure is a central venous pressure (CVP) higher than the pulmonary artery diastolic pressure (PAD) or pulmonary capillary wedge pressure (PCWP). TEE is an excellent mode of RV assessment and diagnosis of RV failure.[119] The treatment of RV dysfunction begins by optimizing preload to a CVP of 18–20 mmHg. Pushing the CVP higher may result in RV dilatation and exacerbation of RV dysfunction. Also, a distended RV can have an adverse effect on the LV by shifting the intraventricular septum into the LV and impairing LV filling and stoke volume. Hypoxemia, hypercarbia, and acidosis must be corrected as these adversely affect RV function. There must be active transport of volume from the right atrium to the RV, so it is imperative that atrioventricular (AV) conduction be maintained or established using sequential AV pacing if necessary. The addition of inotropic support is often necessary. Inotropes that support biventricular function and are pulmonary vasodilators should be selected. The phosphodiesterase inhibitors are reasonable agents, but their action on the SVR may necessitate the use of α-adrenergic agents and lead to further vasoconstriction of the pulmonary vasculature. Isoproterenol may improve RV contractility, but its proarrhythmic effects may not be well tolerated.

When RV failure is associated with an elevated pulmonary vascular resistance (PVR), it is mandatory to decrease RV afterload by using a *pulmonary vasodilator*. The pulmonary vasodilators have no direct effect on RV or LV inotropy. Their effect is indirect by afterload reduction of the RV. *Nesiritide* (see prior description) is a synthetic β-type natriuretic peptide that reduces pulmonary artery pressure and unloads the RV. It also has vasodilatory effects on the SVR and renal arterioles resulting in improved cardiac output and a synergistic effect with loop diuretics.[120,121] *Inhaled nitric oxide* (iNO) is a selective pulmonary vasodilator and decreases RV afterload. This results in enhanced RV performance. It has little, if any, effect on the SVR.[122] Inhaled nitric oxide is administered through a ventilator circuit designed to mix O_2 and NO. This generates a low level of NO_2, which must be monitored as it is toxic to lung parenchymal tissue. Inhaled nitric oxide is quite effective, but it is cumbersome and expensive. The usual dose is 10–40 ppm administered through a ventilator circuit. *Prostaglandin* E_1 and its analogs, *epoprostenol* and *iloprost,* are potent pulmonary vasodilators effective in the treatment of pulmonary hypertension. These agents are most frequently used in cardiac transplantation, but have been used effectively after mitral valve surgery.[58,123,124]

Diastolic dysfunction is a function of impaired myocardial relaxation. In the postoperative period, it results in LCO with normal or elevated filling pressures in patients with normal or hyperdynamic LV function. It is commonly seen in small women with left ventricular hypertrophy from hypertensive cardiovascular disease or aortic stenosis. Severe diastolic dysfunction is associated with reduced left ventricular compliance exacerbated by edema often associated with ischemic cross-clamping, reperfusion, and CPB. Inotropic agents used to treat the LCO in the postoperative period will worsen diastolic dysfunction. Diastolic dysfunction is frequently associated with tachycardia.[125] The filling pressures are high and stroke volume reduced because the impaired left ventricular relaxation leads to impaired filling of the LV and a deceased LV end-diastolic volume (LVEDV). Swan–Ganz monitoring confirms high left-sided filling pressures and LCO. The SVR is elevated as a compensatory mechanism. TEE is diagnostic. It confirms a hypertrophic LV with decreased compliance and filling. The LV may be so hyperdynamic as to obliterate the LV cavity at end-systole. Diastolic dysfunction is difficult to manage. If not managed successfully, end-organ dysfunction is inevitable. The initial steps in management are to assure AV synchrony and adequate preload. Volume should be infused until the PCWP is 20–25 mmHg to increase LVEDV. Intuitively, it may seem inappropriate to give volume in the setting of elevated filling pressures, but the elevated filling pressures are the consequence of impaired LV compliance and not volume overload. Inotropic agents should be replaced with lusitropic agents. ACE inhibitors may improve diastolic compliance. Calcium channel blockers also have some lusitropy and may be of benefit. Finally, inamrinone and milrinone have lusitropic properties as does nesiritide. There is no one agent

shown to be better than the others and often management requires courses of therapy and observation. If the patient can be guided through the first few days, the cardiac output gradually improves.[22]

Arrhythmias

Cardiac arrhythmias carry a source of morbidity and mortality in the postoperative surgical patient. These arrhythmia are usually an indicator of some underlying abnormality and should alert the clinician to closely evaluate the patient. In addition to standard electrocardiograms (EKG), the temporary atrial and ventricular pacing wires are useful in the diagnosing and treatment of postoperative arrhythmias.[126] The ideal postoperative rhythm is sinus rhythm at 70–110 bpm.[127] *Sinus tachycardia* is frequently seen in the early postoperative period and is most commonly caused by vasodilatation secondary to rewarming, reperfusion injury to the left ventricle secondary to cardiopulmonary bypass, sympathomimetic drugs, pain and anxiety as the patient awakens from anesthesia, normovolemic anemia, withdrawal from β-blocker therapy, occasionally fever, and idiopathic.

Ventricular Ectopy

Isolated ventricular ectopy may be an indication of ongoing myocardial ischemia, particularly within the first 6 h postoperatively. Other causes of ventricular ectopy are hypokalemia, hypomagnesemia, hypoxia, preexisting ectopy, sympathomimetic drugs, and mechanical irritation from the Swan–Ganz catheter. There remains controversy as to the significance of isolated ventricular ectopy. It is not clear what the incidence of isolated premature ventricular contractions (PVCs) degenerating to malignant ventricular arrhythmias actually is. However, most agree that in the presence of active myocardial ischemia, pharmacologic suppression is indicated and this concept includes those patients in the first 24 h after surgery when the myocardium may be irritable. Unlike chronic pharmacologic treatment of isolated ventricular ectopy, treatment in the acute postoperative period is not usually associated with the risk of proarrhythmia. Treatment is particularly beneficial in patients with LV dysfunction and ejection fractions less than 40%. In the first 24 h after surgery, ventricular ectopy is treated if the ectopic beats occur at a rate greater than 6 beats/min or ventricular tachycardia of less than 1 min. The treatment of PVCs begins with the correction of any underlying correctable cause such as hypokalemia or hypomagnesemia. If atrial wires are present, overdrive atrial pacing at a rate greater than the current sinus rate can be tried. *Lidocaine* is the initial drug treatment for ventricular ectopy. The dosage is an initial loading dose of 1 mg/kg as an initial bolus followed by one or two additional doses of 0.5 mg/kg mg every 10 min. After the initial bolus, an infusion of 1–2 mg/min can be started. An alternative option is an initial bolus of 75 mg followed by a loading infusion of 150 mg over 20 min. The loading dose is followed by a maintenance dose of 1.5–2.5 mg/min. If the ectopy is uncontrolled, an additional bolus of 25–50 mg can be given and the infusion rate increased. Lidocaine toxicity is a significant risk at infusion rates greater than 4 mg/min, especially in the elderly. If lidocaine does not suppress ectopy, it can be elected not to treat unless ventricular tachycardia occurs or with intravenous amiodarone.

Sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) are usually associated with acute myocardial ischemia or infarction or an electrolyte imbalance, but can occur without the obvious presence of either.[128] These arrhythmias are most often seen in patients with previous infarcts and subsequent revascularization to the infarcted area, and occur with a frequency of 1–3% after cardiac surgery.[129] Reperfusion of areas of ischemia or infarction can precipitate VT of VF as the areas of ischemic myocardium are reperfused. The reperfusion arrhythmias occur in patients with unstable angina, recent infarction, and ejection fractions of less than 40%. In these circumstances, nonviable myofibrils embedded in the scar are triggered and this leads to an altered dispersion of repolarization and the development of reentry arrhythmias. The resultant ventricular arrhythmia is usually a sustained polymorphic VT with a normal QT interval as compared to the monomorphic VT noted in patients with a previous myocardial infarction and depressed LV function. This reentry arrhythmia rarely responds to lidocaine and usually requires amiodarone and possible β-blockade. The treatment of nonsustained VT in patients with preserved LV function is similar to the treatment of PVCs. In patients with ejection fractions less than 30% and nonsustained VT, the prognosis is poor without treatment, and an electrophysiologic evaluation is necessary as an implantable cardioverter-defibrillator may be indicated.[130] Sustained VT without hemodynamic instability can be managed with ventricular overdrive pacing. Cardioversion may be necessary if overdrive pacing is not successful or if the patient becomes unstable. An *amiodarone* bolus of 150 mg infused over 15 min followed by an infusion of 1 mg/min for 6 h, then 0.5 mg/min for 18 h should be prescribed. These patients will ultimately need an electrophysiologic evaluation. All patients with VT or AF with hemodynamic instability require immediate defibrillation as per ACLS protocol.[131] If the patient is unresponsive to defibrillation or persistence of hemodynamic instability, the sternotomy must be reopened emergently at the bedside. *Torsades de pointes* is an uncommon but malignant arrhythmia not often related to the postoperative cardiac surgical patient. On the EKG monitor, the QRS complex appears to "twist" around the isoelectric baseline. Its onset is usually pause-dependent, initiated by a PVC occurring at the end of a T wave. It is usually associated with a prolonged QT interval. Treatment of torsades de pointes is immediate cardioversion. If the patient is not hyperkalemic, potassium chloride should be administered to shorten the QT interval. Magnesium and β-blockers may eliminate the trigger and prevent recurrence. Finally, ventricular pacing at 90–100 bpm or an isoproterenol infusion of 1–4 mcg/min will shorten the action potential and prevent early afterdepolarization.[132,133] Be aware that a wide complex tachyarrhythmia does not necessarily indicate ventricular tachycardia because atrial fibrillation with a rapid ventricular response

can result in RBBB with aberrant conduction (so-called Ashman phenomenon) mimicking ventricular tachycardia.[20]

Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia after cardiac surgery. Despite the recent institution of prophylactic regimens for AF, the overall incidence remains 25–30%. It has an occurrence of 10–40% after coronary artery bypass graft (CABG) surgery and up to 65% of patients undergoing combined CABG valve procedures.[134–136] After on-pump coronary artery bypass surgery, the incidence is 27–33%,[127,135] after minimally invasive CABG it is 19%, and following valve surgery it is 30–70%.[137,138] There is controversy as to whether off-pump CABG has a lower incidence of AF.[139] Patient's age appears to be the most powerful predictor of the occurrence of AF. The incidence is 3.7% in patients less than 40 years of age and 28% in those older than 70.[127,135] Other predictors are a history of congestive heart failure, preoperative atrial fibrillation, and chronic obstructive pulmonary disease.[140–142] Atrial fibrillation is most likely to occur 2–4 days after surgery. The episodes of these arrhythmias may recur or persist for up to 6 weeks before resolving spontaneously. Ten to 15% of patients are discharged in atrial fibrillation whereas 80% will return to sinus rhythm within 1–3 days with only digoxin or β-blockade therapy.[138,143–145] It is a leading cause for readmission after early discharge.

The management of postoperative AF begins with an assessment of the patient. If the patient is unstable, immediate *cardioversion* is indicated. A synchronized shock of 50–100 J is applied. Rarely is this the only treatment necessary, as the patient often reverts back to AF, especially if this occurs in the early postoperative period. If the patient is hemodynamically stable, the initial treatment of postoperative AF is rate control and is indicated if it lasts longer than 15–30 min or is associated with severe symptoms.[138] The most important aspect of the treatment of postoperative AF is the control of the ventricular rate. In many protocols, the first-line agent for rate control is the calcium channel blocker *diltiazem*. Therapy is initiated with a bolus of 0.25 mg/kg over 2 min and followed by an infusion of 10–15 mg/h to titrate the heart rate to less than 120 bpm. Slowing of the ventricular rate is usually noted within 3 min and is more effective for atrial fibrillation than atrial flutter. The use of diltiazem is limited by hypotension, which occurs with an incidence of 5–20%.[146,147] Pretreatment with 500 mg of calcium may lessen the hypotensive effect. Diltiazem has a mild negative inotropic effect and must be used with caution in patients with compromised left ventricular function. While diltiazem is extremely effective in slowing the ventricular rate, it converts fewer than 10% to sinus rhythm. *Verapamil* can be used in lieu of diltiazem for rate control in rapid atrial fibrillation. Begin with a bolus of 20–25 mg, then an infusion of 10–15 mg/h. If the blood pressure is tenuous, pretreat with 500–1,000 mg of calcium chloride. While calcium channel blockers are effective rate control agents, they are not as effective as β-blockers in converting patients back to normal sinus rhythm (NSR). Beta-blockers are equally or more effective for rate control and also can effect conversion to NSR 50% of the time.[148,149] They are not used as frequently for postoperative AF by some clinicians because of their negative inotropic properties. *Esmolol* is a short acting, selective β-blocker. It must be used in an ICU setting with appropriate monitoring because of its propensity to cause hypotension, particularly in patients with poor LV function. The loading dose is 0.25–0.5 mg/kg over 1 min followed by an infusion of 50–200 mcg/kg/min. *Metoprolol* has less of a tendency to cause hypotension and is more suited for use in a non-ICU area. It is a long-acting, selective β-blocker. It is dosed at 5 mg IV every 5 min to a total dose of 15 mg. *Digoxin* has only a modest response in the acute setting. There is only a 10–15% decrease in ventricular rate with digoxin alone.[150]

At least half of the patients remain in AF after the rate has been slowed. An effort should be made to cardiovert the patient back to sinus rhythm. If the patient is hemodynamically unstable, electrical cardioversion is an option. There is a high incidence of recurrent atrial arrhythmia unless an antiarrhythmic regimen is instituted.

Currently in many institutions the antiarrhythmic of choice is *amiodarone*. Amiodarone has properties of class III antiarrhythmics and β-blockade. It is becoming the drug of choice for postoperative AF because it is safe and effective. It is associated with only modest hypotension and has no proarrhythmic effects. It does slow the ventricular rate as effectively as β-blockers or calcium channel blockers, which are often used as adjuncts to amiodarone.[151] It does have a higher rate of cardioversion than either calcium channel blockers or β-blockers. Amiodarone has the same frequency of cardioversion as type 1C antiarrhythmics, but takes longer.[152] Amiodarone has fewer adverse side effects than those antiarrhythmics. It can be given intravenously, but is just as effective orally for non-life-threatening arrhythmias. The half-life of the drug is long, up to 120 days, and its long-term use is associated with visual disturbances, tremors and other neurologic sequelae, hepatitis, pulmonary fibrosis, photosensitivity, skin discoloration, thyroid abnormalities, and cardiac conduction disturbances. These side effects, however, are rarely a factor when used to treat postoperative atrial fibrillation because amiodarone is administered only for 6 weeks. If given intravenously, the initial loading dose is 150 mg over 15 min, followed by an infusion of 1 mg/min for 6 h, then 0.5 mg/min for 18 h. An oral taper dose is then prescribed of 400 mg bid for 1 week, 400 mg daily for 1 week, then 200 mg daily for 2 weeks. If the patient has no further episodes of AF, it can be discontinued at that time.

Procainamide is a type 1A antiarrhythmic that once was a first-line antiarrhythmic for the postoperative cardioversion of AF in most centers. It restores NSR in 87% of patients within 40 min.[153] Procainamide is proarrhythmic and has a mild negative inotropic effect. It is associated with more short-term side effects than amiodarone. It has vasolytic properties and as such should not be used until the ventricular rate has been slowed to

less than 120 bpm. The loading dose is an intravenous bolus of 17 mg/kg (dose not to exceed 1 g total) at a rate not exceeding 30 mg/min. This can be followed by an infusion of 2 mg/min or converted to an oral procainamide derivative in 24 h. Up to one-third of patients cannot tolerate procainamide because of gastrointestinal, hematological, or immunologic side effects. This drug is cleared by the kidneys and blood levels of procainamide and its active metabolite, *N*-acetyl procainamide (NAPA), should be monitored, particularly, in patients with renal and hepatic dysfunction.[154]

Ibutilide is a rather new agent for the treatment of postoperative atrial fibrillation. The incidence of torsades de pointes is about 1–2%, which is considerably higher than with either procainamide or amiodarone.[154] Ibutilide is useful in patients with poor left ventricular function or chronic lung disease, but its use is limited by its proarrhythmic effect. Conversion to sinus rhythm occurs at a rate of 30–50% for atrial fibrillation and 50–70% for atrial flutter.[155] The dose begins with a bolus of 1 mg over 10 min with a second infusion 10 min later. No further dosing is indicated. The drug must be stopped if QT prolongation occurs as it may contribute to torsades, but sustained polymorphic ventricular tachycardia may occur even in the absence of QT interval prolongation.

There are several strictly oral agents that can be used for pharmacologic conversion back to sinus rhythm. *Sotalol* is useful as a single-agent therapy for atrial fibrillation cardioversion. It is a class III antiarrhythmic with beta-blocking activity. It can cause prolongation of the QT interval and initiation of therapy must be done while monitoring the patient. The drug is limited mainly by its beta-blocking effects such as reactive airway disease, depression, and negative inotropy. The dose is 80–160 mg twice daily. *Quinidine* is still used by some clinicians for the conversion of atrial fibrillation to sinus rhythm. It may be slightly more effective than amiodarone, but it is being used with decreasing frequency.[156,157] Though quinidine is cost-effective and has very little negative inotropy, it is associated with a high incidence of side effects, particularly gastrointestinal, neurological, and hematological. Also, the proarrhythmic and frequent dosing make other agents a better choice. *Flecainide* can also be used for the management of atrial fibrillation. Flecainide was found to be associated with an increased mortality when given after a myocardial infarction, and created much concern when given with ischemic heart disease. It is not recommended for patients with structural heart disease.[158]

Postoperative atrial fibrillation is associated with increased morbidity and cost; therefore, there is great interest in the prophylaxis of postoperative atrial fibrillation. Multiple trials and multiple protocols have been investigated searching for an effective prophylactic regimen. The most effective and practical regimens all include preoperative β-blockade therapy started 12–24 h preoperatively.[159–162] Beta-blockade therapy given preoperatively and through the postoperative period is superior to their use only postoperatively. When given preoperatively and postoperatively, the incidence of AF is 17%.[163–165]

Magnesium sulfate has been used as prevention for postoperative AF. Hypomagnesemia is common after cardiac surgery and is associated with atrial arrhythmias. There is a debate as to whether routine magnesium administration lowers the incidence of postoperative AF.[166] It may be effective when used with β-blockers and when the serum magnesium is low.[167,168] Since it is relatively benign and may be potentially effective, some recommend its routine administration through the first postoperative day.

Sotalol is a β-blocker with class III antiarrhythmic properties. It reduces the incidence of postoperative AF by as much as 65% when given preoperatively and postoperatively.[169] Because it has β-blocker action, it must be used with caution in patients with LV dysfunction and those with marginal systemic blood pressure. It is excreted by the kidneys and is not recommended in patients with renal insufficiency. Sotalol can also cause QT interval prolongation and has been associated with torsades de pointes. It is not well tolerated in 20% of patients and must be withdrawn. The dose of sotalol is 80 mg twice daily.

Amiodarone is a class III antiarrhythmic with some properties of class I, II, and IV drugs. It is as effective as sotalol in preventing postoperative AF and can be used alone or in conjunction with β-blockers.[170–173] Amiodarone is particularly useful in patients with intolerance to β-blockers. It is rarely associated with pulmonary toxicity when used as a short-term therapy, but the rare incidence of amiodarone toxicity can cause hypoxemia.[174] As prophylaxis, amiodarone is started in the operating room as a 150 mg bolus over 15 min followed by an infusion of 1 mg/min for 6 h then 0.5 mg/min for 18 h. The oral dose of 400 mg twice daily is continued for 1 week. If the patient should develop AF, a 6-week regimen is recommended. In the event the patient should develop AF with either the sotalol or amiodarone prophylactic regimen, the ventricular response rate is usually slow and easier to manage. The efficacy of both sotalol and amiodarone as prophylaxis is better if started several days preoperatively.

Postoperative stroke as a consequence of atrial fibrillation is well documented. The incidence of stroke is between 3 and 7% in patients with postoperative atrial fibrillation as compared to 1–1.5% in patients without atrial fibrillation.[141,175] The risk of embolic stroke is substantial after 48 h or more of atrial fibrillation.[176] All patients with postoperative atrial fibrillation should be anticoagulated unless there is a contraindication. Anticoagulation should be started within 24–36 h of the onset AF.

Bradycardia

Bradycardia requiring pacing occurs in approximately 10% of postoperative patients. The most common defect is right bundle branch block (RBBB). About 5% of the patients will have permanent conduction abnormalities. The associated bradycardia is treated with temporary epicardial pacing. The most commonly used mode is ventricular pacing. In all the open-heart patients, temporary epicardial ventricular pacing wires are fixed to the right ventricle and, in many, right atrial wires are also placed.

Bradycardia from any etiology is an indication for ventricular pacing. If the patient is hemodynamically unstable with simple ventricular pacing, physiologic pacing may be required if atrial electrodes are available. If an atrial electrode was not fixed to the heart, a temporary transvenous atrial pacing electrode can be inserted. Simple ventricular pacing is accomplished by connecting the temporary electrodes to an external pacemaker. These pacemaker units are bipolar and require the ventricular lead electrode be connected to the negative pole and an indifferent electrode, often a skin wire, connected to the positive pole of the pacemaker. The output is set initially at 10 mA and the threshold adjusted to assure a safe margin of capture. A decision is then made as to the mode of pacing; i.e., synchronous (demand) or asynchronous (fixed). The synchronous mode is chosen to avoid pacer stimulation on the T wave and the resulting ventricular fibrillation. The asynchronous mode is used only in unusual situations, such as the use of electrocautery, when other electrical activity interfere with the sensing in the synchronous mode. The rate must be set depending on the needs of the patient. Physiologic pacing requires choosing the desired mode, atrial thresholds, atrioventricular intervals, as well as the ventricular settings. Failure to pace may be the result of faulty electrical connections, dislodgment of the epicardial electrodes from the heart, a faulty pacemaker, the development of electrically silent areas of the myocardium in the region of the electrodes, or the development of a rhythm incompatible with pacing such as atrial or ventricular fibrillation.

Hemorrhagic Complications of Open-Heart Surgery

Postoperative bleeding is always present to some extent. It is related to mechanical factors and coagulopathy. Mechanical factors are considered surgically correctable. Less than 3% of postoperative bleeding is from surgically correctable causes. It is usually indicated by bleeding greater than 200 mL/h with normal or near-normal coagulation studies. Mechanical bleeding is characterized by clots in the drainage tubes.[177]

Etiology of Coagulopathy

Coagulopathy is present to some extent in all patients after cardiopulmonary bypass. With the current aggressive use of percutaneous catheter intervention for the treatment of various acute coronary syndromes (ACS), drug-induced coagulopathy is frequently seen. Following deployment of stents for ACS, patients are placed on platelet inhibitors such as glycoprotein IIb/IIIa inhibitors (eptifibatide, tirofiban, or abciximab) or the ADP binding inhibitor clopidogrel. In some instances, acute myocardial infarctions are treated with thrombolytic therapy and this results in a profound coagulopathy.[178,179]

Fibrinolysis results from the activation of the fibrinolytic system either intrinsically from cardiopulmonary bypass or therapeutically from preoperative thrombolytic therapy.[180,181] This appears to be the primary cause in coagulopathy following cardiopulmonary bypass (CPB). A progressive fibrinolytic state occurs and its intensity is directly related to the duration of cardiopulmonary bypass.[182] It is associated with the degradation of clotting factors as well as platelet dysfunction.

Platelet defects are also an important cause of postoperative bleeding. The platelet-related bleeding diathesis is a result of a decrease in the absolute platelet number, and more importantly, secondary to impaired platelet function.[183,184] The decrease in the platelet number, or quantitative defect, results from hemodilution, preoperative thrombocytopenia from medications, and the consumption of platelets by the cardiopulmonary bypass circuit. The CPB circuit itself can reduce the platelet count by 30–50% and worsens as the duration of bypass lengthens. The diminished platelet function, or qualitative defect, may be directly related to the duration of CPB. Passage of platelets through the cardiopulmonary bypass circuit results in decreased platelet membrane receptors for fibrinogen and glycoprotein Ib and glycoprotein IIb/IIIa complex.[185] Thrombocytopenia may also be caused by *heparin-induced thrombocytopenia*. This usually occurs in patients with a previous exposure to heparin within 3 months. It is the result of heparin antibodies causing platelet aggregation. There is often a history of heparin resistance during CPB.[186] The qualitative defect in platelets may also be related to preoperative medications such as aspirin, heparin, and the glycoprotein IIb/IIIa inhibitors.[187,188] *Residual heparin effect* can account for a postoperative bleeding diathesis. Heparin effect is usually reversed by the time the patient gets to the intensive care unit. It should always be considered as a possibility in the bleeding patient. *Heparin rebound* is the recurrence of measurable heparin activity after complete protamine neutralization. It is associated with larger heparin doses given intraoperatively, after long CPB runs, and obese patients.[189] It is thought to be the result of elution of heparin from plasma proteins[190] *Hypothermia* is a significant cause for postoperative coagulopathy. The coagulation cascade is mediated by enzymatic reactions. These reactions are temperature-sensitive and occur most efficiently at normothermia. Hypothermia retards the normal coagulation cascade as a result of this altered enzymatic activity. *Hemodilution* of CPB is another source of coagulopathy and affects all blood elements including coagulation factors. Most factors are reduced by 50% and factor V by 80%.[191] This phenomenon affects patients with small blood volumes more profoundly. Also, coagulation factors are lost with cell saving.

Diagnosis of Coagulopathy

An attempt should be made to specifically diagnose the coagulopathy. The specific abnormalities can usually be diagnosed if appropriate studies are ordered. *Platelet defects* are both quantitative and qualitative. The diagnosis of quantitative defects, thrombocytopenia, can be made early in the postoperative period with a simple platelet count. If thrombocytopenia occurs later in the course, consider HIT and obtain a heparin–platelet aggregation test to confirm the presence of heparin

antibodies. Qualitative platelet defects, thrombasthenia, can be present with a normal platelet count but platelet function will be abnormal and the clot formation inadequate. The bleeding time is prolonged and indicates abnormal platelet aggregation and adhesiveness. *Residual heparin effect* is diagnosed by a prolonged partial thromboplastin time (PTT) and/or activated clotting time (ACT). Either a PTT or an ACT should be measured on admission to the intensive care unit because inadequate heparin reversal with protamine is usually seen early in the postoperative period. Generally, other laboratory values will be normal. A heparin–protamine titration test can be performed if the Hepcon system (Medtronic Inc., Minneapolis, Minnesota) is available. This test directly quantifies the amount of heparin circulating. It will detect any residual heparin and also allow for a calculation of the appropriate dose of protamine needed to neutralize the residual heparin. If the PTT or ACT are elevated 5 h after the last heparin dose, it is unlikely secondary to heparin as the half-life of heparin is 1 h; if heparin effect is suspected at this time, obtain heparin levels to confirm the diagnosis.[191]

Fibrinolysis is associated with an elevated PT and PTT; decreased levels of factors I, V, and VIII; rapid euglobulin clot lysis; and the presence of D-dimers. D-dimers indicate the presence of fibrin monomers, and their presence is diagnostic for fibrinolysis if accompanied by decreased fibrinogen levels. An elevated D-dimer alone is not uncommon, particularly if shed blood is being reinfused and in itself is not diagnostic of fibrinolysis.[192] *Disseminated intravascular coagulation* (DIC) is the severest form of coagulopathy. From a laboratory standpoint, it is manifested by an elevated PT and PTT, decreased fibrinogen levels, thrombocytopenia, and an elevated fibrin-split products (greater than 40 mcg/mL) and D-dimer.[193] DIC is rarely seen in the early postoperative period and usually is associated with other complications.[194]

Thromboelastography [195] and Sonoclot [196] analysis are two studies available in some institutions that have been shown to specifically identify the source of the bleeding diathesis. These studies are not commonly available. *Coagulation factor deficiencies* either from hemodilution or true deficiencies can be diagnosed by measuring the specific factors, but in the acute setting this may not be practical as obtaining these results is time-consuming. Increased PTT and PT (prothrombin time) usually manifest factor deficiencies. Specific studies can be ordered, but it is usually reasonable to proceed with the empiric treatment before results are available. There must be a high degree of suspicion for factor deficiencies in the patient with a previous or family history of abnormal bleeding, liver disease, prior warfarin therapy, hemodilution, or clinical evidence of disseminated intravascular coagulation.

Treatment of Coagulopathy

The treatment of a postoperative coagulopathy must be prompt and aggressive. The bleeding cycle must be interrupted as "bleeding begets bleeding."[195] The specific treatment consists of blood component therapy based on an accurate diagnosis. Initial therapy begins by sending coagulation studies to include a PT, PTT, platelet count, and fibrinogen level. Then, notify the blood bank that component therapy will be needed and an adequate supply of cross-matched packed red blood cells, fresh frozen plasma (contains all coagulation factors except platelets), cryoprecipitate (factor VIII and fibrinogen), and platelet concentrates should be readily available. Next, hypothermia should be corrected. Within the first 2 h and even before the coagulation studies are available, consider the empiric use of protamine sulfate in the event residual heparin or heparin rebound is the cause. If the bleeding continues after the hypothermia is corrected and the empiric protamine is given, an algorithmic approach can be used.[194] This algorithm begins by sending coagulation studies. Then, transfuse platelets, 1 unit/10 kg body weight, and draw post-transfusion platelet count. If the bleeding continues and the posttransfusion platelet count is less than 100,000, repeat the platelet transfusion of 1 unit/10 kg body weight. If the posttransfusion platelet count is greater than 100,000, *but* the fibrinogen is less than 100 mg/100 mL, give 1 unit of cryoprecipitate/4 kg body weight. If the posttransfusion platelet count is greater than 100,000, *but* fibrinogen is greater than 100 mg/100 mL, *and* the PT or PTT is less than 1.5 times control value, recheck for surgical bleeding and do a bleeding time; and if it is greater than 9 min, give desmopressin 0.3 mcg/kg IV. If the posttransfusion platelet count is greater than 100,000, *but* the fibrinogen is greater than 100 mg/100 mL, *and* the PT or PTT is greater than 1.5 times control value, give fresh frozen plasma 15 mL/kg. If bleeding persists at the completion of the algorithm, consult a hematologist.

In addition to blood component therapy, there are drugs available for the treatment of postoperative coagulopathy. *Protamine* is the specific drug for the reversal of heparin. The dosage is 25–50 mg increments given IV over 10 min. Be aware there are three types of adverse reactions to protamine administration. Type I reaction is systemic hypotension from rapid administration that usually occurs if the entire neutralizing dose is given in less than 3 min. It is a histamine release reaction that causes a reduction in the SVR and PVR. It can be avoided by giving the dose over 10–15 min. Type II reaction is an anaphylactic or anaphylactoid reaction resulting in hypotension, bronchospasm, flushing, and edema. It is further divided into Type IIA that is an idiosyncratic reaction mediated by IgE or IgG and is caused by the release of histamine or leukotrienes producing a capillary leak syndrome with hypotension and edema. It usually occurs within the first 10 min of administration. Type IIB is an immediate reaction and is not related to immunoglobulins. Type IIC is a delayed reaction occurring after 20 min or longer, and seems to be related to complement activation and leukotriene release producing bronchospasm and a capillary leak syndrome that leads to hypovolemia and noncardiac pulmonary edema. Type III reaction is catastrophic pulmonary vasoconstriction with acute pulmonary hypertension, right ventricular failure, and severe peripheral

vasodilatation with hypotension and myocardial depression. It occurs 10–20 min after the protamine is given and is thought to be secondary to the heparin–protamine complex. This complex incites leukocyte aggregation and the release of liposomal enzymes that damage pulmonary tissue. Type III reactions are highly lethal unless cardiopulmonary bypass can be reinstituted to support the patient. Treatment is initially calcium chloride and α-agonists to support the SVR. It may also be beneficial to add β-agonists to reduce the PVR. Specific drugs to lower the PVR (such as prostaglandin E) may be helpful, but usually it is necessary to readminister heparin and reinstitute cardiopulmonary bypass.

Desmopressin (DDAPV) has not been shown to be of benefit in the uncomplicated patient, but is of value in patients with platelet dysfunction secondary to uremia, liver dysfunction, and antiplatelet medications.[196–198] It is specific therapy for patients with an acquired defect in platelet plug formation as a result of a deficiency in von Willebrand's factor. The dosage is 0.3–0.4 mcg/kg IV over 20 min. *Epsilon-aminocaproic acid* (EACA) is an antifibrinolytic agent that inhibits conversion of plasminogen to plasmin. It may act to preserve platelet function. EACA is best used when given before cardiopulmonary bypass prophylactically, but it can also be used as a rescue agent for severe bleeding, especially if fibrinolysis is present.[199] It should be used with caution or not at all with aprotinin as the combination appears to cause a prothrombotic state with associated graft closure, renal dysfunction, and stroke. The rescue dose for postoperative bleeding is usually 5–10 g IV bolus.

Aprotinin is a serine protease inhibitor that preserves adhesive platelet receptors (GPIb) during the early phase of cardiopulmonary bypass. It also has antifibrinolytic properties by inhibiting plasmin. Aprotinin has been demonstrated to reduce blood loss when given before and during cardiopulmonary bypass in patients at high risk for postoperative bleeding, such as thrombocytopenia, uremia, hepatic dysfunction, and long complex procedures, particularly reoperations.[200] It does have a role as a rescue agent for postoperative bleeding, but must be used with caution as it may be prothrombotic in the nonheparinized patient.[201] The rescue dose is two million KIU. Aprotinin therapy has been associated with an increased morbidity and mortality in some studies and its use is controversial.

Blood Component Therapy

Blood component therapy includes packed red blood cells (RBCs), fresh frozen plasma (FFP), cryoprecipitate (factor VIII and von Willebrand's factor), and platelets. RBC transfusion should be managed by protocol and determined by the clinical status of the patient. RBCs are indicated in the anemic patient with normal LV function when the hematocrit is 22–24%.[29,202] If the patient is actively bleeding, the hematocrit should be maintained at 26% to afford a margin of safety.[22] If the patient is elderly or has LV dysfunction and cannot increase the cardiac output in response to anemia, the hematocrit should be maintained at a higher level. Platelet transfusions are indicated for a platelet count under 70,000 if the patient is bleeding excessively. FFP is recommended in the excessively bleeding patient for an INR (International Normalized Ratio) of greater than 1.5–1.7. Specific treatment with cryoprecipitate and other components is indicated in the presence of a consumptive coagulopathy as reflected by a diminished fibrinogen level, positive D-dimer assay, or the presence of fibrin degradation products.[91]

Blood Conservation

Blood conservation is an important part of managing the postoperative patient both with and without significant bleeding. There are preoperative measures, intraoperative measures, and postoperative measures. The preoperative measures include autologous blood donation for elective cardiac procedures. This must be done with care, particularly in the patient with ischemic heart disease or congestive heart failure secondary to valvular heart disease. Therefore, it is not a measure widely practiced. Another preoperative measure is the modification of the preoperative antiplatelet regimen within limits of therapeutic prudence. And, finally, preoperative erythropoietin can be used in the anemic patient to improve hemoglobin levels sufficiently to avoid perioperative transfusions.[203] Intraoperatively, the crystalloid prime of cardiopulmonary bypass circuit with resultant hemodilution to hematocrit of 20–30% minimizes the loss of red cells. Also, blood salvage with reinfusion of washed, centrifuged red cells, both from the field and from the circuit after separation from cardiopulmonary bypass, conserves blood. Careful operative hemostasis is a must for blood conservation. Postoperative autotransfusion and cell saving also conserve blood and reduce the complications of transfusions. The "cell saver" in most institutions has supplanted traditional autotransfusion techniques. The cell saver is a system that combines washing and centrifuging shed blood before reinfusing, as opposed to directly reinfusing shed blood after passing it though a filter. Shed blood does not require an anticoagulant because it has undergone fibrinolysis, unless the hemorrhage was extremely rapid. Shed, traditional autotransfused blood has low levels of factors VIII and fibrinogen as well as platelets, but the platelets present are dysfunctional. Autotransfused blood does contain fibrin-split products. Conversely, cell saver blood is devoid of clotting factors and platelets as well as fibrin-split products.[204] Transfusion of less than one liter of either autotransfusion blood or cell saver blood is without significant risk of exacerbating a coagulopathy. Transfusion of greater amounts can potentially worsen the coagulopathy by infusing fibrin monomers, in the case of autotransfusion, and from platelet and factor depletion with both.[205,206] Autotransfusion of greater than 1,500 mL of shed blood should be avoided and blood component therapy should be used to augment reinfusion of cell saver blood to avoid depletion of platelets and clotting factors.

Mediastinal Bleeding

Multiple factors contribute to postoperative bleeding.[207,208] Despite deficiencies in the coagulation cascade and multiple potential sites of surgical bleeding, mediastinal drainage slows

over the first few hours in the majority of patients. Aggressive management of the bleeding patient is generally successful, such that only about 1–3% of patients require reoperation for persistent bleeding. Normally, when the patient returns from the operating room, mediastinal drainage is in the order of 100–300 mL/h for the first 2–3 h and 50 mL/h thereafter.

The initial steps in managing the bleeding patient after open-heart surgery are aggressive treatment of hypothermia and hypertension, order coagulation studies, notify the blood bank to have blood products available, and consider an empiric dose of protamine. If coagulation studies indicate a coagulopathy, proceed with the algorithm for management. In any patient with excessive mediastinal drainage, cardiac tamponade must be considered. Be alert for the followings signs of tamponade: equalization of filling pressures, low cardiac output, hypotension, wide respiration variation of systolic blood pressure with positive pressure ventilation, and a narrowed pulse pressure. At times, the classic findings of tamponade may be absent, but the following points may signal tamponade: the sudden cessation of chest tube drainage, progressive low cardiac output in a patient with a previously normal cardiac output, an unexplained left or right heart failure, severe peripheral vasoconstriction with cyanosis of the ears and digits, progressive fall in the urine output, an unexplained tachycardia, mediastinal widening on chest X-ray, pleural effusion, and diminished ECG voltage.

There are caveats regarding cardiac tamponade in the immediate postoperative setting. First, a pulsus paradoxus is not an applicable sign of tamponade in the patient on positive pressure ventilation. Positive pressure ventilation reverses blood pressure response to respiration. On the ventilator, during early inspiration, the positive airway pressure causes a compression of the pulmonary veins augmenting left heart filling and thus blood pressure, whereas, later in the inspiratory cycle, left heart filling is diminished and the blood pressure falls. This early rise in the blood pressure is opposite of the fall in blood pressure seen during spontaneous inspiration and makes pulsus paradoxus an unreliable sign of tamponade during positive pressure ventilation. Also, it is not unusual for a clot to accumulate next to the right or left atrium and cause unequal elevations of the RA or LA pressures. Most important, the diagnosis will be made only if a high degree of suspicion is maintained. The diagnostic modality of choice for cardiac tamponade in the postoperative period is transesophageal echocardiography.

The definition of excessive mediastinal bleeding is 500 mL/h for 1 h, 400 mL/h for 2 h, and 300 mL/h for 3 h. If mediastinal bleeding persists despite correction of the coagulopathy or if the patient demonstrates evidence of hemodynamic compromise, mediastinal reexploration in the operating room is indicated. An aggressive approach to mediastinal reexploration is in the best interest of the patient. Reexploration is associated with increased mortality and morbidity usually because of a delay in proceeding.[209] Early reexploration reduces these complications.[210] An emergency reexploration in the intensive care unit is indicated for exsanguinating hemorrhage or impending arrest from any cause.

The technique for emergency reexploration begins with a call for the necessary assistance. Intubate the patient if necessary and hand ventilate the patient with inspired oxygen of 100%. Remove the dressing and pour antiseptic over the sternotomy incision and block drape the site with sterile towels. Reopen the incision with a scalpel and cut or untwist the wires. The sternum is opened with a sternal spreader. Then, evacuate the hematoma and attempt to identify the source of bleeding. If a bleeding site is identified, tamponade it with digital pressure. Proceed to complete the resuscitation of the patient. Ideally, the site of hemorrhage should be repaired in the operating room, but if this is not practical or feasible, repair it in the ICU.

If internal cardiac massage is needed, do so with two hands by placing the left hand beneath the heart and compressing the anterior aspect of the heart with the right hand using the palm and flattened fingers and take care not to injure the grafts. If the patient has a prosthetic mitral valve in place, take care not to injure the posterior left ventricle with the struts during internal massage. Once some semblance of hemodynamic stability has returned, return the patient to the operating room for repair of the bleeding site, irrigation of the mediastinum, and closure. If the reason for emergency re-sternotomy was hemodynamic collapse not related to bleeding or tamponade, placement of an IABP is highly recommended.

Noncardiac Complications of Open-Heart Surgery

Pulmonary Complications

After the heart, the lungs are the organs most likely to be dysfunctional after CPB. During CPB, neutrophils are sequestered in the pulmonary vasculature and oxygen free radicals cause peroxidation of membrane lipids. These changes produce pulmonary vasoconstriction and are thought to increase the permeability of the alveolar–capillary barrier and consequently produce interstitial edema within the lungs. Leukocytes are also activated and cause an inflammatory response of the pulmonary vasculature.[211] During CPB and diminished pulmonary arterial flow, plasma thromboxane B_2 increases, further contributing to the pulmonary vascular inflammation.[212] The cumulative effect of these responses is a more permeable alveolar–capillary membrane and a predisposition to interstitial pulmonary edema.[213] Atelectasis also contributes to pulmonary dysfunction. This appears in some way to be linked to a decrease in pulmonary surfactant, and may partially explain the left lower atelectasis seen almost universally after cardiac surgery.[214] Thermal injury to the phrenic nerve and/or diaphragmatic dysfunction as well as effusions, pain, and chest tubes are other contributing factors to altered pulmonary function postoperatively. Lung and chest wall compliance decrease significantly following cardiac surgery, with the maximum decrease occurring at 3 days and lasting as long as 6 days.

The respiratory management of the postoperative cardiac surgical patient is not unlike any other postoperative patient, but there are several factors that are unique to these patients. The unique factors include: incision pain, the interference of chest tubes with the respiratory function, an element of diaphragmatic dysfunction, elevated left heart filling pressures with alveolar edema and diminished compliance, and capillary permeability.[20,31,215] Atelectasis is the most common pulmonary complication occurring in 70% of these patients.[216] After cardiac surgery, atelectasis occurs most commonly in the left lower lobe. The exact etiology of this phenomenon remains unclear. It is associated with left phrenic nerve paralysis only in 11% of patients.[217] Alterations of the chest wall result in a decrease in the FEV_1 and FRC and persist for 6 weeks. These alterations lead to an increased respiratory rate, decrease tidal volume, decreased respiratory efficiency, and increased oxygen utilization. Pulmonary infiltrates are the result of pneumonia, pulmonary embolism, and adult respiratory distress syndrome (ARDS) – although with ARDS, there is typically more of a diffuse process and is associated with more severe hypoxemia. The basic treatment of pneumonia and ARDS includes blood and sputum cultures, hemodynamic maintenance, euvolemic fluid management with a consideration of fluid restriction and the use of colloid for ARDS, and the maintenance of an arterial saturation greater than 50 mmHg with minimum inspired oxygen content.[218–220] Bronchospasm can occur immediately after CPB and may interfere with hemodynamic stability. The probable cause is activation of C5a anaphylatoxin by CPB. Other causes include pulmonary edema, exacerbation of preexisting reactive airway disease, the use of β-blockers, and a reaction to protamine.[216] The treatment for bronchospasm includes the exclusion of heart failure, inhaled β_2-agonists, the addition of cholinergic agents, a short course of systemic steroids for refractory bronchospasm, and intravenous aminophylline. Aminophylline is reserved for refractory situations because of its arrhythmogenicity in the postoperative period.

Renal Complications

During CPB, renal blood flow and glomerular filtration rate are reduced 25–75%, with partial but not complete recovery in the first day after CPB.[221,222] This is thought to be secondary to renal artery vasoconstriction, hypothermia, and loss of pulsatile flow. The nonpulsatile blood flow of CPB promotes renal artery vasoconstriction and diminishes renal blood flow to the cortex. In addition, angiotensin II levels are elevated by nonpulsatile flow.[223,224] There appears to be a relationship between length of CPB and renal insufficiency, but not pressure or flow rates while on pump.[225] Other factors associated with renal failure include preexisting renal dysfunction (creatinine greater than 1.5 mg/dL), older age, poor left ventricular function and congestive heart failure, emergency surgery, the use of deep hypothermic circulatory arrest, moderate hypothermia, a preoperative history of hypertension, diabetes, and peripheral vascular disease, isolated valve operations, and the use of radiocontrast dye agents immediately preoperatively. Postoperative factors contributing to renal insufficiency include: low cardiac output; hypotension; vasoconstriction; atheroembolism from the IABP; sepsis; RV failure with systemic venous hypertension; respiratory insufficiency with hypoxemia; and medications such as cephalosporins, aminoglycosides, and ACE-inhibitors.[22,226–232] The incidence of renal complications following open-heart surgery has been reported as high as 35%. The frequency of oliguric renal failure requiring dialysis is 2–3% with a mortality of 50%.[230–233]

The most common form of renal failure after CPB, is nonoliguric renal failure. Nonoliguric renal failure has a better prognosis with a mortality rate of 10–17%.[231,234] The management goal of nonoliguric renal failure is the maintenance of an appropriate glomerular filtration rate by maintaining an adequate cardiac output and an adequate systemic blood pressure. The use of loop diuretics is controversial. They are unlikely to prevent the progression of nonoliguric to oliguric renal failure. Dopamine at a "renal dose" of 1–2.5 mcg/kg/min is commonly used to preserve renal function. There are no studies demonstrating a renoprotective effect. Dopamine may increase urine output, but it has been shown to be associated with renal tubular necrosis equal to or worse than controls.[41,235] In patients with a serum creatinine of >1.4 mg/dL, infusion of fenoldopam of 0.03–0.1 mcg/kg/min has been shown to preserve renal function.[236]

The best management of oliguric renal failure is prevention by early identification and treatment of deteriorating renal function. This prevention begins by avoiding hypotension and low cardiac output states, optimizing volume status, considering the early use of inotropic agents and pressors, and the early use of IABP. Once oliguric renal failure occurs, a nephrology consultation is in order. Strict euvolemia must be maintained, as well as careful monitoring of metabolic status and electrolyte balance and the daily review of medications looking for drugs excreted by kidneys. If renal failure occurs several days following surgery, it is most likely not related to CPB but more likely as a result of sepsis, nephrotoxic drugs, low cardiac output, and obstruction of the urinary tract.

Gastrointestinal Complications

The perfusion of intra-abdominal viscera is also adversely effected by CPB. The blood flow to the liver is reduced by 19% during CPB and there is concomitant relative hypoperfusion of splanchnic and gastric flow. The decrease in gastric flow results in gradual decreasing of gastric pH and is associated with the appearance of endotoxin in the circulation, suggesting that the intestinal barrier is compromised and translocation is a possibility.[237,238] Gastrointestinal complications are generally not a common source of significant morbidity after open-heart surgery. They occur at a rate of approximately 1–2%. These complications are the result of a low cardiac output state with its associated sympathetic vasoconstriction and hypoperfusion of the abdominal organs. The most common serious complication after CPB

is gastrointestinal hemorrhage from gastritis or gastroduodenal ulcer disease.[239] The pathology is usually hemorrhagic gastritis or duodenitis.[240,241] Occasionally, the hemorrhage is from previous duodenal ulcer disease and rarely from the colon.[242]

Gastrointestinal hemorrhage occurs in only about 1% of cases and the risks are higher in patients with COPD, hypotension, excessive postoperative bleeding, reoperation, and a prior history of peptic ulcer disease.[234] It is recommended that these high-risk patients have prophylactic ulcer therapy.[243] An appropriate prophylactic regimen would include sucralfate 1 g q6h orally or down a nasogastric tube. Another option is omeprazalone 20 mg daily. Ranitidine appears to be the best option with a lower rate of gastrointestinal hemorrhage and an equivalent incidence of pneumonia.[244]

Hepatic dysfunction is marked by transient elevation of liver function tests in 20% of patients. Less than 1% of the patients will develop significant hepatocellular damage resulting in either chronic hepatitis or liver failure.[245,246] The risk factors for these complications are prolonged CPB, multiple transfusions, and multiple valve replacements. Elevated LFTs in association with hyperbilirubinemia occurring within the first 1–10 days is a result of low cardiac output and "shock liver." Shock liver may cause hemodynamic instability with low systemic vascular resistance. Hyperbilirubinemia without elevated LFTs, if it occurs early, may be the result of cholestasis from red blood cell trauma and destruction, as well as from right heart failure with passive congestion of the liver, although the alkaline phosphatase may be elevated in this instance. Bilirubin usually normalizes in 1–14 days with observation only. If isolated hyperbilirubinemia occurs late, it is caused by infection from transfused blood products. The risk of infection after transfusion depends on the number of units transfused and types of products transfused. The most common infections are non-A, non-B hepatitis (seen more often after clotting factor transfusions), cytomegalovirus, Epstein–Barr virus, and acute cholecystitis.[247] Acute cholecystitis is seen more often in the elderly after prolonged CPB, suggesting hypoperfusion may be a factor. Transient hyperamylasemia can be found in as many as 35% of patients after CPB, yet is associated with pancreatitis in only 1–3% of the patients.[248] The risk factors include long CPB time and multiple transfusions. It is a must to exclude postoperative pancreatitis as this is a serious problem with a high mortality rate.[249] Ischemic bowel syndrome as a result of mesenteric ischemia is a catastrophic complication. It is often associated with the hypoperfusion of low cardiac output, particularly the elderly patient requiring inotropic or IABP support.

Metabolic Complications

Electrolyte imbalances are common after cardiopulmonary bypass. Potassium alterations are the result of rapid shifts that occur during cardiac surgery and CPB. The factors related to *potassium* fluxes are hyperkalemic cardioplegia, renal dysfunction while on CPB, low cardiac output and associated oliguria and acidosis, hemolysis of red cells, diuresis, and diminished potassium uptake in the face of diabetes mellitus.[20] Certain medications also impair potassium excretion and cause hyperkalemia. This list of medications include ACE inhibitors, potassium-sparing diuretics, non-steroidal anti-inflammatory drugs, angiotensin receptor blockers, and β-blockers.[22] The principal adverse effect of potassium alterations is on the electrical activity of the heart and can be life-threatening. Hyperkalemia manifests itself predominantly electrocardiographically. Asystolic arrest can occur when potassium rises rapidly to a level exceeding 6.5 mEq/L. The EKG findings are more related to the rate of rise of potassium level than to an absolute level. They are peaked T waves, ST depression, prolonged PR interval, loss of P wave, QRS widening, bradycardia, and asystole. Hyperkalemia may result in failure of the heart to respond to the pacemaker stimulus and this may be a factor during resuscitation. Treatment includes optimizing cardiac function and shifting potassium into the cells and increasing its excretion. The cardiac function is optimized with calcium gluconate. If there is evidence of cardiac toxicity, 0.5–1 g of calcium gluconate is given intravenously over 15 min. Potassium is shifted into the cells by giving 50 mEq of $NaHCO_3$ to correct acidosis and giving 10 units of regular insulin and 25 g of 50% dextrose. Potassium excretion is enhanced with furosemide 10–200 mg IV, Kayexalate enema 50 g in water enema or 50 g PO with sorbitol or dialysis. Hypokalemia is usually a result of diuresis without adequate replacement of potassium. Diuresis is usually profound after CPB owing to hemodilution. Diuretics, insulin administration, or alkalosis may exacerbate this diuresis. Hypokalemia promotes atrial, junctional, and ventricular ectopy.[22] It can cause life-threatening ventricular tachycardia, but usually does not become clinically evident until serum concentration is less than 2.5 mEq/L. Hypokalemia can also be the cause of metabolic alkalosis as hydrogen ions replace potassium within the cells. The treatment is potassium chloride (KCl) administration through a central line at 10–20 mEq/h. Serum potassium raises approximately 0.1 mEq/L for each 2 mEq of KCl given. A slower rate is recommended in the presence of renal insufficiency.

Calcium plays a complex role in myocardial reperfusion damage and energetics. Ionized calcium should be measured during and after CPB because hemodilution, hypothermia, pH shifts, and use of citrated blood will affect protein binding of calcium. Hypocalcium is the most frequently seen calcium abnormality in the perioperative period. The treatment of hypocalcemia is a calcium chloride bolus of 0.5–1 g. Calcium gluconate 10 mL of 10% solution will have fewer cardiovascular effects than calcium chloride.

Hypomagnesemia is not uncommon after CPB. The incidence is 70%.[250] The most common etiology for hypomagnesemia is the diuresis and hemodilution associated with CPB. The effects of hypomagnesemia are mainly cardiac effects and similar to those of potassium on the electrical activity of the heart. Manifestations of hypomagnesemia include atrial

and ventricular dysrhythmias, potentiation of digoxin-related dysrhythmias, and a predilection to coronary spasm. Since magnesium is also related to energy metabolism, prolonged ventilator support has also been related to low serum magnesium levels. Treatment is an infusion of 2 g magnesium sulfate in 100 mL of solution to raise the serum level to 2 mEq/L. Note that magnesium has been shown to inhibit the vasoconstrictive effect of epinephrine but not its cardiotonic effect.[251]

Hyperglycemia routinely occurs during CPB. Modest elevations are present during hypothermia, but more marked elevations of blood glucose happen during rewarming. Hyperglycemia is caused by increased glucose mobilization related to increases in cortisol, catecholamines, and growth hormone levels during CPB. There also appears to be a blunted insulin response and impaired insulin production as well as a peripheral insulin resistance during CPB.[20] The impaired insulin secretory response may last 24 h. These changes are exaggerated in the diabetic patient, and insulin requirement may be seven times greater than preoperative requirements in the first 4 h after surgery.[252] Hyperglycemia postoperatively is associated with osmotic diuresis, impaired wound healing, increased risk of infection, and impaired blood pressure regulation.[22]

Hyperosmolar, hyperglycemic, non-ketotic coma is unusual following open-heart surgery. It usually occurs in type II diabetics 4–7 days after surgery.[253] Diabetic ketoacidosis is rarely encountered in the postoperative period. The most efficient method of managing the postoperative patient is with an insulin infusion. The usual dose is 0.1 unit/kg/h of regular insulin in a saline mix. Blood glucose levels must be monitored every 4 h to maintain serum glucose of 70–200 mg/dL. Type II diabetics should be restarted on their oral regimen as soon as they are taking PO.

Hematologic Complications

The most common and most frequent hematologic complication of open-heart surgery is thrombocytopenia and platelet dysfunction.[207,254] Platelet counts decrease rapidly by 50% soon after the institution of CPB but usually remain above 100K. Platelet counts less than 150,000/mm^3 occur in approximately 62% of patients on postoperative day one.[20] Platelet counts begin to increase by the third postoperative day. Bleeding from thrombocytopenia is usually not a problem until the platelet count falls below 60,000/mm^3. Of greater clinical significance is the progressive deterioration of platelet function during CPB. Within minutes of CPB, platelet aggregation is impaired and continues to worsen throughout CPB. This platelet dysfunction is precipitated by contact of the platelets with synthetic surfaces of the CPB circuit as well as by hypothermia. Also, the mechanical stresses of CPB cause fragmentation of the platelets and a temporary depletion in the membrane antigen for glycoproteins IB, IIb, and IIIa.[255] Hypothermia impairs platelet thromboxane A2 synthesis resulting in reversible platelet dysfunction. Bleeding time returns to normal in about 2–4 h and the platelet count is restored in several days.[208,256,257] Platelet dysfunction occurs less commonly with the use of antifibrinolytic drugs, such as ε-aminocaproic acid, because these agents act in part by reducing platelet activation during CPB.

Indications for platelet transfusion are as follows: a platelet count less than 20–30,000/mm^3, ongoing bleeding with a platelet count less than 100,000/mm^3, and a platelet count less than 60,000/mm^3 if a surgical procedure is planned.[22] CPB also effects the plasma concentration of *coagulation factors* II, V, VII, IX, X, and XIII. The plasma concentration of these factors decline during CPB secondary to hemodilution but remain at levels adequate for hemostasis, and, with the exception of fibrinogen, return to normal by 12 h.[208,256] Fibrinogen and plasminogen decrease during CPB from dilution and not consumption, and usually return to normal by 24 h.

Heparin-induced thrombocytopenia (HIT) is an infrequent but serious complication with a high mortality rate if the fulminant course progresses to heparin-induced thrombotic thrombocytopenia (HITT).[186] HIT is caused by the formation of IgG platelet membrane antibodies, which, in the presence of heparin, produce platelet aggregates and heparin resistance. The range of intensity of HIT and HITT spans from only moderate thrombocytopenia to a syndrome of arterial or venous thrombosis caused by platelet aggregation and bleeding from profound thrombocytopenia.[258,259] If the diagnosis of HIT is suspected, all heparin must be discontinued including therapeutic infusions, line flushes, heparin-coated monitoring lines, and low-molecular-weight heparins. The laboratory confirmation by platelet aggregation testing is important, but may take at least 24 h to confirm; therapy should be instituted as soon as the diagnosis is suspected. Platelet counts must be monitored on a daily basis.

Infectious Complications

In-hospital, postoperative infections after open-heart surgery occur at a rate of 12–20%. The most common infections are the respiratory, urinary, and wound or surgical site infections.[260] While all postoperative infections adversely affect outcomes, it is the sternal wound infection and mediastinitis that have the greatest adverse effects. The overall incidence of sternal wound infections is 0.8–1.4%.[261,262] When sternal wound infections are associated with mediastinitis, the mortality varies from 6 to 70%.[263] When recognized early and effectively treated, the mortality is 5–10%[264] The rate of mediastinitis is higher in valvular procedures and in combined procedures.[265] The use of bilateral internal mammary arteries increases the risk of sternal wound complications to 5%.[262] *Staphylococcus aureus* and *Staphylococcus epidermidis* are the most common pathogens encountered accounting for 42% of infections.[266]

Preoperative predisposing factors include type and timing of skin preparation, cardiopulmonary failure, need for an IABP, diabetes mellitus, steroid use, a history of mediastinal radiation, osteoporosis, age, and COPD.[264,267] Intraoperative factors are a CPB run greater than 3 h, excessive bleeding, the

use of bilateral internal mammary arteries, valve procedures, combined procedures, and inadequate sternal fixation.[268] Postoperative bleeding will increase the risk for sternal wound complications, as will low-flow states, concurrent infections, tracheotomies, and prolonged ventilatory support.[269]

The most obvious sign of a wound infection is purulent drainage from the incision. There should be a heightened level of suspicion in a patient whose pain begins to increase toward the end of the first postoperative week rather than decrease.[268] Also the wound is reddened and swollen and there is a localized area of skin necrosis associated with the drainage. The drainage is serous if the complication is minor, involving only the superficial soft tissue. However, if the complication is a major one with mediastinitis there is extensive purulent drainage with infection extending down to the sternum and mediastinum. These findings may not always be an indication of infection, but could be aseptic necrosis from internal mammary artery mobilization.

Fever, leukocytosis, or gram-positive bacteremia should raise the suspicion of a sternal wound infection. Any fever of undetermined etiology should raise the question of wound sepsis, particularly in diabetics where few other local or systemic signs may be present as a result of a poor inflammatory response. The evaluation begins with a culture of the purulent drainage. If there is no drainage, a likely area of the wound should be opened and careful cultures obtained. Radiographic workup is of limited value. Routine chest X-rays are of little help. A chest computed tomography (CT) scan may identify indolent, retrosternal infections, particularly if gas-forming organisms are present.[270–272]

Minor infections usually respond to treatment with antibiotics and local care, including wound packing. Major infections require mediastinal exploration and debridement of infected tissue, including the sternum. If the sternum is necrotic or grossly infected, removal of the sternum is necessary and requires closure with a muscle flap, either a pectoralis major or rectus abdominis flap. Omentum can also be used to provide a vascular bed for healing, but omental mobilization is associated with a higher morbidity than the creation of a muscle flap. Appropriate parenteral antibiotics are required for a 6-week period.

The incidence of leg wound infections is 1–10%. These complications may result from poor surgical technique with a creation of flaps, failure to eliminate dead space, or hematoma formation. The risk factors are obese women, use of thigh veins, diabetes, and severe peripheral vascular disease.[273] The prevention of leg infections involves careful surgical technique and the use of suction drains to eliminate dead space in the leg. The treatment is appropriate antibiotic coverage, debridement, and a consideration for early plastic surgery involvement.

Prophylactic antibiotics should be administered for 48 h starting in the operating room just prior to the incision. First- or second-generation cephalosporins are used because of their effectiveness against gram-positive cocci. Vancomycin is used in patients with true anaphylactic allergy to penicillin or cephalosporins. If the patient does not have a documented history of a severe anaphylactic reaction to penicillin or a cephalosporin, a cephalosporin should be used. Attempts must be made to limit the use of vancomycin for prophylaxis to lessen the likelihood of vancomycin-resistant *Enterobacter* infections.

Neurologic Complications

Neurologic complications following open-heart surgery are dreaded sequelae. The overall incidence of focal deficits is 1–3%.[274,275] These usually occur intraoperatively and are noted in the first 24–48 h. Some 30% of the deficits may develop postoperatively as a result of hemodynamic instability or arrhythmia.[22] Risk factors of stroke for the open-heart patient include increasing age (a risk up to 15% in patients older than 75 years), diabetes mellitus, preexisting cerebrovascular disease especially with a history of recent stroke, perioperative hypotension, atherosclerotic plaques and calcifications in the ascending aorta, left ventricular mural thrombus, opening a cardiac chamber, postoperative atrial fibrillation, long duration of CPB, and warm blood CPB.[276–279]

The presentation of neurologic complications depends on the site and extent of the insult. Transient ischemic attacks present with focal deficits of hemiparesis or hemiplegia, aphasia, dysarthria, hand incoordination, visual deficits (either retinal or central), and coma. If an interventional neurologist is available, an immediate consultation should be obtained. An evaluation begins with a careful neurologic examination, then a CT scan of the brain with contrast infusion, an echocardiogram (surface or transesophageal) to exclude a cardiac source, and noninvasive carotid studies. If there is no evidence of an intracranial hemorrhage on CT scan, heparin is started, and then warfarin if the stroke is thought to be embolic. If the deficit occurs during surgery, there is some debate as to the need for anticoagulation versus just antiplatelet therapy. Other therapy includes the standard measures to reduce intracranial pressure and even a carotid endarterectomy in patients with severe carotid stenosis and transient neurologic deficits. Physical therapy is started soon after the event is diagnosed. As regards prognosis, patients with focal deficits have an excellent prognosis. In patients with coma, the prognosis is poor with a mortality rate of 50% and a high percentage of survivors staying in the vegetative state.[22]

Postoperative encephalopathy and delirium occur in approximately 30% after open-heart surgery.[280] The risk factors include older age, recent alcoholism, preoperative organic brain syndrome, severe cardiac disease, multiple associated medical illnesses, and complex and prolonged surgical procedures on CPB. Common causes of delirium are medication toxicity, metabolic disturbances, alcohol withdrawal, low cardiac output syndromes, periods of marginal cerebral blood flow during CPB, hypoxia, sepsis, and a recent stroke. The evaluation of delirium begins with a review of the patient's current medications and drug levels, an identification of a possible history of recent alcoholism or substance abuse, neurologic examination, and ABGs, electrolytes, BUN, creatinine, CBC, magnesium,

and calcium determinations. The management of delirium begins by correcting any metabolic abnormalities, discontinuing inappropriate medications, and psychotropic medications for agitation such as haloperidol 2.5–5.0 mg PO/IM/IV q6h. The treatment of suspected alcohol withdrawal include benzodiazepines, thiamine, and folate.

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Postoperative Care Following Major Vascular Surgery

Giuseppe Papia and Thomas F. Lindsay

Routine postoperative management following major vascular surgery has evolved significantly. Surgical techniques are moving toward minimizing the invasiveness of procedures such as endovascular repair of complicated aortic aneurysms and the use of local and/or regional blocks when performing operations. Anesthesiologists attempt to minimize physiologic derangements during operations, and fewer patients are routinely admitted to intensive care units (ICUs). This current paradigm must raise a red flag as conferring a false sense of security. Although vascular surgery patients seem more "stable" than in the past, they remain among the highest at risk for postoperative myocardial infarctions, stroke, renal failure, and bleeding complications when the entire cohort of postoperative patients is considered. Vascular surgical patients require close postoperative monitoring, which mandates that they be triaged to the appropriate environment for postoperative care for early identification and treatment of complications. Complications can occur late in the postoperative course, which requires continued attention to detail throughout the patient's stay in the ICU. Risk reduction through optimization of postoperative medical management and continual maintenance of a high index of suspicion for complications remains the best armament to improved postoperative outcomes. This chapter will address common postoperative management issues in vascular surgical patients and highlight related procedure-specific issues.

Postoperative Triage

A patient's preoperative medical comorbidities and his or her perioperative hemodynamic stability are the major factors that determine the most appropriate place for postoperative admission and monitoring. Age and comorbidities such as coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease (COPD), and chronic renal failure are predictors of increased mortality in surgical vascular patients.[1,2] In addition, emergency operations independently increase perioperative morbidity and mortality risk.[2] With proper risk stratification, selective use of ICU resources and step-down units (SDUs) can be safe and cost-effective.[3] Major vascular surgery carries a 30-day mortality rate of 5% – mostly, a result of adverse cardiac events.[4] Myocardial infarction (MI) is the most common cause of mortality and morbidity following major vascular surgery. In addition, poor preoperative nutritional status directly correlates with the increased incidence and increased severity of the systemic inflammatory response syndrome (SIRS) in patients after major vascular surgery.[5]

Patients with preoperative severe coronary artery disease (ejection fraction <40%, congestive heart failure, New York Heart Association [NYHA] class III or IV angina), COPD (forced expiratory volume 1 [FEV1] <1L), and chronic renal failure (dialysis-dependent) should be admitted directly to an ICU postoperatively following an elective abdominal aorta aneurysm (AAA) repair.[6] Perioperative markers for direct ICU admission include sustained hemodynamic instability (systolic blood pressure <90 mmHg), clinically significant cardiac ischemia, ventilatory failure, hypothermia (<35°C), and transfusion of multiple blood products.[6]

Patients undergoing less involved vascular procedures associated with fewer fluid shifts, such as carotid endarterectomy (CEA), also require close monitoring in the immediate postoperative period when they are at highest risk of stroke and MI. The event rate for these patients is highest in the first 8 h postoperatively. Thus, patients should be monitored in high

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dependency units for 8–12 h; often, they can be discharged directly to home if they are neurologically intact and have suffered no complications.

General Postoperative Considerations

Postoperative Hemodynamics and Bleeding

The primary objective postoperatively is the immediate but safe return of the patient's preoperative hemodynamics and homeostasis. It is therefore critical to know the patient's preoperative blood pressure, cardiac function, presence of valvular disease, and presence of pulmonary hypertension, as these will impact appropriate postoperative management. The goal remains to decrease myocardial oxygen demand through rewarming, control of hemodynamics, and effective control of pain. The routine use of pulmonary artery catheters is not recommended and has been suggested to cause possible harm in this patient population.[7] However, the use of pulmonary artery catheters should be individualized based on the need to have specific information in specialized situations.

Blood-pressure targets must be balanced to avoid both hypotension and hypertension. Many authors recommend targeting a systolic blood pressure between 20 mmHg above and 20 mmHg below the patient's baseline. It is important to avoid high blood pressures, which place undue shear stresses on new grafts and increase hemorrhage risk at fresh anastomotic sites. Mean arterial pressure greater than 20% above preoperative levels should be treated with antihypertensives.[8] Common causes of postoperative hypertension – such as pain, agitation, hypoxia, hypercarbia, hypervolemia, and bladder or gastric distention – must also be ruled out and treated.[9] Mild increases in pressure may respond to topical nitrates; however, sustained increases will require intravenous therapy with beta-blockers or vasodilators if beta blockade is already in place.

It is also important to avoid hypotension and hypovolemia. Low-flow states cause stasis of blood in grafts and increase the risk of thrombosis. In addition, hypotension further increases risk of myocardial ischemia, increases rates of renal failure caused by low renal perfusion, and is a major cause of stroke (approximately 20%) post-CEA.[10] It is crucial to rule out hemorrhage as the major cause of hypotension in patients who are having greater than expected fluid requirements in the early postoperative period.[11] Surgical bleeding potentiates coagulopathy that is resistant to medical correction, and this should also alert intensivists that early surgical intervention might be required. The authors recommend aggressive fluid resuscitation with crystalloids in the early postoperative period with the judicious use of vasopressors. Excessive fluid requirements may also reflect bowel ischemia, which will be discussed later.

Early postoperative coagulopathy is often dilutional and can be secondary to failure to fully reverse intraoperative heparin administration. Response to platelet administration appears better than to fresh frozen plasma (FFP).[11] Platelet function is enhanced at a higher temperature, a key reason why it is important to quickly correct postoperative hypothermia.[11] Prolonged hemorrhage may result in fibrinogen depletion and fibrinolysis, which may also require transfusion of cryoprecipitate. Conservative blood transfusion threshold of 7 g/dL has been demonstrated to be safe in critically ill patients, with the exception of those with active bleeding or myocardial ischemia.[12,13] In the immediate postoperative period, hemoglobin should be maintained at 9–10 g/dL, given the prevalence of myocardial ischemia and cardiac disease.

Myocardial Ischemia

MI is the most common cause of death following major vascular surgery,[11,14] which is not surprising because the prevalence of coronary artery disease in these patients approaches 90%. Most postoperative MIs in vascular patients are frequently asymptomatic and may not be preceded by changes in heart rate or blood pressure.[14] An increase in postoperative cardiac troponin I is a consistent predictor of increased cardiac events and increased mortality following major vascular surgery.[15] Even in the absence of other signs of clinically significant cardiac ischemia, an elevated troponin has been shown to correlate with increased 30-day in-hospital mortality. Intraoperative hypothermia has also been demonstrated to be an independent predictor of postoperative myocardial ischemia.[16]

Perioperative cardiovascular optimization is key to reducing postoperative myocardial events. Routine use of beta blockers (target heart rate 60–65 bpm) is recommended for patients undergoing vascular surgery.[17] This has led to a 75–90% reduction in mortality, with most of the benefit seen in the highest risk patients.[18] It is important to note that beta-blocker withdrawal perioperatively in patients on chronic beta blockers is associated with increased mortality.[19] There has been theoretical concern about aspirin increasing postoperative bleeding despite its cardioprotective properties. However, aspirin has even been demonstrated to be safe in patients undergoing CEA. The authors therefore recommend that aspirin can be continued to be used perioperatively in all vascular patients in the absence of serious bleeding risk. Patients taking clopidogrel preoperatively who cannot take aspirin should not have this discontinued; however, this may limit the use of epidural catheters in these selective patients.

Statins are used in primary and secondary prevention to decrease the risk of MI and stroke. They have also been shown to decrease the risk of perioperative cardiac events.[20] In addition to their lipid-lowering properties, statins have positive effects on the vascular system as antioxidants, through stabilization of plaques, improved endothelial function, and decreased platelet aggregation.[21] Statins are believed to contribute to the improved outcomes seen in patients receiving statins postoperatively. Also, the discontinuation of statin therapy (for 4 days) following major vascular surgery has been

shown to be an independent predictor of adverse postoperative cardiac events.[22,23] Le Manach et al. demonstrated that patients who had a delay of more than 4 days to restarting their statins following major vascular surgery had increased biochemical evidence of myonecrosis compared to patients who had them started within the first day postoperatively.[22] This study also showed that the early resumption of statin therapy was associated with a further cardioprotective effect. Short-term treatment with atorvastatin versus placebo has previously demonstrated a reduction in postoperative cardiac-related morbidity and mortality.[24] Schouten et al. have suggested that perioperative treatment with extended-release formulas may be associated with better outcomes following vascular surgery.[23] In addition, the combination of beta blockade and statin therapy may further enhance postoperative risk reduction in high-risk patients.[25]

Renal Failure

Patients with preoperative renal insufficiency are at highest risk for the development of postoperative renal failure. In addition, patients who have a suprarenal clamp, have a ruptured aneurysm, or receive significant amounts of contrast agents intraoperatively are also at high risk. The development of this complication is significant because it carries a postoperative mortality rate of 60–80% in vascular patients.[11] The major pathophysiologic contributor to renal failure is perioperative hypotension and ischemia, causing acute tubular necrosis (ATN).

Medical strategies to reduce this complication have been disappointing. Renal-dose dopamine has not been demonstrated to reduce morbidity, mortality, or need for renal-replacement therapy despite an increase in urine output.[26] Small studies using fenoldopam, a potent renal vasodilator and natriuretic, have demonstrated improved renal outcome when given intraoperatively and postoperatively.[27,28] However, larger randomized trials are needed. Forced diuresis can be detrimental because it increases oxygen demand in the most hypoxic region of the kidney and can therefore exacerbate hypoxic injury.[29] Loop diuretics, however, have several theoretical benefits. They may cause the dislodgment of tubular casts due to increased flow and they decrease oxygen consumption of the kidney by inhibiting the adenosinetriphosphatase in the medullary thick ascending limb.[30] The use of *N*-acetylcysteine for its antioxidant and vasodilator properties has also not been shown to confer any perioperative renal protection.[31] Thus, the optimal postoperative strategy remains to ensure adequate intravascular volume and renal perfusion and to avoid the administration of possible nephrotoxins such as nonsteroidal anti-inflammatory drugs (NSAIDs) or aminoglycosides.

Respiratory Complications

Postoperative respiratory failure is also associated with increased mortality both short-term (30-day mortality of 36.5%)[32] and long-term.[33] Johnson et al. reported a reduced median long-term survival by 87% in patients who suffered from a pulmonary complication in the first 30 days following surgery. Unfortunately, in postoperative patients in general, few interventions have clearly demonstrated a reduction in pulmonary complications.[34,35] Evidence has only suggested that pulmonary complications, after open abdominal surgery, can be reduced with lung-expansion therapy (incentive spirometry or deep-breathing exercises).[35] There is also a suggestion that short-acting neuromuscular blockers in these patients may result in decreased pulmonary complications caused by decreased residual blocking effect and, therefore, early and effective return of function.[35]

Most patients are extubated in the operating room following major vascular surgery. Those patients who require intubation and mechanical ventilation postoperatively have often experienced major intraoperative hemorrhage, a prolonged and/or proximal aortic clamp, hypothermia, or have undergone an emergency operation. Once in the ICU, these patients should be rewarmed aggressively and stabilized, which will frequently result in rapid extubation. Patients who require prolonged mechanical ventilation are generally those who have suffered a postoperative MI, renal failure, bowel ischemia, or sepsis, or who develop early acute respiratory distress syndrome (ARDS).

The patients at highest risk for early postoperative ARDS are those who have undergone urgent ruptured AAA repair and who are very hemodynamically unstable. This is because of the "two-hit" nature of AAA rupture and repair in addition to the large volumes of crystalloid and blood products administered.[36] Patients with early ARDS will naturally benefit from a lung protective ventilation strategy. Prolonged requirement of mechanical ventilation will also put patients at risk for ventilator-associated pneumonia (VAP).

Patients who fail to wean may also require tracheostomy. Although tracheostomy in this patient population is correlated with poor outcome and increased in-hospital mortality,[37] there has been some suggestion that in patients with COPD, tracheostomy may actually improve outcome.[38] However, the need for postoperative reintubation, prolonged ventilatory support, and tracheostomy seriously impacts hospital mortality and long-term prognosis.

Gastrointestinal Complications

Two potentially lethal postoperative gastrointestinal (GI) complications worthy of special mention are bowel ischemia and abdominal compartment syndrome. These complications are most commonly associated with patients who undergo aortic surgery for a ruptured AAA. Colonic ischemia affects less than 2% of patients undergoing elective AAA repair but carries a mortality rate of 40–65%.[39] Patients operated on for a ruptured AAA have rates of colonic ischemia that range from 15 to 65%.[40] As previously stated, excessive fluid requirements may be an indication of bowel ischemia. Certainly, persistent

acidosis and refractory shock are worrisome markers. It is important to maintain a high index of suspicion and to check the patient for elevated lactate, leukocytosis, acidosis, GI bleeding, portal-venous gas on plain abdominal X-ray, or pneumatosis intestinalis on computed tomography (CT) scan. Patients may have necrosis and sloughing of intestinal mucosa presenting with bloody bowel movements. Flexible sigmoidoscopy and colonoscopy are useful tools in making the diagnosis of bowel ischemia. If the diagnosis is delayed, the patient can progress to full transmural ischemia, which carries a mortality of 80–100%.[41] Mild bowel ischemia limited to colonic mucosa can be treated conservatively with broad-spectrum antibiotics and bowel rest if the patient is hemodynamically stable. More extensive ischemia and hemodynamic instability requires urgent resection.

Abdominal compartment syndrome can present with oliguria in the patient with adequate volume resuscitation. Patients who have received massive volume resuscitation with fluids and blood products are at particularly high risk. A bladder pressure greater than 12 mmHg is indicative of intra-abdominal hypertension and pressures above 25 mmHg place patients at high risk for abdominal compartment syndrome.[42] The full syndrome is marked by global hypoperfusion and oliguria, decreased cardiac output, hypotension, and high ventilatory pressures caused by reduced pulmonary compliance. Early recognition and treatment can significantly improve patient survival. Decompressive laparotomy is indicated, and patients are often left with an open abdomen. Ongoing fluid leakage from an open abdomen results in high protein and volume losses and presents a significant management challenge. These patients become intravascularly depleted secondary to the fluid losses and need aggressive fluid therapy. A pulmonary artery catheter is often indicated to guide management. The wound often gets infected and patients are at high risk of skin breakdown. The authors recommend a suction-type wound-management system to minimize complications. Also, abdominal decompression may be followed by reperfusion injury and hypotension before improved hemodynamics is achieved.

Pain Management

Effective postoperative analgesia has a significant impact on outcome. Patients with adequate postoperative analgesia based on pain scores have lower rates of myocardial ischemia despite no differences in heart rate, blood pressure, or requirement for vasoactive agents compared with patients with poor analgesia.[43] Epidural analgesia is a frequently used postoperative analgesic strategy. Thoracic epidurals can improve hemodynamic stability, whereas lumbar epidurals can worsen cardiac segmental wall-motion abnormalities.[44] The benefit of thoracic epidurals is the achievement of effective analgesia with lower doses of local anesthetic, which precipitate fewer subsequent hypotensive events. The other potential benefits to epidural analgesia over intravenous opiates are reduced incidence of delayed gastric emptying, reduced postoperative ileus, and increased mobility. Increased mobility has the further theoretical benefit of reduced thrombotic complications and reduced rates of nosocomial pneumonia.

Multisystem Organ Failure

Currently, multisystem organ failure occurs most frequently after repair of ruptured aortic aneurysms. No interventions have been demonstrated to prevent this condition in these patients. Although respiratory failure is common, it is frequently not the main cause of early death. Renal dysfunction is an early indicator of a poor prognosis; however, hepatic dysfunction occurring near the end of the first week postoperatively also is a poor prognostic sign.[45]

Surgery-Specific Considerations

Carotid Endarterectomy

Carotid endarterectomy is one of the most frequently performed peripheral vascular operations in the United States.[46] Patients who are experiencing cerebrovascular events at the time of surgery have higher rates of postoperative stroke and mortality. It is important to note, however, that these symptomatic patients receive the greatest absolute risk reduction of stroke if operated on within 2 weeks of their last neurologic event.[46]

Monitoring in a high dependency unit postoperatively with adequate nurse-to-patient ratio is mandatory. Patients need to be monitored for early hemorrhage, which can present with a rapidly expanding neck hematoma and lead to a loss in the airway. The surgeon, anesthesiologist, and operating room coordinator need to be contacted immediately. It is important to facilitate the expeditious transfer of the patient back to the operating room, which is the optimal location to secure a potentially very difficult airway, as well as to deal with the hemorrhage. Even in the absence of hemorrhage, airway swelling and edema can still occur.

Stroke is the most feared complication of this operation because the intention of CEA is prophylaxis against the development of a stroke. Some evidence suggests that those patients who receive preoperative statins and/or diuretics have a lower likelihood of having cerebrovascular symptoms at the time of CEA.[47] Perioperative statin use during CEA has been shown to significantly reduce 30-day stroke, transient ischemic attack (TIA), and mortality.[48] The common causes of stroke after CEA are embolization or thrombosis, or as secondary to a low-flow insult from hypotension. Most events are manifested within 8 h of surgery.[49] Development of stroke symptoms in the immediate postoperative period demands urgent attention. Anticoagulation and rapid duplex scanning to assess for endarterectomy-site thrombosis is the preferred management. If the patient awakens with a stroke and a patent

internal carotid artery is visualized by duplex scanning, the patient is not returned to the operating room. If duplex scanning is not immediately available, the rapid return to the operating room for assessment of thrombosis and thrombectomy is mandatory. Thrombosis at the site is frequently caused by a white-platelet-rich thrombus, and enhanced antiplatelet therapy is required.

Patients with carotid artery disease have a high incidence of concomitant severe coronary artery disease and are thus also at high risk for MI. Thirteen percent of patients undergoing CEA have an increased postoperative troponin I, which correlates with a worse prognosis, as discussed earlier in this chapter.[50] It is quite common for patients to be bradycardic following CEA because of the increased blood pressure sensed at the endarterectomized carotid bulb. In the absence of hypotension, bradycardia by itself is not treated. Hypotension with bradycardia requires therapy to prevent the precipitation of stroke and MI. Aspirin, as mentioned earlier, should be continued throughout the perioperative period.

Reduction in the sensitivity of the baroreceptor reflex can also cause postoperative hypertension. One concern is an excessive increase in cerebral perfusion, causing hyperperfusion syndrome. Hyperperfusion syndrome can affect 1–3% of patients following CEA.[51] These patients have a dramatic increase in postoperative cerebral blood flow, with velocities in the middle cerebral artery increased up to 100% above preoperative values.[51] The constellation of symptoms and signs includes ipsilateral headache, hypertension, seizures, and focal neurological deficits. Without immediate aggressive antihypertensive treatment, this syndrome can progress to cerebral edema, intracerebral or subdural hemorrhage, and death. It has been suggested that patients who have had compromised cerebral perfusion caused by a tight carotid stenosis are maximally vasodilated preoperatively. They are unable to vasoconstrict when cerebral pressure is restored and are therefore at greatest risk. In symptomatic patients, immediate blood pressure targets of 90–140 mmHg systolic should be the goal.[52] In those patients with severe headaches without hemodynamic changes, intracranial hemorrhage needs to be ruled out.

Cranial nerve deficits can complicate up to 12.5% of CEA.[53] The most common nerves involved are the hypoglossal, recurrent laryngeal, superior laryngeal, marginal mandibular, and greater auricular. These are mostly secondary to traction injuries, the majority of which resolve by 6 months.[51]

Open AAA Repair

One-third of patients who have undergone an elective repair of an abdominal aorta aneurysm (AAA) will suffer from one or more postoperative complications,[54] depending on the location and duration of the aortic clamp. The incidence of renal failure after elective infrarenal AAA is 5.4%, with less than 1% requiring hemodialysis.[55] An infrarenally placed aortic clamp can decrease renal blood flow by 40%.[56] The incidence of renal failure and other complications is much higher with a suprarenal or supraceliac clamp. It is important that, prior to aortic clamping, the patient have adequate intravascular volume to ensure renal perfusion in advance of obligate blood loss upon aortic opening.

Another common problem following AAA involves postoperative nasogastric (NG) tube management and postoperative feeding. In the absence of high NG outputs (>500 cc/24 h) or clear evidence of paralytic ileus, NG tubes should be routinely removed on the first postoperative day following elective repair. At this time, patients will often tolerate sips of fluid. Determining when to commence feeding patients postoperatively should be individualized, with the caveat that early feeding is best. Gastric emptying has been shown to return to normal by 18 h following elective AAA, with small bowel function normalizing by 47 h.[57,58] In patients who require prolonged mechanical ventilation, low-volume tube feeding should be started early and progressed based on the patient's residuals or established ICU feeding protocols. Important oral medications, such as acetylsalicylic acid (ASA), beta blockers, and statins, can be given through the NG tube on the first postoperative day, although the efficacy of gastric absorption is unknown.

Ruptured AAA Repair

Despite advances over the past few decades in the perioperative management of patients with vascular disease, in patients with a ruptured AAA the mortality rate remains 40–50%. More than 8,000 patients die each year in the United States from AAA ruptures.[59] These are the most difficult postoperative vascular patients to manage and they have the highest rates of all of the aforementioned complications. The rapid rewarming and stabilization of the patient is important. Patients are frequently cold and coagulopathic when emerging from the operating room. Aggressive reversal of medical coagulopathy with blood products and adjuncts is vital. Third-space fluid losses can be significant, and patients may require a large amount of volume resuscitation. Acidosis is common and must be addressed with adequate volume resuscitation in an early goal-directed fashion, adjustments in ventilation support, and use of bicarbonate infusions for severe acidosis. Large fluid and blood-product administration puts patients at risk for abdominal compartment syndrome and early ARDS. The development of abdominal compartment syndrome is significant after ruptured AAA because of the large retroperitoneal hematoma and bowel edema. It is important to maintain a high index of suspicion for all of the complications that require an immediate intervention.

Endovascular Aortic Repair

Endovascular treatments of AAA have been used in clinical practice for 15 years. In the United States, 65% of elective AAA repairs are now being performed by this method. This will increase further as new endovascular aortic repair

(EVAR) methods become widely disseminated to deal with short aneurysm ostia (necks). Instead of making a large abdominal incision, EVAR generally involves making small femoral incisions or percutaneous approaches, allowing the devices to be introduced via the femoral arteries. Fluoroscopy is used to guide the devices to the proper location, where they are deployed, relining the diseased aorta with a stent graft.[60] The early advantages of EVAR include rapid recovery, less pain, reduced blood loss, and decreased rates of postoperative medical complications (MI, need for mechanical ventilation, renal failure). Randomized studies have shown significant reductions in major complications and 30-day mortality.[61,62] In a study by Bertrand et al. consisting of 386 patients followed prospectively after AAA repair,[63] patients were assigned to an open versus endovascular approach purely on the basis of aortic anatomy and not on the basis of, or with consideration for, medical health. They found that the endovascular group suffered fewer renal and respiratory complications, had lower intraoperative events of blood loss, required fewer blood transfusions, and had shorter hospital stays.

Compared with open-repair patients, those undergoing EVAR have lower rates of SIRS (44% vs. 91%), lower incidence of sepsis (6% vs. 49%), and fewer postoperative complications.[64] Again, it is imperative not to be lulled into a false sense of security with these high-risk patients. Some centers opt for an endovascular rather than open approach because patients have high medical comorbid risks prohibiting an open repair. Physicians must maintain a high index of suspicion of the aforementioned medical complications and treat them appropriately.

As mentioned previously, the most common route of deployment involves bilateral femoral artery cutdowns. It is important to monitor these patients for postoperative acute limb ischemia for which they are at risk because of embolization, thrombosis, or dissection of the vessel. Further, the deployment of the devices involves the introduction of several guide wires and sheaths up the femoral arteries into the aorta and through the aneurysm. Iatrogenic damage and rupture of vessels caused by shearing forces applied have been described. Patients can present with hypovolemia, hypotension, and hemorrhagic shock from vessel rupture. Although a completion angiogram is performed at the end of the procedure, injuries can be missed if they occur in areas not imaged. Because the inferior mesenteric artery is covered by this procedure, ischemic colitis, although rare, is possible. Finally, these patients receive a generous amount of radiocontrast during the procedure, so it is imperative to maintain adequate hydration and urine output postoperatively to minimize the risk of contrast nephropathy.

Repairing the ruptured AAA by EVAR is becoming more prevalent. Several studies have reported lower perioperative mortality (50% vs. 23%) and morbidity (90% vs. 53%) in properly selected patients.[65,66] Although this is promising, it is limited by logistical barriers, including the need for an endovascular center, a wide range of readily available in-house stock of devices, expertise, imaging criteria, and a relatively hemodynamically stable patient.

Thoracoabdominal Aortic Repair

Postoperative renal, pulmonary, visceral, and cardiac complication rates and mortality are higher with open thoracoabdominal aneurysm repair compared to open AAA.[67] Pulmonary complications are the most common and impact significantly on patient outcome. The risk is much higher because of the invasiveness of a left thoracotomy or thoracoabdominal incision compared to a laparotomy, and its subsequent impact on physiology and pain management. Independent of all other factors, division of the diaphragm is associated with prolonged ventilatory support compared with patients whose diaphragm is preserved.[68] Etz et al. performed early tracheostomy, postoperative days 5–7, on all patients with significant pulmonary problems in order to aid care and early mobilization.[67] In both univariate and multivariate analysis, this did not correlate with increased mortality, perhaps suggesting a benefit to early tracheostomy in this patient population. A recent review of long-term follow-up of these patients demonstrated that renal failure, neurologic events, and ventricular dysfunction decreased late survival as well as early survival.[69]

A devastating complication following this operation is spinal cord ischemia. Spinal drains are often placed to minimize this complication. These drains are used for a period of 72 h with a target pressure of <10 mmHg to reduce cerebrospinal fluid (CSF) pressure and improve spinal cord perfusion. Also, critical to spinal cord perfusion is adequate tissue perfusion, which frequently requires large volumes of fluids to maintain adequate preload, and to avoid hypotensive episodes, which can precipitate spinal cord ischemia. Subsequent induction of vigorous diuresis to achieve early extubation should be discouraged in these patients to avoid precipitating hypotension and delayed paraplegia, which can occur up to 7 days postoperatively.[70] Gentle diuresis can begin on the second or third postoperative day if the inflammatory response secondary to the operation is felt to have subsided.[67]

There are no standard approaches to chest-tube management or to the timing of their removal. Chest tubes should be placed and kept on suction at −20 cm water. Air leaks are rare but indicative of possible lung injury; therefore, they require judicious monitoring and follow-up chest X-rays (CXRs) to rule out a persistent pneumothorax or evidence of barotrauma. It is important to remove chest tubes as early as possible to minimize complications of infection and maximize patient mobilization. The common procedure is to wait until the drainage has decreased to less than 150–200 cc over 24 h. If there is no pneumothorax and no air leak, the chest tube is placed on water seal for 24 h. If a repeated CXR in 24 h shows that the lung has expanded, the chest tube can be removed.

Revascularization for Peripheral Artery Disease

Cases of peripheral artery disease (PAD) are divided into aortofemoral and femoral popliteal or tibial reconstructions. Those cases requiring aortic surgery differ little from those requiring aneurysm repairs. Patients who require distal leg reconstructions for critical limb ischemia have advanced atherosclerosis and must have adequate perioperative risk reduction. A significant concern after peripheral revascularization is early graft failure and occlusion. Early graft failure implies a technical problem and patients should be returned to the operating room for exploration, thrombectomy, or revision. Postoperative patients should be continued on aspirin and statin therapy with selective use of oral anticoagulation, which may be beneficial in specific high-risk patients. This, however, must be balanced with the risk of increased bleeding.[71]

Compartment syndrome in the revascularized limb is more common in the emergent setting, such as post-embolectomy or thrombectomy. Early identification requires a high index of suspicion and continuous assessment by nursing personnel looking after the patient. Early symptoms include pain, pain with passive or active flexion or extension, paresthesias, decreased movement, and paralysis. In this setting, urgent four-compartment leg fasciotomies are indicated. Fasciotomy wounds can often be managed with delayed primary closure. If they cannot be closed, management with suction-type wound managers is effective. They can also be controlled with simple wet-to-dry dressings and delayed skin grafting.

Rhabdomyolysis can complicate the reperfusion of the acutely ischemic limb. Healthier patients tend to be at higher risk because they have a normal glomerular filtration rate (GFR) and larger muscle mass than cachectic individuals with a low GFR. Myoglobin can cause direct renal damage to tubules if urine pH is <6.0 or precipitate collects in tubules during low urine output states, leading to ATN. Testing the urine for myoglobin is unreliable because the qualitative test can be negative. Thus, serum creatinine kinase (CK) levels are a better marker of patients at risk. Preventive therapy with adequate hydration and urine alkalinization is best. Patients with high CK should be treated similarly.

Conclusion

Patients undergoing major vascular surgery present many challenges in the postoperative period. They are at high risk for MI, renal failure, respiratory complications, and overall mortality. The more invasive the procedure, the higher the risk involved, with patients undergoing open thoracoabdominal aneurysm and ruptured AAA repair being at the highest risk and creating the greatest challenge to manage. Every effort should be made to reduce myocardial oxygen demand postoperatively through adequate volume resuscitation, rewarming, and effective analgesia. It is equally important to avoid both hypotension and hypertension. MI is the most common cause of death following major vascular surgery. Proper preoperative preparation with maximal risk-reduction strategies that include aspirin, beta blockers, and statin therapies is critical. These medications need to be rapidly resumed postoperatively. Maintenance of a high index of suspicion and immediate treatment for common and procedure-specific complications will significantly improve the outcomes of these patients.

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Postoperative Care After Bariatric Surgery

Fredric M. Pieracci, Alfons Pomp, and Philip S. Barie

Bariatric surgery is now commonplace throughout the developed world because of both the obesity pandemic[1] and a substantial body of literature documenting the safety and efficacy of these procedures for the treatment of morbid obesity.[2–4] Currently, over one-half of Americans are overweight, over 30% are obese, and more than 5% are morbidly obese (Table 49.1).[5–7] Obesity is a leading cause of preventable death in the United States, resulting in more than 100,000 excess deaths per year[8] and an estimated annual cost of $70 billion, accounting for nearly 10% of national health care expenditures.[9]

Bariatric surgery is indicated for the treatment of morbid obesity, as well as class II obesity (Table 49.1) associated with one or more obesity-related complications (e.g., type II diabetes mellitus, obstructive sleep apnea syndrome [OSAS]).[10] Most bariatric surgical procedures, including gastric bypass and gastric banding, are now reimbursed by third-party payors, and subsequently the number of the procedures has increased exponentially over the last 10 years.[10–13]

The increased prevalence of obesity, morbid obesity, and bariatric surgery has resulted in a corresponding increase in the number of obese patients admitted to intensive care units (ICUs). Recent data indicate that as many as one-fifth of ICU patients are obese, and up to 7% are morbidly obese.[14] Furthermore, a substantial portion of bariatric surgical patients may require prolonged ICU care. Nguyen et al. reported that 7.6% of laparoscopic gastric bypass patients and 21.1% of open gastric bypass patients required ICU care following surgery.[15] Similarly, recent series have documented that 6–24% of bariatric surgical patients require more than 24 h of critical care.[16–18]

Both chronic inflammation and diminished physiologic reserve place obese patients at risk for postoperative complications, as well as worse outcomes once these complications occur. Furthermore, although several case series from experienced, large-volume centers have reported relatively low morbidity and mortality following bariatric surgery,[2,19] recent population-based data suggest less favorable outcomes,[20,21] underscoring the importance of vigilant perioperative care. Care of critically ill, bariatric patients requires both knowledge of the specific effects of obesity on all organ systems and utilization of specialized resources. This chapter reviews the pathophysiology of obesity, the response of the obese patient to critical illness, and the postoperative care of the critically ill, bariatric patient.

Pathophysiology of Obesity

Inflammation, hypercoagulability, and insulin resistance characterize obesity as a disease process that mimics critical illness. Adipose tissue is highly active metabolically, producing an array of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, transforming growth factor-β, eotaxin, and leptin. Altered immunoregulation also characterizes the obese patient, resulting in impaired neutrophil chemotaxis and activation.[22] Increased concentrations of fibrinogen and plasminogen activator inhibitor-1 (PAI-1) are found in obese patients, as well as decreased concentrations of antithrombin-III (AT-III) and decreased fibrinolysis.[23] Increased body mass index (BMI) requires increased cardiovascular, respiratory, and metabolic work, resulting in a markedly diminished physiologic reserve. Major physiologic derangements associated with obesity are outlined below and summarized in Table 49.2.

Pulmonary

Pulmonary pathophysiology secondary to obesity involves both restrictive and obstructive components. Increases in both pulmonary blood volume and chest wall mass result in a restrictive lung pattern. Abnormal diaphragm position, upper airway resis-

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tance, altered smooth muscle function, and increased daily CO_2 production exacerbate respiratory load and further increase the work of breathing. The consequences of this restrictive pattern are a decreased functional residual capacity (FRC), total lung capacity, expiratory reserve volume, and minute ventilatory volume (with compensatory rapid, shallow breathing) (Fig. 49.1). Obese patients also exhibit an obstructive airflow pathology that manifests itself as an increased ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1:FVC).[24,25] Obesity is correlated strongly with asthma,[26] which usually resolves following bariatric surgery.[27]

Table 49.1. Current National Institutes of Health/World Health Organization classification schema for overweight and obesity.

BMI (kg/m^2)	Category
<18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Overweight
30.0–34.5	Class I obesity
35.0–39.9	Class II obesity
40.0–49.9	Morbid obesity
≥50	Super obesity

Categories are based on the body mass index (BMI), which is calculated as the weight (kg) divided by height (m^2).

Table 49.2. Major organ system derangements in obesity.

Organ system	Pathology
Respiratory	↓ FRC, TLC, VC, IC, ERV
	↑ FEV_1:FVC
	Obstructive sleep apnea syndrome
Cardiovascular	↑ Blood volume
	↑ Vascular tone
	↓ Ventricular contractility
Renal	↑ Clearance of renally excreted drugs
	Hypertensive and diabetic nephropathy
Hematologic	↑ Fibrinogen
	↑ PAI-1
	↓ AT-III
	Venous stasis
Gastrointestinal	Hiatal hernia
	↑ Gastric secretion volume
	↓ Gastric pH
Metabolic/endocrine	↑ Resting energy expenditure
	Insulin resistance
	↑ Proteolysis
Immunologic	↑ TNF-α
	↑ IL-6
	Impaired neutrophil function

FRC functional residual capacity; *TLC* total lung capacity; *VC* vital capacity; *IC* inspiratory capacity; *ERV* expiratory reserve volume; *FEV_1:FVC* ratio of forced expiratory volume in 1 s to forced vital capacity; *PAI-1* plasminogen activator inhibitor-1; *AT-III* antithrombin-III; *TNF-α* tumor necrosis factor-α; *IL-6* interleukin-6.

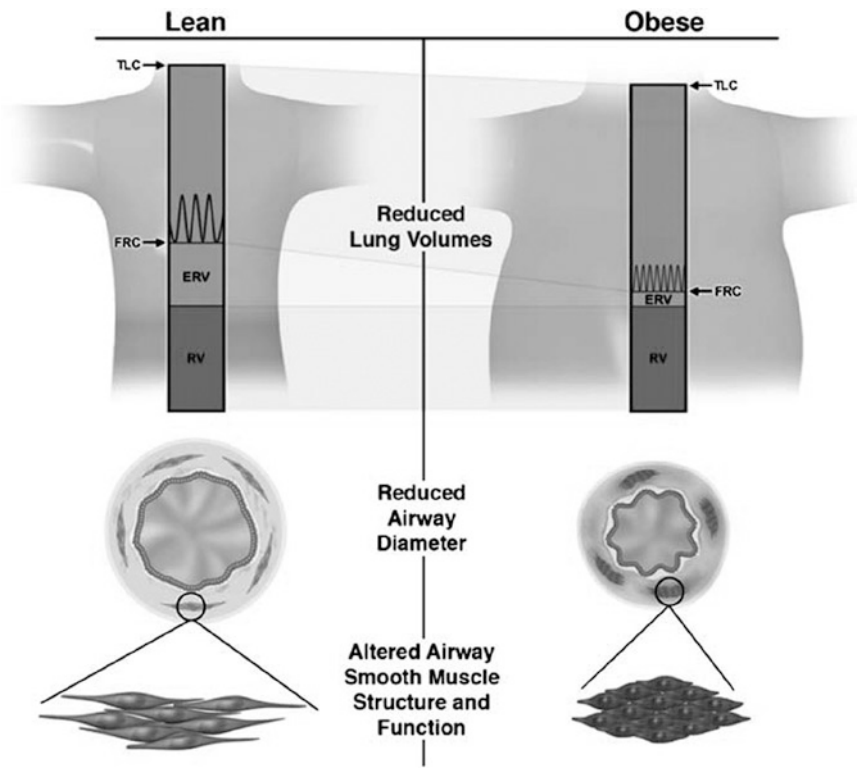

Fig. 49.1. Obesity leads to alterations in lung volumes, reduced peripheral airway diameter, and alterations in smooth muscle structure and function. The combined result entails reduced lung volumes and airway hyper-responsiveness, which is exacerbated by upper airway obstruction because of increased soft-tissue mass. Reproduced from ref.[24] by permission from the American Thoracic Society.

Obstructive sleep apnea syndrome (OSAS)– a condition characterized by repetitive partial or complete obstruction of the upper airway that is associated with arterial blood oxygen desaturations and arousals from sleep – is found with increased prevalence in bariatric surgical patients.[28,29] A decreased respiratory rate and ultimately periods of apnea occur frequently, with resultant self-limited periods of severe hypoxia.[30] Associated symptoms include snoring, systemic and pulmonary hypertension, nocturnal angina, sleep-related cardiac dysrhythmias, gastroesophageal reflux disease (GERD), insomnia, polycythemia, and daytime somnolence.[31,32] Apneic episodes occur with greatest frequency during rapid eye movement sleep, which, in turn, usually does not resume until the third to fifth night following surgery.[33]

The prevalence of OSAS in large series of bariatric surgical patients ranges from 40%[34] to 70%.[35] Polysomnography (PSG) is recommended for preoperative evaluation of all bariatric surgical patients. Empiric continuous positive airway pressure (CPAP) via mask (10 cmH_2O) may be instituted if patients are unable to complete PSG prior to surgery.[36] The CPAP acts to displace the tongue and pharyngeal soft tissues, preventing airway obstruction. Although CPAP may cause gastric distention from ingested air at increased pressure, CPAP has not been found to increase the rate of anastomotic failure. In a series of 1,067 consecutive gastric bypass patients, Livingston et al. noted similar rates of anastomotic leak in patients receiving CPAP (2/159, 1.3%) compared to those not receiving CPAP (10/908, 1.3%).[34]

An increased incidence of hiatal hernia and increased intra-abdominal pressure secondary to large abdominal panniculus may augment the risk of aspiration in the obese population.[37] Altered gastric pH and fluid volume have been found in obese surgical patients. In a cross-sectional study by Vaughan et al., 42 of 56 (75%) obese patients compared to 0 of 50 (0%) normal-weight controls shared the combination of gastric secretion volume greater than 250 mL and pH less than 2.5.[38] These levels are believed to place the adult patient at risk for aspiration pneumonitis.[39] However, Zacchi et al. found normal gastroesophageal junction resistance gradients in obese patients without GERD or hiatal hernia, and concluded that obesity alone was not a risk factor for aspiration.[40] In light of these incomplete data, it is prudent to take precautions against acid aspiration in the critically ill, obese patient. Histamine H_2-antagonists maintain gastric volume <250 mL and gastric pH > 2.5 effectively in morbidly obese patients.[41]

Obese patients' relatively short, wide necks and redundant oropharyngeal tissue render elective intubation difficult. Effective preoxygenation is rarely possible, and rapid arterial desaturation is common after induction of anesthesia. The use of a laryngeal mask airway is frequently helpful in cases of difficult endotracheal intubation.[42]

Mechanical ventilation for the obese patient with respiratory failure is particularly challenging. Delivered tidal volume should be calculated based on ideal body weight (IBW) rather than actual body weight (ABW) to avoid high airway pressures, alveolar overdistension, and barotrauma. End-tidal CO_2 monitors are unreliable because of widened alveolar–arterial gradients present in most obese patients.[43] Providing an intubated, morbidly obese patient with positive end-expiratory pressure (PEEP) of 10 cm H_2O improves lung volumes, arterial blood oxygen (PaO_2), arterial blood carbon dioxide ($PaCO_2$), elasticity, and intra-abdominal pressure compared to non-obese controls.[44] Finally, the reverse Trendelenburg position at 45° facilitates liberation from the ventilator and extubation by improving ventilatory mechanics. In a population of critically ill, obese patients, reverse Trendelenburg positioning at 45° resulted in an increased PaO_2 and tidal volume, and a decreased respiratory rate as compared to the supine position.[45]

A substantial fraction of bariatric surgery patients may require greater than 24 h of mechanical ventilation postoperatively. Helling et al. reported that 44 of 250 (18%) consecutive bariatric surgery patients remained intubated for greater than 24 h after surgery.[16] Prolonged respiratory failure following bariatric surgery, however, appears to be rare. Livingston et al. reported only nine of 1,067 (0.6%) cases of respiratory failure in their series of gastric bypass patients.[34] Furthermore, using the 2002 Healthcare Cost and Utilization Project Nationwide Inpatient Sample, Poulose et al. documented 7.3 cases of respiratory failure per 1,000 bariatric patients.[46]

Obese patients with respiratory failure may benefit from early tracheostomy. Tracheostomy is hazardous and technically demanding in these patients owing to the aforementioned cervical anatomy. Longer tracheostomy tubes with sharper angles may be necessary to accommodate increased neck girth and tracheal depth in obese patients.[47,48] Percutaneous tracheostomy remains controversial for these patients. Mansharamani et al. reported no complications in 13 consecutive obese patients,[49] but Byhahn et al. reported a 2.7-fold increased risk of perioperative complications in obese patients compared to non-obese controls (95% confidence interval [CI] 1.8–4.1, $p<0.001$), with a 4.9-fold increased risk of serious complications (95% CI 3.1–7.8, $p<0.001$).[35] The overall complication rate of percutaneous tracheostomy for 73 obese patients was 43.8%.

Effective pulmonary toilet is of crucial importance in preventing postoperative complications in the bariatric patient, as splinting and atelectasis exacerbate preexisting pathology. Several authors have noted that morbidly obese patients fare worse once pulmonary complications develop.[37,50–52] El-Solh et al. reported that, compared to non-obese controls, morbidly obese patients spent significantly more time on the ventilator (10.6 days vs. 4.6 days, $p=0.0004$), required more time to achieve extubation (3.2 days vs. 1.8 days, $p=0.009$), and required more oxygen throughout hospitalization (fraction of inspired oxygen [FiO_2] 38.4% vs. 31.1%, $p<0.001$).[50] A review of 24,157 post-anesthesia care unit patients revealed that obese patients were more than twice as likely to suffer from a critical respiratory event defined as unanticipated hypoxemia, hypoventilation, or upper airway obstruction requiring an active intervention.[52]

Early ambulation and minimal time spent in the supine position following bariatric surgery are of paramount importance. Ambulation within 2 h of surgery and frequently thereafter is common to many postoperative bariatric protocols.[53] Finally, respiratory decompensation following gastric bypass should always alert the clinician to the possibility of an anastomotic dehiscence (discussed below).

Cardiovascular

The obese state is an independent risk factor for coronary artery disease, apart from the increased prevalence of hypertension, hypercholesterolemia, and type II diabetes mellitus associated with obesity.[54] Owing to a usually sedentary lifestyle, symptoms of angina or congestive heart failure may not be elicited easily.

The pathophysiology of cardiovascular disease in obese patients results from an increase in both preload and afterload. Circulating blood volume is increased to supply additional adipose tissue.[55] Increased blood volume increases preload, stroke volume, cardiac output, and myocardial work.[56] Elevated circulating concentrations of catecholamines, mineralocorticoids, renin, and aldosterone increase afterload.[57] Hyperkinesis, myocardial hypertrophy, decreased compliance, diastolic dysfunction, and eventually ventricular failure ensue.[58,59]

The diastolic dysfunction seen with obesity results in altered Starling mechanics, characterized by a relatively narrow range of left ventricular filling pressures prior to decompensation. A pulmonary artery catheter may be useful in obese patients who require large-volume fluid resuscitation, although the value of this modality is controversial and must be weighed against the risks of both catheter-related infection and pneumothorax. Noninvasive blood pressure monitoring by cuff sphygmomanometer is often inaccurate because of size discrepancy; therefore, an indwelling arterial catheter should be employed when hemodynamic stability is in question. Finally, although the use of perioperative β-blockade in patients at risk for cardiovascular disease decreases morbidity and mortality from cardiovascular events,[60] β-blockade should be used cautiously for obese patients because of impaired ventricular contractility due to decreased β-adrenergic receptors.[61]

Both CO_2 pneumoperitoneum and reverse Trendelenburg positioning have been implicated in impairing cardiac function during laparoscopic gastric bypass.[62] In a recent trial, Nguyen et al. randomized 51 patients to receive either open or laparoscopic gastric bypass.[63] Both groups were placed in the reverse Trendelenburg position. Abdominal insufflation in the laparoscopic group resulted in increased systemic vascular resistance and decreased cardiac output compared to both baseline and the open gastric bypass group immediately after incision. However, systemic vascular resistance and cardiac output recovered within 1.5 and 2.5 h of abdominal insufflation, respectively, in the laparoscopic group and no adverse sequelae were noted. Transient hypercarbia was controlled effectively through ventilator manipulation.

Reverse Trendelenburg positioning during bariatric surgery likely has a small effect on cardiac dynamics.[62] In the aforementioned study by Nguyen et al., cardiac output increased significantly after incision in open gastric bypass patients despite being placed in the reverse Trendelenburg position.[63]

Nutrition

Malnutrition and obesity are not mutually exclusive, and the supposition that "starving" obese patients during critical illness is well tolerated or even beneficial is erroneous. Obese patients have an increased resting energy expenditure secondary to increased BMI, with central adipose tissue being more metabolically active than peripheral adipose tissue.[64]

Obesity is characterized by the "metabolic X syndrome:" hyperinsulinemia, insulin resistance, hyperglycemia, coronary artery disease, hypertension, and hyperlipidemia.[65] Elevated basal insulin concentrations in obesity suppress lipid mobilization, causing accelerated proteolysis to support gluconeogenesis, which in turn results in rapid muscle loss and early deconditioning. A case-control study of obese blunt trauma patients revealed that obese patients mobilized relatively more protein and less fat compared to non-obese controls.[66] This shift from fat to carbohydrate metabolism increases the respiratory quotient, causing hypercarbia that may impede extubation.

Nutrition in critically ill, obese patients should supply enough glucose to spare protein. Calories should be supplied primarily as carbohydrates, with fats given to prevent essential fatty acid deficiency.[67] Most recommended enteral feeding regimens supply 30 kcal/kg and 2.0 g/kg protein/day, based on IBW.[43,68,69] The benefit of hypocaloric feedings in the critically ill, obese patient has been investigated. Dickerson et al. reviewed 40 critically ill, obese surgical patients and found that those who received hypocaloric enteral feedings (<20 kcal/kg/day based on IBW) had decreased ICU length of stay (LOS), received fewer days of antibiotics, and decreased length of mechanical ventilation compared to those fed isocaloric feedings (≥20 kcal/kg/day).[70] The authors postulated that improved outcome in the hypocaloric group was related to fewer complications of overfeeding. Prospective trials are warranted.

Total parenteral nutrition (TPN) is used often in postoperative bariatric patients when enteral feeding is impossible. However, although data specifically addressing the bariatric patient population are not available, TPN has not been shown to decrease major postoperative complication rates or mortality in critically ill, postoperative patients.[71,72] Placement of a feeding gastrostomy tube at the time of surgery should be considered when a prolonged period of critical illness is anticipated.

Strict glycemic control using intensive insulin therapy has been an important recent development in the care of the critically ill, surgical patient.[73] Critically ill, morbidly obese patients are more likely to require an insulin infusion

and require more mean units of insulin per hour to maintain euglycemia as compared to non-morbidly obese patients.[74] However, if an aggressive approach to euglycemia is appropriately employed in morbidly obese patients, the risk of adverse outcomes is decreased, including nosocomial infection.[74]

Pharmacology

Obese patients with normal renal function have an increased glomerular filtration rate and thus an increased clearance of drugs excreted by the kidney.[75,76] However, type II diabetes mellitus and hypertension, which frequently complicate obesity, may cause renal dysfunction. Therefore, renal function must be determined on an individual basis. Furthermore, calculated and measured creatinine clearance correlate poorly in obesity,[77] mandating measurement of creatinine clearance with timed urine specimens in all obese patients with suspected renal dysfunction.

An increased ratio of adipose to lean body mass alters the volume of distribution (V_d) of lipophilic drugs. Accumulation of lipophilic drugs in adipose tissue not only increases the dose necessary to gain effect, but also prolongs the elimination half-life.[78,79] Dosing of these drugs in obese patients is generally approximated best using ABW rather than IBW.[80] Conversely, the V_d of hydrophilic drugs, in general, relates better to lean body mass (approximated by IBW) because of poor penetration into adipose tissue. Dosing of hydrophilic drugs based on ABW in the obese patient population may overestimate necessary dosages, leading to toxicity.[81] However, blood, extracellular fluid, body organ, and connective tissue volume, to which hydrophilic drugs may distribute, are all also increased in obese patients.[82] Thus, whereas dosing of hydrophilic drugs should initially be based on IBW, serum concentrations should be monitored whenever possible to ensure therapeutic concentrations.[83,84]

Owing to variable alterations in V_d, clearance, and elimination half-life, dosing adjustments for specific drugs in obese patients can be complex. Individual drugs used commonly in critical illness that have been studied in obese patients are discussed as follows:

Propofol

Propofol is a hypnotic, lipophilic drug with a rapid onset and short duration of action.[85] Both V_d and clearance of propofol are increased in obese patients and correlate with ABW.[86] Elimination half-life is unchanged compared to non-obese controls. Dosing of propofol for both induction and maintenance of anesthesia should thus be based on ABW.

Benzodiazepines

The lipophilic benzodiazepines demonstrate markedly increased V_d, similar clearance, and increased elimination half-life in obese patients.[87] On the basis of these data, single dosing of benzodiazepines in obese patients (e.g., premedication for bedside procedures) should be calculated based on ABW to account for the increased V_d of the drug.[88] However, dose calculations for continuous infusion in obese patients should follow IBW as clearance is not significantly different from non-obese patients. Frequent interruptions in infusion with assessment of patient response are necessary to avoid delayed liberation from the ventilator and prolonged ICU LOS.[89]

Fentanyl

Fentanyl is a synthetic, lipophilic opioid with a rapid onset of action and minimal histamine-related vasodilation.[90] Pharmacokinetics of fentanyl are similar in obese as compared to non-obese patients, suggesting dosing based on IBW. Shibutani et al. reported a poor linear correlation between the fentanyl doses required for analgesia and ABW.[91] They derived a correction factor (Table 49.3) for the weight-based dosing of fentanyl in the postoperative period, termed "pharmacokinetic mass," that correlated well with fentanyl dose over a range of 48–181 kg.

Antimicrobials

Although the pharmacokinetics of many antimicrobials in obese patients are unknown, several exceptions warrant discussion. Both the V_d and clearance of vancomycin correlate better with ABW than with IBW in morbidly obese patients.[92,93] The shorter elimination half-life of vancomycin relative to non-obese patients may require shorter dosing intervals to achieve therapeutic steady-state trough concentrations (e.g., every 8 h [q8h] versus every 12 h [q12h]).[93] Owing to variability in both dosage amount and dosage interval, serum concentrations of vancomycin should be monitored in obese patients.[94]

Linezolid is an oxazolidinone with activity against multidrug-resistant gram-positive bacteria.[95,96] Data regarding the pharmacokinetics of linezolid in obese patients are currently limited to case series involving non-critically ill, patients with cellulitis.[97,98] In these reports, clinical cure was achieved using the standard dosing regimen of 600 mg PO q12h.

Table 49.3. Dosing weights in obese patients for selected drugs used commonly in critical illness.

Drug	Dosing weight
Propofol	ABW
Benzodiazepines	
Single dosage	ABW
Continuous infusion	IBW
Fentanyl	$52/[1+(196.4\times e^{-0.025\ ABW}-53.66)/100]$
Vancomycin	ABW
Aminoglycosides	IBW + [0.40 × (ABW − IBW)]
Fluoroquinolones	IBW + [0.40 × (ABW − IBW)]
Drotrecogin alfa (activated)	ABW

ABW actual body weight; *IBW* ideal body weight.

Data involving critically ill patients are necessary prior to formulating meaningful recommendations.

The hydrophilic aminoglycosides and fluoroquinolones require use of a predetermined dosing weight correction factor (DWCF) to calculate dosing weight (Table 49.3). Clinical studies suggest a DWCF of approximately 0.45 for both aminoglycosides[99] and quinolones.[100] However, because a wide range of DWCF for aminoglycosides has been reported in the literature,[101–103] subsequent dosing should be based on serum concentrations. Monitoring serum concentrations of aminoglycosides is of particular importance in obesity because of an increased susceptibility to nephrotoxicity.[104,105] Alterations of dosage interval in obese patients with normal renal function are usually unnecessary.[83,106] Once-daily dosing of aminoglycosides in obese patients has not been studied and is not recommended.

Drotrecogin Alfa

The Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial of drotrecogin alfa (activated) (APC)[107] excluded patients weighing more than 135 kg. A subsequent study that included morbidly obese patients documented similar plasma concentrations and elimination half-lives of APC when dosed by ABW.[108] Therefore, APC may be used for treatment of severe sepsis in morbidly obese patients and should be dosed according to ABW without limitation of dosage. Dosing weights in obese patients for drugs used commonly in critical illness are summarized in Table 49.3.

Hematologic

Obese patients are believed to be at increased risk of thromboembolic complications because of increased blood viscosity, decreased concentration of AT-III, and increased concentration of both fibrinogen and PAI-1 produced by adipocytes.[23,109] Sedentary lifestyle, venous stasis, and pulmonary hypertension augment this risk.[109–111] Endothelial injury as a result of surgery further predisposes the obese surgical patient to thromboembolic complications.

Several prospective studies have identified obesity as a risk factor for postoperative venous thromboembolism (VTE) after elective major abdominal surgery.[111–113] Two large autopsy series revealed that 67%[114] and 75%[115] of patients with no preexisting risk factors who died of acute pulmonary thromboembolism were obese.

Despite an increased risk within the obese population, the reported incidence of VTE following bariatric surgery is low. Prospective studies have reported an incidence of VTE from 0 to 2.4%, and pulmonary embolism from 0 to 1.2%.[16,116–123] However, variable methods of prophylaxis were used, and the majority of patients were not critically ill. Gonzalez et al. identified age greater than 50 years, anastomotic leak, a history of smoking, and a history of VTE as independently predictive of postoperative VTE in 660 consecutive patients who underwent gastric bypass.[124]

Although VTE is rare, pulmonary embolism is the most common cause of postoperative mortality[16,125] and an independent risk factor for death following bariatric surgery.[121] In a review of 3,464 bariatric surgery patients, pulmonary embolism accounted for 50% of deaths.[120] Livingston et al. documented nine postoperative pulmonary emboli in 1,067 bariatric surgery patients, of which six were fatal.[34]

Whereas more than 95% of obesity surgeons use some form of thromboprophylaxis routinely,[126] no specific regimen is employed universally. Scholten et al. documented a low incidence of postoperative VTE with a multimodality prophylaxis protocol including early ambulation, graded compression stockings, intermittent pneumatic compression (IPC) stockings, and enoxaparin 40 mg subcutaneously q12h.[127] A recent meta-analysis recommended unfractionated heparin, low-molecular-weight heparin, or IPC stockings for high-risk patients undergoing elective abdominal surgery.[128] Emphasis must be placed on proper timing of prophylaxis, with the initial dose of pharmacoprophylaxis given 1–2 h preoperatively.

Prophylactic inferior vena cava (IVC) filter placement may be beneficial for those bariatric patients at extremely high risk for postoperative VTE. A higher incidence of VTE has been reported in super-obese patients, patients with truncal obesity, venous stasis disease, or a prior history of VTE.[122,129,130] Although no randomized trials exist addressing the value of prophylactic IVC filter placement in this population, the preoperative placement of retrievable IVC filters appears feasible for patients with one or more of these high-risk factors.[131]

Specific Complications Following Bariatric Surgery

Anastomotic Leak

Anastomotic leak is the second leading cause of mortality following gastric bypass surgery[125] and may occur at either the gastrojejunostomy (Fig. 49.2) or, less commonly, at the jejunojejunostomy. Recent case series have reported an incidence ranging from 0.5 to 2%.[17,34,120,122,132] Bariatric patients who sustain a postoperative anastomotic leak suffer increased hospital LOS, ICU LOS, and mortality.[121,131]

In a recent review of 210 consecutive laparoscopic Roux-en-Y gastric bypass patients, Hamilton et al. found severe tachycardia (HR ≥ 120 bpm) and respiratory failure (the development of an increasing oxygen requirement after discharge from the post-anesthesia care unit, oxygen saturation [SaO_2] < 92% on room air, or respiratory rate ≥ 24 breaths/min) to be the two most common presenting manifestations of anastomotic leak.[133] Eight of nine patients (89%) with anastomotic leaks experienced severe tachycardia, and six of nine patients (67%) experienced respiratory distress. By multivariable analysis, both respiratory distress (odds ratio [OR] = 6.0, 95% C.I. [2.57–208.5], $p < 0.01$) and severe tachycardia (OR = 23.2, 95% C.I. [1.2–29.4], $p < 0.05$) were independent predictors

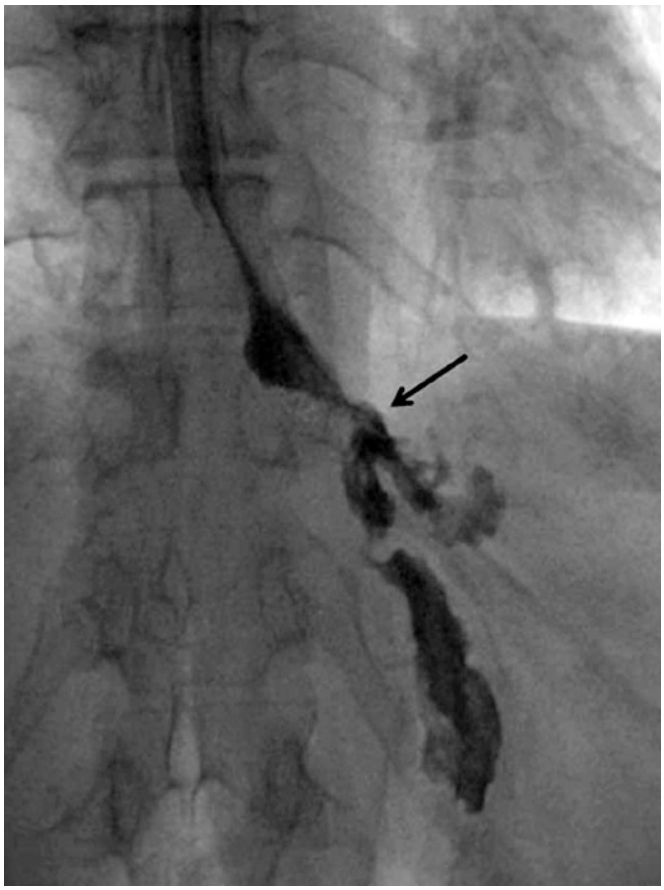

FIG. 49.2. Upper gastrointestinal series demonstrating extravasation of contrast at the site of the gastrojejunostomy (*arrow*) following laparoscopic gastric bypass, consistent with an anastomotic leak.

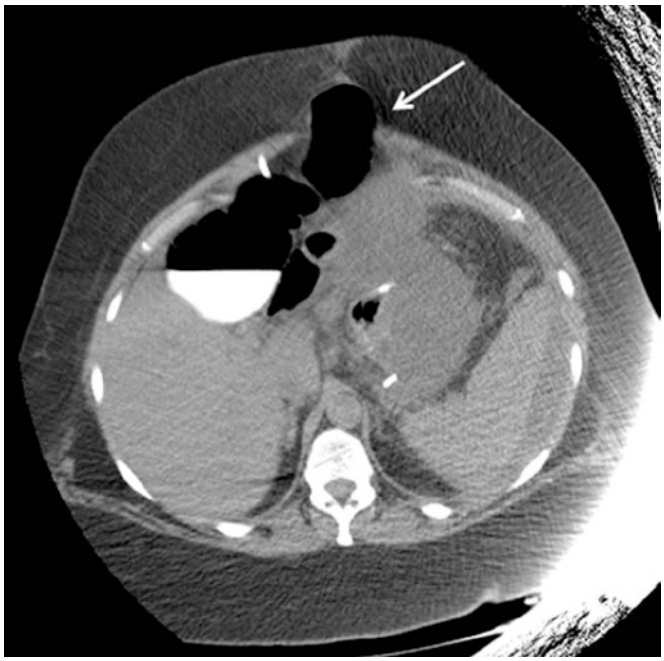

FIG. 49.3. Epigastric trocar site hernia (*arrow*) following laparoscopic Roux-en-Y gastric bypass.

of anastomotic leak. Failure of progression to extubation or sudden respiratory decompensation in the immediate postoperative period should thus raise suspicion of intra-abdominal pathology. Concurrent symptoms and findings, such as left shoulder pain, increasing abdominal pain, a perception of impending doom, or an isolated left pleural effusion on chest radiograph, may aid in differentiating anastomotic leak from other common causes of postoperative respiratory decline, most notably pulmonary embolism.

Upper gastrointestinal (UGI) contrast imaging can be very useful and is routinely employed to diagnose anastomotic failure. A negative study, however, does not exclude the diagnosis. In a study by Hamilton et al., a water-soluble contrast imaging revealed an anastomotic leak in only two of nine patients (22%). A more recent study underscored the poor sensitivity of UGI imaging for detecting suspected jejunojejunostomy leaks; nine of ten leaks at this site were not detected.[132] Mortality for this group of patients was 40%. Routine UGI imaging following gastric bypass does not appear to offer any benefit over selective use.[134,135]

Because failure to recognize an anastomotic leak can result in rapid deterioration and death, all postoperative bariatric patients with persistent tachycardia or respiratory distress in whom pulmonary embolism has been ruled out should undergo exploratory laparoscopy or laparotomy, regardless of UGI imaging results. Most morbidly obese patients exceed the weight limitation for the gantry of computed tomography (CT) scanners, precluding the use of CT to image the abdomen.

Early Small Bowel Obstruction

Small bowel obstruction (SBO) within the first month of surgery has become an increasingly recognized serious complication following both laparoscopic and open gastric bypass, occurring in approximately 2% of cases.[125,136–139] The most common causes of early SBOs are technical, involving kinking at the jejunojejunostomy, anastomotic stenosis due to tissue edema, or external compression of the Roux-en-Y limb at the location of the transverse mesocolon. Less commonly, herniation through trocar sites (following laparoscopic surgery) (Fig. 49.3), and adhesions have been reported to cause early SBOs.

Sudden and severe abdominal pain, tachycardia, nausea, vomiting, and obstipation are both the most common and most concerning symptoms reported by patients with early postoperative SBOs. Because isolated obstruction of the excluded biliopancreatic limb may occur following gastric bypass surgery (termed bypass obstruction[125]), both gastric and intestinal ischemia and frank necrosis may occur in the absence of obstipation. Such cases of bypass obstruction portend a grave prognosis because of massive fluid and electrolyte loss into the massively distended, excluded stomach (Fig. 49.4),

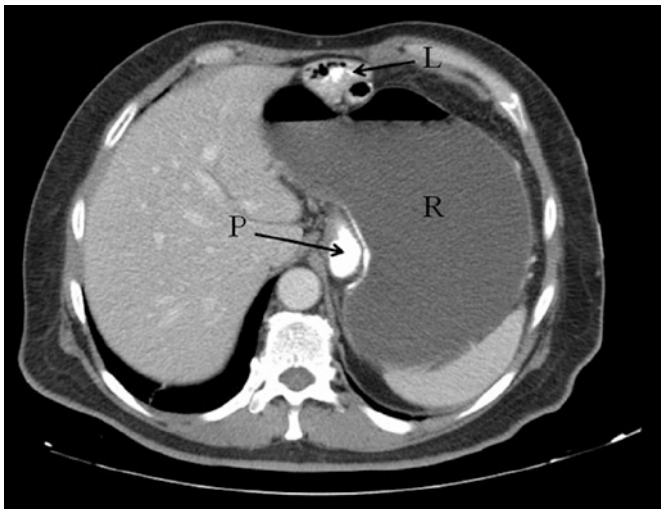

Fig. 49.4. Bypass obstruction. Note the distended, fluid-filled gastric remnant (R) surrounding the contrast-filled gastric pouch (P), and posterior to the antegastric, antecolic Roux limb (L), also filled with contrast.

with resultant hypovolemic shock, perforation, sepsis, and death.[140,141] Distention may arise from either torsion of the lengthy diverted limb or adynamic ileus. Nasogastric tube decompression is ineffective in this situation as the excluded stomach is inaccessible via this route.

As is the case with a suspected anastomotic leak, diagnostic imaging with either CT or UGI contrast study may prove useful in confirming the diagnosis of a postoperative SBO. However, the sensitivity of these modalities is poor, and the decision to proceed to surgical intervention is predominantly clinical. Abdominal pain and hemodynamic instability warrants prompt surgical intervention, even in the absence of nausea, vomiting, and obstipation. Ischemic and frankly gangrenous bowel is discovered frequently upon reexploration in this patient population.[136,141]

Pressure-Induced Rhabdomyolysis

Pressure-induced rhabdomyolysis is a rare, but well-described, postoperative complication that results from prolonged, unrelieved pressure to muscle during surgery.[142–145] Major risk factors include prolonged operative time and obesity. Rhabdomyolysis following bariatric surgery may affect the lower extremity, gluteal, or lumbar regions.[146–149] In a recent review, mean operating room time, mean BMI (67 kg/m^2 vs. 56 kg/m^2), and the incidence of diabetes mellitus were significantly greater in patients who developed rhabdomyolysis.[147] Prevention of rhabdomyolysis and related complications includes attention to padding and positioning on the operating table, minimization of operative time, and maintenance of a high index of suspicion postoperatively.

Although the most common clinical presentation of rhabdomyolysis is numbness and muscular pain, patients may lack symptoms due to perioperative epidural anesthesia. Cutaneous eruptions (e.g., purpura, epidermolysis) over sites of muscle injury have been described.[150] Muscle breakdown leads to the release of intracellular myoglobin and creatine phosphokinase (CPK). Myoglobinuria is suspected in the presence of brown urine, and confirmed by a positive urine dipstick test for hemoglobin in the absence of erythrocytes on urinalysis. Serum CPK concentrations peak on the second to fifth postoperative day, and usually resolve within 2 weeks of surgery.[146]

Patients suspected of having rhabdomyolysis should be monitored in the ICU. Treatment is instituted once the CPK concentration increases above 5,000 international units per liter (IU/L), including aggressive hydration and diuresis with mannitol to a target urine output of 1.5 mL/kg/h. Mannitol mobilizes muscular interstitial fluid, increases renal tubular flow, and scavenges the reactive oxygen species generated as myoglobin is metabolized.[151] Alkalization of urine with sodium bicarbonate increases the solubility of myoglobin in a pH-dependent manner.[152]

Compartment syndrome, acute renal failure, and mortality may complicate rhabdomyolysis. Acute renal failure results from hypovolemia, tubular obstruction, acidosis, and free radical release.[153] Factors predictive of renal failure in rhabdomyolysis include age greater than 70 years, serum CPK concentration > 16,000 IU/L, degree of hypoalbuminemia, and sepsis.[154] Fortunately, complete recovery of tubular function is the norm, albeit after a variable period of renal replacement therapy.[143] Hemofiltration has the added advantage of rapid clearance of myoglobin.

Outcomes

The obese, critically ill patient has been considered traditionally at increased risk of mortality because of both underlying organ dysfunction and increased difficulty encountered during routine ICU procedures (e.g., endotracheal intubation). Conversely, in what has been termed the "obesity paradox," an increase in both adipose and muscle reserve, alterations in cell-mediated immunity, and increased lipoprotein concentrations may confer a survival advantage upon the obese, critically ill patient.[155]

Outcomes research, conducted at both the single-institution and national level, has failed to reach a consensus regarding an association between obesity and mortality of critical illness, and this issue remains contested fervently within the critical care literature.[155–158] Reported associations range from a protective effect of obesity[159–163] to a markedly increased risk-adjusted likelihood of mortality.[164–166] However, the few studies that have investigated specifically morbidly obese, critically ill, surgical patients[14,167] suggest that this patient group is at increased risk of both morbidity and mortality of critical illness. Future studies employing rigorous methodology are warranted.

Table 49.4. Risk factors for intensive care unit admission, and postoperative complications following bariatric surgery.

Male gender
Age > 50 years
BMI > 60 kg/m2
Diabetes mellitus
Cardiovascular disease
Obstructive sleep apnea syndrome
Venous stasis
Intraoperative complications

BMI body mass index.

Far less information is available as to the course of bariatric surgical patients requiring ICU care. In a retrospective review of 250 patients undergoing either vertical banded gastroplasty or gastric bypass, Helling et al. noted that hospital LOS doubled for those patients requiring greater than 24 h of ICU care following surgery.[16] Factors predictive of ICU admission after bariatric surgery are summarized in Table 49.4.[16,34,53]

Conclusion

Bariatric surgical patients now comprise a substantial percentage of ICU admissions. Recent data indicate that, compared to their normal weight counterparts, morbidly obese patients are at increased risk for both mortality and a variety of postoperative complications during critical illness. This increased risk is likely due to organ dysfunction inherent to the obese state, as well as technical difficulty encountered by physicians and ancillary staff alike during the daily care of morbidly obese patients. Knowledge of the pathophysiology of obesity as well as the presentation and treatment of serious complications of bariatric surgery are necessary to manage these patients effectively. In general, decreased pulmonary, cardiac, and metabolic reserves attenuate the physiologic resilience of obese patients. Furthermore, chronic inflammation and alterations in body composition mandate novel strategies for pharmacologic prophylaxis as well as therapy. Respiratory decomposition, as well as unexplained tachycardia in the immediate postoperative period, should alert the intensivist to the possibility of either an anastomotic leak or early SBO, both of which require prompt surgical intervention. Increased experience caring for the postoperative bariatric surgery patient will hopefully generate the next iteration of evidence-based recommendations for this rapidly expanding demographic.

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Care of the Organ Donor

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Since 1952 when the first kidney transplant was accomplished, nearly 400,000 transplantations have been performed with donors being from both deceased and living donors. However, almost 100,000 patients with end-stage organ failure remain on the United Network for Organ Sharing (UNOS) waiting list for organ transplantation. There has been a steady increase in the number of patients awaiting transplantation, the time to receive a transplant, and waiting-list deaths. The waiting list is increasing two to three times faster than the rate of organs available for transplantation despite a large potential organ donor population. It is estimated that only 15–20% of potential donors become actual donors. Meanwhile, the waiting time on the list has increased to more than 2 years for half of the listed patients. Ten percent of adult patients die awaiting transplantation.

The geographic rate of organ donation varies based on population characteristics, OPOs (organ procurement organizations), and legislation. The disparity between organ supply and availability continues despite annual increases in the number of organ donors. Although transplantation is the standard of care for those patients with end-organ failure who fail medical therapy, the shortage of organ transplants is now a national crisis in the United States.

There have been numerous local, state and federal programs developed to increase the rate of organ donation in the US. However, there have been only moderate increases in the number of cadaveric donors and the number of organs transplanted per donor, compared to the growing number of patients requiring transplantation. The Uniform Anatomical Gift Act of 1968 made it easy for individuals to donate with written documentation, i.e., executed donor card, donor driver's license, living will, durable power of attorney, or other document of gift. Many states have implemented the *first person consent* legislation (also known as donor designation), which declares that an individual's decision to donate takes legal precedence over the family's wishes. A major initiative sponsored by the US Department of Health and Human Services in 2003 is the *Organ Donation and Transplantation Breakthrough Collaborative*, whose goal is to share best practices with the nation's transplant hospitals. The Collaborative consists of expertise from OPOs, transplant programs, and the critical care community. The expectation is that this collaboration could ultimately increase the number of organs transplanted in the US by more than 40% and increase the number of organs transplanted per donor to a mean of 3.75 or more. The Department of Health and Human Services has also offered more than 26 million dollars in grants to develop ways to increase organ donation in the US. The US Senate passed the Organ Donation and Recovery Improvement Act in 2004, which promotes public education campaigns about organ donation and funds hospital organ donation programs. Many US states are now utilizing donor registries, which allow individuals to record their wishes regarding organ donation electronically, with subsequent easy retrieval by OPOs and hospitals. The Centers for Medicare and Medicaid Services require all US hospitals to notify their local OPO prior to a patient's anticipated death if the patient is thought to be a potential organ donor and that all requests for donations to be made by trained experts. This is the time before brain death is declared or before life support is withdrawn, so that suitability of the potential donor can be determined and then discussed with their family.

Consent rates and donor rates (calculated as actual donors divided by reported eligible deaths) have increased modestly after the implementation of this law. All of these initiatives have encouraged best practices in organ donation. Although the use of *expanded criteria donors* has increased the numbers of potential donors, there has also been more discarding of procured organs because of poor quality and decreased organ function. The modest increase in donors who meet the expanded criteria has resulted from the use of donors 50 years of age or older and from donors with preexisting medical

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conditions. Kidneys and livers from donors more than 80 years old have been successfully transplanted; and there is no upper age limit for the donation of eyes, bone, and skin. The use of organs from living-related, living-unrelated, and donation after cardiac death (DCD) has also increased the donor pool, as have split-liver transplants and the use of high-risk donors (e.g., patients with cancer, bacteremia, and hepatitis C).

Although there have been significant advances in the field of transplantation medicine, advances in the area of organ donation have not been as forthcoming. There is significant disparity between the number of potential donors and the number of actual donors. Potential donors fail to become actual donors for a variety of reasons: their families refuse to give consent for organ donation; brain-dead donors suffer hemodynamic collapse and cardiac arrest before organ procurement occurs; or donors turn out to be medically unsuitable. Lack of consent to a request for donation appears to be the main reason that explains the disparity in numbers.[1] In addition, 25% of lost donor organs from brain-dead patients result from inadequate medical care prior to organ procurement.[2] Aggressive protocols for donor management, including hemodynamic monitoring and treatment, have decreased the medical failure rate as well as improving the donor retrieval rate. The Crystal City Consensus Conference in 2001, sponsored by the American Society of Transplant Surgeons and the American Society of Transplantation, reported that standard protocols for aggressive and intensive donor management lead to improved management of the organ donors prior to procurement and ultimately to an improvement in the function of the transplanted organs.[3] Mechanisms to increase the number of transplantable organs include increasing consent rates of available donors by continued education. Equally important is increasing the potential donor pool and the number of organs transplanted per donor by allowing older donors, making changes in the donor classification and selection criteria, and optimizing medical management of organ donor patients prior to procurement and transplantation.

Evaluation and Selection of Donors

Almost anyone dying in hospital is a potential organ or tissue donor. A potential organ donor is an individual who is either brain-dead or has had a cardiac death after withdrawal of life support and has no absolute contraindications to organ donation. Living-related and living, unrelated donors may also donate specific organs, such as kidney; bone marrow; lobe of a lung; and portion of the liver, pancreas, or intestine. The number of living donors exceeds the number of deceased donors, although the donation rate from living donors has plateaued.

There are few absolute contraindications to organ donation because of the growing crisis and demand for more organs for transplantation. Absolute contraindications include seropositivity to the human immunodeficiency virus (HIV) and infection with the human T-lymphotropic virus (HTLV). Overwhelming infection generally precludes organ donation, although organs transplanted from bacteremic donors rarely transmit bacterial infections. Outcomes for the recipients of organs from donors who had bacterial infections are not significantly worse than those without infection. Organs from patients infected with the hepatitis B or C virus or the cytomegalovirus may be transplanted into recipients who have the same virus, and even in recipients who are not infected with the virus but may otherwise die without the transplant. Patients with active malignant disease are not candidates for organ donation, except for certain primary brain tumors and non-melanoma skin cancers. However, there is variability of exclusion criteria for organ donation from different regions.

The number of ideal donors – who are relatively young with irreversible and irreparable brain damage, no comorbidities, and excellent multiorgan function – has decreased over time. Diseased donors are pronounced dead using either neurologic or cardiac criteria. In adults, traumatic brain injury, intracranial hemorrhage, subarachnoid hemorrhage, and global ischemic/anoxic insults are the most frequent causes of brain death. In the US, brain death is defined as complete and irreversible cessation of *whole brain function*; i.e., cerebral and brainstem death. Brain death can be determined solely by clinical criteria in adults. The diagnosis of brain death requires the absence of brainstem reflexes, motor responses, and respiratory drive in a normothermic, normotensive patient (the patient can be receiving vasopressor support to maintain the systolic blood pressure greater than 90 mmHg), as well as unresponsiveness without evidence of a drug or metabolic encephalopathy. The clinical examination focuses on demonstrating the absence of brainstem function. Unresponsiveness to verbal and painful stimuli is evidence of absent cerebral function. Except for spinal reflexes, which may persist in the brain-dead patient, the patient is flaccid with no motor response to painful stimulation. Pupillary, corneal, cough, gag, oculocephalic (doll's eyes) and oculovestibular (caloric) reflexes are all absent in brainstem death. Apnea must be present when ventilator support is withdrawn using the apnea (Table 50.1) or hypoventilation test. The brain-dead patient will not be stimulated to breathe

Table 50.1. Procedure for apnea testing.

1. Prerequisites are: core temperature 36.5°C or 97°F or higher; systolic blood pressure 90 mmHg or higher; corrected diabetes insipidus or positive fluid balance in the past 6 h; $PaCO_2$ of 40 mmHg or greater
2. Preoxygenate with 100% FiO_2 or PaO_2 200 mmHg or greater, and reduce minute volume to 5 L/min for 10 min before beginning apnea testing
3. Discontinue mechanical ventilation, insert oxygen cannula into endotracheal tube or tracheostomy to the level of carina, and supply oxygen at 6 L/min. If arterial desaturation occurs during apnea testing, apply manual breaths with Ambu bag to restore saturation and resume apnea. The apnea test must be terminated if the patient becomes cyanotic or hypotensive
4. Observe closely for respiratory movements
5. Draw arterial blood gases approximately 5–7 min after beginning apnea and resume positive pressure ventilation
6. If arterial PCO_2 is > 60 or 20 mmHg higher than the baseline and no respiratory efforts are evident, the apnea criterion is met

even when the partial pressure of carbon dioxide (pCO_2) in the blood increases to 60 mmHg or greater, or the pCO_2 is 20 mmHg higher than the patient's baseline pCO_2. Because of the risk of hemodynamic instability and cardiac arrest at the time of the apnea test, many centers now perform the *hypoventilation test*. The ventilator rate is set at two breaths per minute, the tidal volume is halved, the low exhaled minute volume alarm is set at 0 L/m, and 100% of the fraction of inspired oxygen (FIO_2) is delivered to the patient. The same PCO_2 parameter of 60 mmHg or greater to stimulate respiration is the goal in these patients.

No further tests are required if a clinical examination documenting brain death has been performed (Table 50.2). However, if there are compounding issues – such as drug, electrolyte, and metabolic derangements; or the information obtained from the clinical examination is equivocal; or the apnea/hypoventilation test cannot be performed because of preexisting cardiopulmonary instability – then additional confirmation must be obtained. Adjunctive tests that support the diagnosis of brain death include electroencephalography (EEG) and evoked potentials. An EEG that demonstrates electrocerebral silence (flat EEG) supports the diagnosis of brain death when the apnea test cannot be performed because of severe hypoxia or hemodynamic instability. Confirmatory/Confirmed tests that prove the diagnosis of brain death include cerebral blood flow studies using either technetium or xenon and transcranial Doppler sonography. Absent intracranial circulation is documented with the blood flow study or with the transcranial Dopplers, which demonstrate systolic peaks (without diastolic flow) or a reverberating flow pattern. These findings are pathognomonic for brain death. The actual procurement of organs after the declaration of brain death is often delayed for several hours while awaiting results of the evaluative laboratory and radiographic examinations necessary prior to transplantation.

Although the majority of deceased donors are brain-dead patients, the donation rate from patients who donate organs after cardiac death/asystole is increasing. Donation after cardiac death (DCD) is considered in patients in whom further medical treatment is deemed futile. These patients have irreversible asystole and apnea after withdrawal of life support. These patients usually have severe and devastating neurologic impairment but do not meet brain death criteria. DCD was relatively common before neurologic criteria for death were introduced in the late 1960s and early 1970s. Since donor survival outcomes were better after procuring organs from brain-dead patients, DCD virtually disappeared for many years before its resurgence in the early 1990s. DCD occurs in two patient subsets. *Controlled DCD* is when organ procurement follows a death after planned removal of life support. In this instance, the patient or family has refused additional life-sustaining treatment and requests withdrawal from life support. *Uncontrolled DCD* is organ procurement after an unexpected cardiac arrest and unsuccessful cardiopulmonary resuscitation. Although relatively uncommon, this occurs in the emergency department or in the ICU where organ preservation (infusion of cold organ-preserving solution) and procurement activities can be instituted immediately based on the patient's wish or the family's wish to donate. A major predictive determinant in organ transplantation is the ischemic time from cessation of cardiac output in the host, until restoration of circulation in the recipient. In particular, the warm ischemic time from loss of perfusion until flushing and cooling with preservative solution is crucial. In brain-dead donors, the ischemic time is kept to a minimum. More recently, improved preservation techniques and better assessment of organ function have enabled transplant teams to procure kidneys, livers, lungs, and pancreases from asystolic donors. Apnea, absent circulation, and unresponsiveness must be observed for a period of 2–5 min after cardiac death before the organs can be procured. Reports of return of spontaneous circulation at less than 2 min of observation after death have occurred. Since donation must occur within minutes of the determination of cardiac death because of the risk of prolonging ischemia to the organs, withdrawal of life support is usually performed in the operating room or in the ICU if close to an operating room. No patient may be certified dead by a physician who takes part in the procurement or organ transplantation process. When life support is withdrawn, the patient should be given medications to prevent and alleviate pain, although these medications may hasten death. It is important to remember in these instances that the object of drug therapy is not to prolong life but to make the dying process pain-free and without suffering.

Table 50.2. Clinical brain death certification.

Absence of confounding factors
• Systolic blood pressure ≥90 mmHg or not <10 mmHg below patient's baseline blood pressure
• Temperature > 32°C
• No central nervous system depressants
• No uremia, meningoencephalitis, hepatic encephalopathy, or other metabolic encephalopathies
Absence of cerebral and brainstem functions
• Unresponsiveness to painful stimuli (supraorbital pressure)
• No spontaneous movements, posturing, or seizures
• Pupils fixed and dilated
• Absent corneal reflexes
• Absent response to upper and lower airway suctioning (pharyngeal and tracheal suctioning)
• Absent oculocephalic reflexes (doll's eyes)
• Absent oculovestibular reflexes (irrigation of both ears with 50 mL of ice water)
• Apnea with pCO_2 > 60 or 20 mmHg above patient's baseline

Pathophysiology of Brain Death

Early recognition of imminent brain death and institution of rapid therapeutic measures that result in successful donation and transplantation requires understanding of the physiologic changes that occur during the evolution of brain death. Regardless of the various mechanisms involved in primary

injury of the brain, ongoing brain damage can progress and lead to intracranial pressure (ICP) elevation and brain edema. If the ICP is not treated aggressively, and even at times with treatment, brain herniation and brain death may occur. This dynamic process results in loss of hemodynamic stability due to autonomic dysregulation.

This initial phase of autonomic dysregulation is characterized by increased sympathetic activity mediated by a catecholamine surge. Cushing's response (arterial hypertension, bradycardia, and respiratory irregularity) can be the first ominous signs of impending brain herniation. Bradycardia may not be seen in the setting of high sympathetic activity. Typical findings during this stage of intense sympathetic outflow are tachycardia and hypertension as a result of a significantly elevated systemic venous resistance. Increases in myocardial oxygen demand and catecholamine-induced coronary vasoconstriction can lead to myocardial ischemia and left ventricular dysfunction. The brief initial period of high sympathetic activity is self-limited and is followed by a more prolonged period of severe vasodilation, causing cardiovascular collapse. There is also impaired inotropy and chronotropy and dysrhythmias. Typically, it is at this stage when medical failure occurs in the management of the potential donor.

Pulmonary edema is a common finding in brain death. The etiology of neurogenic pulmonary edema can be multifactorial. Left ventricular dysfunction caused by autonomic instability can cause hydrostatic pressure pulmonary edema. The generalized inflammatory state associated with brain death can lead to damage in pulmonary capillary endothelium causing increased permeability and edema. Pulmonary edema is further worsened by aggressive volume loading during resuscitative efforts. Aspiration, pneumonia, and atelectasis are other common causes of pulmonary dysfunction. High FIO_2 and positive end-expiratory pressure (PEEP) requirements, often necessary during organ donor management, can make the donor's lung unsuitable for transplant according to traditional criteria for lung donation.

There are several endocrine and metabolic abnormalities seen in brain death. Diabetes insipidus (DI) is the most consistent endocrine disturbance seen in brain-dead patients as a result of damage to the hypothalamic–pituitary axis and related antidiuretic hormone (ADH) deficiency. Cortisol and thyroid hormones also decrease as time progresses after brain death. Hematologic abnormalities are also common findings in brain-dead organ donors. Initially, elevated catecholamine and cortisol levels create a temporary hypercoagulable state. Coagulation abnormalities then occur when tissue thromboplastin released into the circulation from necrotic brain tissue activates the coagulation cascade, resulting in a disseminated intravascular coagulopathy.

Monitoring

The same principles of routine ICU care are applied to patients after brain death, including close hemodynamic monitoring, routine nursing care, and patient safety measures. In accordance with standardized protocols and algorithms that have been adopted recently, use of invasive hemodynamic monitoring has become an integral part of aggressive donor management. A central venous catheter is usually required for continuous central venous pressure (CVP) measurement, administering fluids and medication, and for frequent blood draws. Although the pulmonary artery catheter (PAC) is not routinely recommended in all patients, PAC-guided resuscitation has been linked to favorable outcomes among hemodynamically unstable patients.[4] An arterial line is generally necessary for continuous blood pressure monitoring and frequent blood gas analysis. Echocardiography is an effective screening tool for anatomical abnormalities and function of the donor's heart. Serial measurements of left ventricular function provide invaluable information to decide the suitability of the heart for transplantation. Esophageal Doppler monitoring (EDM) during organ donor resuscitation has been described showing good correlation with PAC cardiac output and preload measurements. EDM may provide minimally invasive hemodynamic monitoring in a prompt fashion.

Medical Management

Timely and appropriate management of the organ donor is crucial to ensure that organs are preserved and protected prior to procurement and to optimize the number and quality of organs and tissues available for transplantation.

Cardiovascular Management

During the initial catecholamine storm after brain death, wide swings in the blood pressure can occur. Due to the unpredictable changes in blood pressure, brief episodes of hypertension can be observed. Treatment with short-acting and titrated agents, such as esmolol or nitroprusside, can be used for persistent and extreme hypertension. Cardiac arrhythmias are frequently encountered in brain-dead patients as a result of the catecholamine surge, metabolic and electrolyte abnormalities, and vasopressor use. Bradycardia is manifested as part of Cushing's response. Treatment with atropine is ineffective since the vagal nuclei are no longer intact in brain death. The absence of heart rate response to atropine is frequently used to assist in the diagnosis of brain death. The atropine test will not be valid in those patients with known autonomic neuropathy or after a cardiac transplant. Pupillary reactions to light must be performed before atropine is administered, and an appropriate length of time allotted after its administration before the pupils are examined again. Isoproterenol, dopamine, or epinephrine can be used to treat bradycardia associated with hypotension and asystole. Tachycardia commonly occurs due to high catecholamine levels during and immediately after brain herniation. Administration of a short-acting beta-blocker, such as esmolol, is preferred because of the labile cardiovascular function. Hypovolemia after brain death is a

relatively common occurrence and results from vasomotor collapse, diabetes insipidus and treatments often used before brain death to decrease intracranial pressure (ICP). Adequate volume replacement is crucial and is the cornerstone of effective brain-dead organ donor management. However, despite the importance of aggressive fluid resuscitation, caution must be taken to avoid fluid overload in the lungs, especially if the lungs are being considered for donation. Low hematocrit levels should be corrected to achieve a level of 30% to maintain adequate oxygen delivery.

Hemodynamically unstable brain-dead donors are frequently dependent on large amounts of inotropic and vasopressor drugs, which can be detrimental to the quality of the organs later procured and transplanted. Investigators have searched for other resuscitative measures to ensure the quality of the organs transplanted. Because of the hemodynamic instability and hormonal imbalances observed after brain death, investigators have studied the potential benefits of hormone replacement therapy to treat cardiovascular instability of the organ donor.[5] The so-called *hormonal resuscitation* with thyroid hormones, corticosteroids, and arginine vasopressin has now been incorporated into most standardized comprehensive donor management protocols.[6] Although there is general consensus that hormonal resuscitation should be utilized, there is not a uniform opinion as to exactly when hormone replacement therapy is indicated.

The Crystal City consensus conference recommendation that was adopted into the UNOS critical care pathway is mainly targeted for the cardiac donor, focusing on improving cardiac function.[3] However, this pathway has been utilized in the care of all organ donors with the expectation that improved cardiac output will result in improved function of other organs and will maximize the use of transplanted organs. In general with conventional management, a central venous pressure (CVP) of 6–10 mmHg and a mean arterial pressure (MAP) >60 mmHg are targeted. When a pulmonary artery catheter (PAC) is used, a pulmonary capillary wedge pressure (PCWP) of 8–12 mmHg, systemic vascular resistance (SVR) 800–1,200 dyne/s/cm^{-5}, cardiac index >2.4 L/min/m^2, and a dopamine or dobutamine infusion at <10 mcg/kg/min are targeted.

Vasopressors are required if hemodynamic instability is not successfully treated with volume resuscitation. Dopamine is generally the first-line vasopressor. If dopamine is required at a dose exceeding 10 mcg/kg/min, then adding a second vasopressor or an inotropic agent is appropriate. Although the use of high doses of exogenous catecholamines, such as alpha-agonists, can cause severe peripheral vasoconstriction and reduce organ perfusion, catecholamine administration has been linked with improved graft function and survival through immunomodulatory effects.[7] Arginine vasopressin can be an alternative drug of choice for treating hypotension as it is also useful in treating diabetes insipidus – another common problem seen in brain-dead donors. It is believed to increase the vascular sensitivity to catecholamines and may decrease other vasopressor and inotrope requirements at a dose range of 0.04–0.1 units/min.

Respiratory Management

The main goal of respiratory care is to optimize the respiratory function in the potential donor, thereby maximizing the quality of donated organs. In an effort to increase potential lung donors, there has been an initiative to liberalize the traditional criteria for lung donation, including using donors up to 65 years of age without lung injury from smoking.[8] Improvements in the lung procurement rate have also resulted from the application of standardized approaches to the management of potential lung donors.[9] The principles of routine respiratory care that govern general ICU patient care apply to donor care. Aggressive pulmonary toilet including aspiration precautions, tracheobronchial suctioning, and physiotherapy for postural drainage, is essential. In addition to routine bronchoscopy that is usually performed as part of the assessment of the potential donor lung, early bronchoscopy can be beneficial in removing secretions and minimizing atelectasis.

Ventilator management should be aimed at using lung-protective strategy to avoid volutrauma and alveolar damage. Maintaining tidal volumes ~6 mL/kg and plateau pressures < 30 cmH_2O are reasonable goals. PEEP is useful in preventing microatelectasis and improving oxygenation, but higher levels should be used cautiously since this may further compromise the hemodynamic status. Intermittent alveolar recruitment maneuvers may also be necessary. If the lungs are being considered for transplant, the FIO_2 should be kept as low as possible to maintain arterial blood oxygen (PaO_2) > 100 mmHg. If hyperventilation was used to treat the elevated ICP before brain death, it should be discontinued to avoid respiratory alkalosis.

The donor lung is particularly susceptible to developing pulmonary edema through mechanisms that are not entirely understood. Rigorous fluid administration as part of resuscitative efforts may result in pulmonary edema. While sufficient fluids should be given to achieve organ perfusion, they should be titrated carefully if the lungs are being considered for transplantation. A PAC is often used in this instance to guide fluid management. If pulmonary edema secondary to volume overload develops, diuretics should be used. Corticosteroid treatment has been shown to improve oxygenation and is associated with an increased rate of lung procurement.[10]

Endocrine and Metabolic Management

Diabetes insipidus (DI) will cause significant polyuria and subsequent volume depletion. These fluid losses should be matched with equal volume replacement. In addition, arginine vasopressin is needed in many cases to correct the polyuria resulting from DI. If unsuccessful, intermittent administration of 1-desamino-8-D-arginine vasopressin (DDAVP), which has more specific antidiuretic effects, may be necessary.

Low levels of circulating thyroid hormone found in brain-dead donors likely induce a change from aerobic to anaerobic metabolism, resulting in lactic acidosis and worsening cardiovascular function. This could explain the improvement in cardiac function in donors when thyroid hormone is administered. However, some studies have failed to show any benefit using thyroid hormone therapy. Despite the controversy, the use of thyroid hormone has been adopted by many centers and has become an integral part of the combination hormonal treatment for hemodynamic instability. Although T4 appears to be as effective as T3, T3 may be preferred because of its rapid onset of action and predictable response.

The beneficial effects of corticosteroid therapy in brain-dead donors on organ function and improved graft function – particularly of the kidney, heart, and lung – have been well described. It has been postulated that these beneficial effects derive from attenuation of the effects of proinflammatory cytokines that are released after brain death.[11]

Hyperglycemia is frequently seen in brain-dead donors. This may result from catecholamine release, altered metabolism, decreased insulin, and the use of dextrose-containing solutions during pre/post brain-death management. Maintaining adequate glucose level prevents osmotic diuresis and appears to be important in pancreatic graft survival. A continuous insulin infusion is generally used to keep the glucose level in a reasonable range (120–180 mg/dL).

The wide variety of endocrine abnormalities seen after brain death has led many investigators to study the potential benefits of hormone replacement therapy. Although there is no definite evidence from controlled trials in humans that address the benefit of individual hormones, many studies have shown the benefits of combination therapy consisting of a thyroid hormone, a corticosteroid, and arginine vasopressin yielding an increase in transplanted organs with improved graft function.[6,12]

Hematologic Management

Coagulation abnormalities associated with disseminated intravascular coagulopathy commonly occur in organ donors. Other causes of coagulation abnormalities include hypothermia, metabolic acidosis, and dilutional thrombocytopenia resulting from massive fluid administration or transfusion. Management should include prompt transfusion with platelets and other clotting factors, as well as correction of reversible causes of coagulation abnormalities, such as hypothermia. Hypothermia ensues as the brain-dead patient loses hypothalamic regulatory function. Hypothermia is associated with cold diuresis, coagulation abnormalities, impaired oxygen delivery, and decreased cardiac output. Temperature should be carefully monitored in the potential donor and should be treated aggressively. Warm blankets, warmed fluids, and heated humidified ventilator systems can all be used.

Immunologic Management

Brain death instigates activation of proinflammatory and immunoregulatory pathways. These immune-activating processes combined with ischemia and reperfusion injury can increase immunogenicity and reduce the quality of the graft. Therapies designed to mitigate the immune response of the graft prior to transplantation include pharmacotherapy, irradiation, cell transfer experiments, and gene modulation therapies. These modalities can be applied by treating the graft itself during perfusion or cold storage, or by treating the donor prior to graft procurement. Although promising, randomized controlled trials are needed in order to adopt these therapies into clinical practice.

Conclusion

The ongoing disparity between potential organ donors and the actual number of transplanted organs has made it obvious that additional strategies and educational reinforcement are needed to improve donor and consent rates, medical management of organ donors, and graft quality and survival. Early recognition and notification of OPOs of potential donors; standardized, consistent, and aggressive treatment protocols and algorithms for donor organ management; and newer treatment modalities have continued to improve. UNOS Critical Pathways encouraging collaborative practice have been designed for adult and pediatric brain death donation and DCD. Brain death donation includes the five phases of (1) referral, (2) declaration of brain death and consent, (3) donor evaluation, (4) donor management, and (5) recovery phase. The UNOS Critical Pathway for DCD includes the phases of identification and referral, preliminary evaluation, family discussion and consent, comprehensive evaluation and donor management, and finally, withdrawal of support, pronouncement of death, and organ recovery. Critical care physicians and all members of the multidisciplinary team caring for potential organ donors should be familiar with these pathways. The critical care practitioner should continue to work closely with OPO personnel in the detection, evaluation, and management of the potential organ donor in order to improve all aspects of the transplantation process.

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Postoperative Care of the Heart Transplant Patient

Nicholas R. Banner, Iman Hamour, Haifa Lyster, Margaret Burke, Michael J. Boscoe, and Gilles Dreyfus

Heart transplantation has become established as a highly successful therapy for selected patients with advanced cardiac failure.[1] Long-term survival rates after transplantation far exceed those achieved by medical therapy for this condition.[2] Transplantation is a complex process that requires careful integration of pre- and postoperative care. Transplant activity is now limited by the supply of suitable donor hearts, leading to increased waiting times before surgery and necessitating careful selection of candidates for transplantation.[1,3] The International Society for Heart and Lung Transplantation (ISHLT) has published up-to-date guidelines for the care of patients prior to heart transplantation and case selection.[4–6]

Medical Evaluation

Heart failure is a common condition with a poor prognosis.[7] Although major advances have been made in medical therapy,[8] this remains of limited benefit when heart failure has reached an advanced stage. Most transplantation centers have a heart failure service that optimizes medical treatment and selects appropriate candidates for transplantation.[1] For patients with stable chronic heart failure, the decision about transplantation should be made after optimizing medical therapy including the maximum possible use of angiotensin-converting enzyme inhibitors and beta-adrenergic receptor antagonists. Electrical device therapy for cardiac resynchronization and the prophylactic use of implantable defibrillators should also be used in appropriately selected cases.[4–6] The authors have reviewed the medical aspects of pre-transplant care in more detail elsewhere.[9]

The cause and severity of the heart failure should be determined. The scarcity of donor organs and the risks associated with transplantation mean that alternative treatments such as "high-risk" revascularization should also be considered. However, clinical decisions in this area remain difficult because of the lack of adequate clinical trials; recurrent heart failure and suboptimal survival remain a cause for concern.[5,10] Revascularization may be combined with surgery to restore ventricular geometry in patients with extensive anteroseptal myocardial infarction[11]; correction of functional mitral regurgitation[12] may also be considered, although the benefit of this procedure is uncertain.[13]

Ambulatory patients who are on optimum medical therapy can be risk stratified using the cardiopulmonary exercise test[14]; and scoring systems such as the Heart Failure Survival

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Score[15,16] can be used to objectively assess the severity of heart failure and expected prognosis. The presence of co morbidity, risk factors, and contraindications to transplantation should be determined.[1] The decision to place a patient on the list for transplantation is usually made at a multidisciplinary review meeting. A number of guideline documents have been published to support listing decisions.[4,17,18]

The treatment of concomitant medical conditions, such as peptic ulcers or cholelithiasis, can reduce the risks at the time of surgery. Preoperative vaccination of nonimmune patients can reduce the risk of some post-transplant infections, including pneumococcal pneumonia, chickenpox, and hepatitis B. Conditions that require special management at the time of surgery, such as pulmonary hypertension complicating left ventricular failure, presence of anti-HLA (human leukocyte antigen) antibodies,[19] and diabetes, should be identified. The ISHLT guidelines address the issue of candidates with pulmonary hypertension and the role of pharmacological testing to assess its reversibility.[4,20,21] Issues related to previous cardiac surgery, especially congenital heart disease in adults, must be documented. A standardized pro forma, which summarizes key information from the assessment, together with a "problem list" speeds data retrieval in the perioperative period.[22] During the waiting period, ambulatory patients are followed regularly to detect any improvement following medical treatment, worsening of their condition or new problems that may necessitate further evaluation and therapy.

Mechanical Circulatory Support: A Bridge to Transplantation

As heart failure is a progressive condition, the scarcity of donor hearts suitable for transplantation and the consequent increased waiting times have resulted in many patients deteriorating during the waiting period. Some of these patients may be stabilized with intravenous inotropes until a suitable heart becomes available, but others need mechanical circulatory support.[5,6]

The intra-aortic balloon pump (IABP) helps the failing left ventricle by reducing afterload and increasing coronary perfusion by augmenting diastolic pressure.[23] The device is relatively simple and can be inserted rapidly in emergency situations.[24,25] Patients can be managed in a monitored area rather than in an intensive care unit (ICU). The device can also be removed relatively easily.[26] It is particularly effective in patients with heart failure resulting from ongoing myocardial ischemia. The degree of assistance, however, is limited; and its impact on cardiac output is frequently insufficient to reverse organ dysfunction in severe heart failure. The risks of such treatment include limb ischemia, thromboembolic complications, infection, and patient immobility.[27] Even when IABP support is satisfactory,-longer waiting times have made this form of treatment a less practical way of sustaining patients until transplantation.

The use of mechanical circulatory support with a ventricular assist device (VAD) has become a standard therapy to temporarily maintain patients until transplantation becomes possible. Circulatory support with a suitable device can allow physiological recovery of other organ systems, allow rehabilitation, and improve functional status prior to the transplant.[28] These advantages must be weighed against the increased complexity of the subsequent transplant surgery.[2,29]

A variety of assist devices that aid, are currently available that can partially or completely replace the pumping function of the heart. "First generation" devices use a pumping chamber to generate pulsatile flow, and may be pneumatically or electrically driven. Some are designed solely for left-ventricular support (e.g., the HeartMate I and Novacor LVADs),[30–32] whereas the Thoratec Pneumatic device[33] and the Abiomed BVS 5000[34] can be used for both left ventricular and biventricular support (Fig. 51.1). First-generation devices are relatively bulky and are unsuitable for implantation into small patients except in a paracorporeal position. "Second generation" devices use an impeller to generate continuous flow (e.g., MicroMed DeBakey, Jarvik, and HeartMate II)[35–37]; because these devices lack a pumping chamber, they are smaller, easier to implant, and suitable for smaller patients.[38] Most of these devices are designed to allow patients to be maintained in the community prior to transplantation.

The total artificial heart has recently been approved as an alternative method for bridging patients to transplantation. It provides biventricular support and total cardiac replacement. It may be particularly suitable for critically ill patients with biventricular failure and for those with a serious anatomical abnormality of the heart (e.g., post-infarct ventricular septal defect [VSD] or adult congenital heart disease [ACHD]). Disadvantages include extensive surgery, total dependence of the patient on the device and at present, a pneumatic drive system.[39–41]

VADs can also be used as long-term ("destination") therapy[42] or as part of a strategy to promote recovery in ventricular function[43] but these applications lie outside the scope of this chapter.

Case selection and appropriate timing of implantation are key determinants of the outcome of a bridge to transplant strategy. The implant procedure places further stress on the patient's organ systems because of surgical tissue trauma, the effects of cardiopulmonary bypass, perioperative bleeding, and hemodynamic instability. Therefore, the late application of this therapy to a patient who is in the last stage, extremis, has a low likelihood of success. Scoring systems have been developed to predict the perioperative risk.[44–47] An important early complication of an LVAD implant is the development of right-sided failure because of poor right ventricular function and increased pulmonary vascular resistance combined with the need for an increased cardiac index/pump flow in a sick patient.[48,49] The initial management is similar to that of right ventricle (RV) failure after transplantation (pulmonary vasodilators, especially inhaled nitric oxide, and inotropes to support the RV),[50]

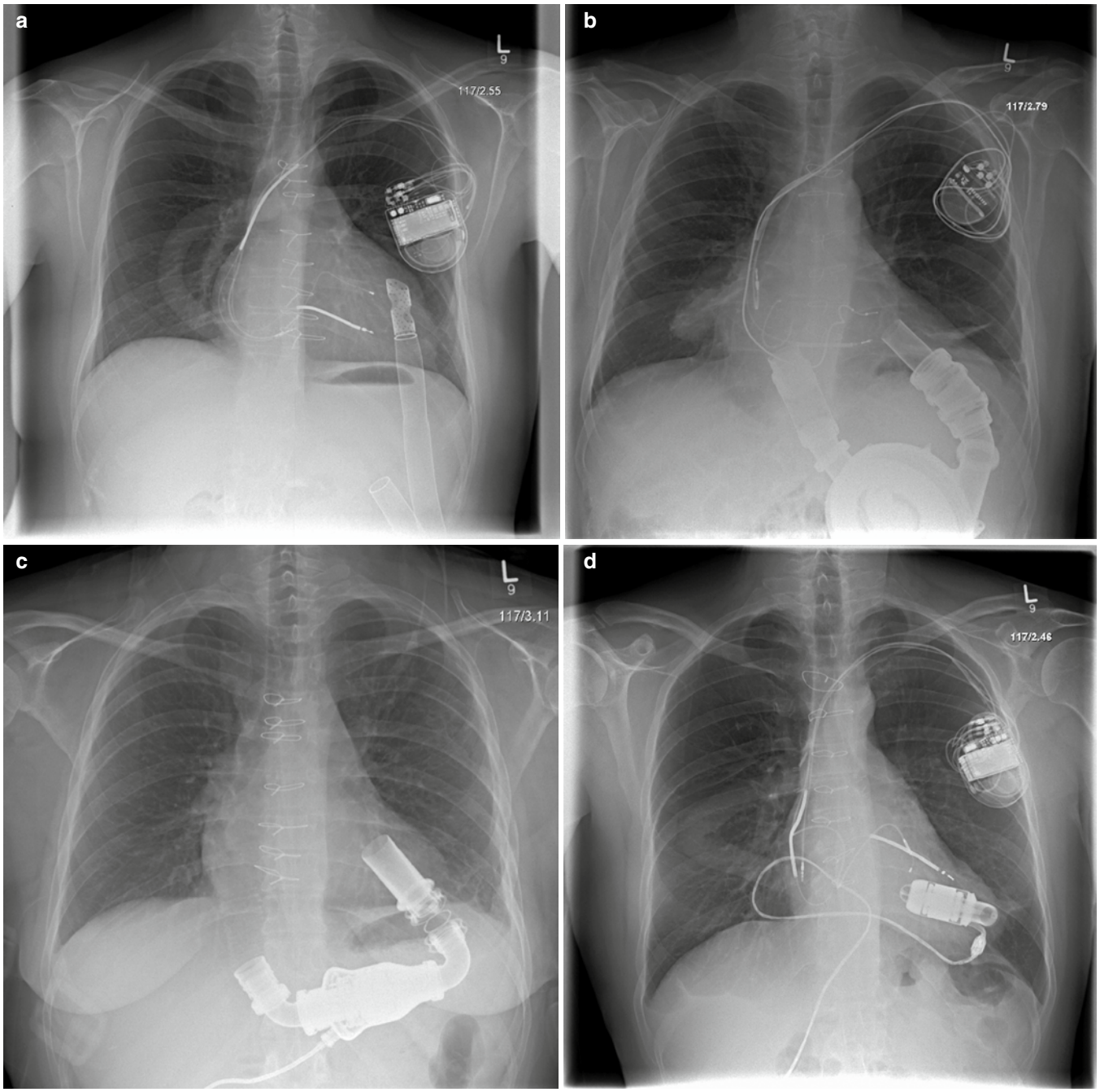

FIG. 51.1. Chest radiographs of patients receiving LVAD support. In each case the inflow is connected to the apex of the left ventricle and the outflow graft to the ascending aorta. Note that second-generation axial impeller devices (**c** and **d**) are much smaller than the first-generation devices. (**a**) Thoratec Pneumatic (paracorporeal) (**b**) HeartMate I (**c**) HeartMate II (**d**) Jarvik.

but up to one-fourth of patients require the use of a temporary right ventricular assist device. The authors have found that the management of such cases has been improved by availability of the Levitronix CentriMag, a low-cost "third generation" (bearingless, magnetically levitated) VAD that can be placed paracorporeally for short-term right ventricular support. Other perioperative problems include hemorrhage, which can be reduced by aprotinin (but see section "Surgery"),[51] and ventricular arrhythmia, which can cause low pump flow because of loss of right ventricle function.

Patients can be discharged from the ICU to their floor/room once their circulation has stabilized and recovery of organ function has begun. Those with suitable devices can be enrolled in an education and rehabilitation program to prepare them for discharge home. Once they are rehabilitated and have achieved a satisfactory nutritional status, with normal renal and hepatic

function, their names should be placed on the transplantation list again. The most common complications while awaiting transplantation are device-related infection, cardiac arrhythmia (which is usually well tolerated in the chronic phase of treatment), thromboembolism, and malfunction of the device. These events are sufficiently frequent that patients receiving LVAD support should be prioritized on the transplant waiting list despite a good quality of life.[52] The use of LVAD support can improve the results of transplantation for patients in advanced heart failure[28] although ISHLT Registry data still indicates that there is an increased overall risk associated with the bridging strategy.[2,29]

Patients who present themselves in cardiogenic shock resulting from an acute event or who are referred late with established dysfunction of other organs represent a special problem. Although mechanical circulatory support can address the underlying heart failure, the success rate is low and such patients use a disproportionate amount of health care resources. One approach to this problem is to use a lower cost, short-term treatment that, if successful, may make the patient a more suitable candidate for LVAD support. The IABP can be used in this way, but it is often ineffective because of the limited support provided. In the authors' experience, the overall results using venoarterial extracorporeal membrane oxygenation (ECMO) to support adult patients with heart failure have been disappointing. However, other centers have reported that temporary ECMO support can salvage some patients and make them suitable for LVAD support (the "Bridge to Bridge" strategy) followed eventually by transplantation.[53] Recently, we have had success using the Levitronix CentriMag device to provide temporary biventricular support to such patients.[54]

Although the bridge to transplant approach is a successful clinical strategy, adding one complex procedure to another has important implications for resource utilization and the approach is not yet cost-effective by standard criteria.[55,56] The need for bridging with a VAD is partly related to the scarcity of suitable donor hearts, because some patients who are bridged would have been suitable for transplantation at an earlier stage if a heart had been available in a timely fashion.

Donor Selection and Management

The scarcity of suitable donor hearts is now the main factor limiting heart transplantation. The reduction in fatalities from traffic accidents has changed the profile of organ donors, and the donor age has been steadily increasing.[2] At the same time, primary graft failure is the most common cause of death early after transplantation.[57] Thus, it is essential that the organs offered for transplantation are carefully evaluated, and the management of the donor is organized to maximize the number of organs that can be used and to ensure satisfactory cardiac function after transplantation.

Brain death produces a transient massive increase in sympathetic activity, severe hypertension, and catecholamine-mediated injury to the myocardium.[58] Following this, there is a progressive loss of homeostatic functions, including sympathetic tone, neurohormonal regulation, and temperature control. Donor selection and management involves review of the donor's previous health and cardiovascular risk profile; review of the cause and circumstances of brain death and any cardiac arrest and resuscitation; a determination of whether there are any general contraindications to transplantation such as a transmissible infection or cancer[59]; the establishment of appropriate physiologic measures to stabilize the circulation; careful assessment of cardiac function by clinical examination, electrocardiography (ECG), and echocardiography; hemodynamic studies; and, finally, direct surgical inspection.

A number of guidelines for the diagnosis of brain death and donor evaluation have been published.[60–62] These share common principles and themes, but all suffer from limitations of the data available.

The ECG rapidly screens for major abnormalities including Q waves, indicating previous myocardial infarction, and signs of left ventricular hypertrophy. Repolarization changes are common after brain death and do not, in themselves, preclude organ donation.[63] Transthoracic echocardiography can be used to exclude structural lesions, including valvular heart disease, and to assess ventricular function. Unfortunately, imaging is sometimes suboptimal in the ventilated patient and transesophageal echocardiography may be required. Ventricular performance is influenced by loading conditions, and invasive hemodynamic measurements obtained using a pulmonary artery flotation catheter (PAFC) aid the overall assessment. The sympathetic storm associated with brain-death causes ventricular dysfunction affecting both ventricles but particularly the right.[64] Clinically, it has been found that left ventricular dysfunction is often reversible after a period of donor resuscitation, so that donor hearts should not be declined on the basis of a single echo showing a low LV ejection fraction.[65,66]

The Crystal City Conference recommended a four-stage approach to donor assessment and management.[61] First, volume status and anemia should be corrected together with any hypoxemia and acidosis; inotropes should be adjusted and, whenever possible, weaned while maintaining a mean arterial pressure > 60 mmHg; care should be taken to avoid hypothermia; whenever possible the inotropic support should be 10 g/kg/min of dopamine or dobutamine. Second, an echocardiogram should be performed to exclude structural abnormality, valve disease, and significant hypertrophy (wall thickness ≥13 mm). If the echocardiographic LV ejection fraction (EF) is greater than 45% at this stage, the retrieval may proceed. Third, if the LVEF is less than 45%, a hormonal resuscitation package of triiodothyronine, arginine vasopressin, and methylprednisolone should be administered together with insulin to control the blood glucose. Fourth, a pulmonary artery flotation catheter should be placed to determine the donor's hemodynamic status and suitability after a period of resuscitation and adjustment of drug therapy lasting at least 2 h (Table 51.1).[67–69] Based on the data that is currently available,

Table 51.1. Hemodynamic criteria for accepting a donor heart after resuscitation.

Acceptance criteria for donor hearts	
Mean arterial pressure	>60 mmHg
Central venous pressure	4–12 mmHg
Pulmonary wedge pressure	8–12 mmHg
Systemic vascular resistance	800–1,200 dyne sec cm^{-5}
Cardiac index	>2.4 l/min/m^2
Dopamine or dobutamine	≤10 µg/kg/min

these guidelines give primacy to the hemodynamic data over the echocardiographic findings for determining donor suitability. Additionally, older donors should undergo coronary angiography. A final assessment and the decision about the heart's suitability for transplantation are made by the surgeon leading the retrieval team after direct inspection of the heart, including palpation of the coronary arteries.

Protocol-driven donor management including "hormonal resuscitation" has increased the number of organs used for transplantation.[70,71]

Donor–Recipient Matching

When a donor organ becomes available, the potential recipient is selected from the waiting list on the basis of absolute matching criteria (blood group compatibility[72] together with a negative actual or virtual HLA crossmatch in those with preformed antibodies) and relative criteria (donor body size, age, and sex) in combination with the clinical urgency for the recipient. Organ allocation systems vary between countries and may be organized in a center-orientated or patient-oriented manner. Due to the shortage of donor hearts, there is a trend toward patient-orientated systems with rules established to prioritize organ allocation within a region to the recipients with a high clinical urgency or specific clinical needs.[52]

Organ Retrieval

The donor operation is usually part of a multiorgan retrieval. Following cessation of mechanical ventilation, the donor heart is vented, the ascending aorta cross-clamped, and cold cardioplegia solution administered via the aortic root to achieve hypothermic diastolic arrest. The ideal composition of cardioplegia and storage solution has not been established and a number are in clinical use.[61] The heart is then excised, with adequate aorta, pulmonary artery, venae cavae, and left atrium for subsequent implantation. Recipients with complex adult congenital heart disease may need additional tissue.

Currently cold storage at 4–8°C is the method generally used for transportation.[73–75] Most hearts tolerate ischemia at this temperature for several hours, but postoperative cardiac dysfunction and the risk of primary graft failure (PGF) remain significant problems. The allowable ischemic time is much shorter than for organs such as the kidney or liver; ischemia of more than 3 h is associated with a progressive risk of cardiac allograft failure in the recipient.

Organ preservation can exacerbate the injury caused by donor brain death.[64] Donor factors may interact to produce a greatly increased risk. For example, the risk associated with the use of an older organ donor is greatly increased if the organ ischemia time is prolonged. Care should be taken to minimize the organ ischemia time when using a "marginal" organ donor.[76]

Recently, there has been renewed interest in transporting hearts in a warm and perfused state using an organ care system with the aim of minimizing the overall ischemic time while allowing longer transport times.[77] Preliminary results obtained with the TransMedics system have been reported recently.[78] It remains to be seen whether this technique will have an important impact on the clinical practice of heart transplantation.

Recipient Assessment Prior to Surgery

There is usually limited time available before surgery. For ambulatory patients, the history and examination should focus on changes that have occurred since the last visit. Critically ill patients already admitted to the hospital require a detailed review of their current status, organ function, treatment in progress, and presence of any new complications such as active infection. Laboratory samples should be sent as early as possible for hematology, biochemistry, and microbiology screens together with samples for blood crossmatch, repeat HLA antibody screen, and for an HLA crossmatch against the donor[19] This is done retrospectively in recipients who are negative for HLA antibodies, but prospectively for those with such antibodies. For patients with well-defined antibodies, current technology allows a "virtual crossmatch" against the donor's tissue-type.[79] Patients who have received anticoagulation therapy with warfarin will need fresh frozen plasma and vitamin K to reverse the anticoagulation after separation from cardiopulmonary bypass. Preoperative warfarin therapy is not associated with excessive postoperative bleeding provided the anticoagulation is reversed.[80] The action of antiplatelet agents can only be countered by platelet transfusion if needed.

Anesthesia

Premedication is often omitted because of time constraints, but administration of an oral benzodiazepine can be helpful in anxious patients. Adequate peripheral venous access and a radial artery cannula to allow continuous monitoring of arterial pressure are placed before induction of anesthesia. In patients already receiving large doses of inotropes, particularly norepinephrine, an aortic-radial gradient may exist and a femoral artery catheter is preferable. For patients who have undergone previous cardiac surgery, including those with a VAD

in situ, preparation should be made so that cardiopulmonary bypass can be established quickly via the femoral approach in the event of cardiovascular instability or cardiac arrest after induction. Anesthesia is induced and maintained with a balanced technique using etomidate or propofol, fentanyl, and a volatile agent (isoflurane or sevoflurane). After induction, a central venous catheter and a sheath for a pulmonary artery flotation catheter (PAFC) are introduced, preferably via the left internal jugular vein (where possible, the right internal jugular vein should be preserved for later endomyocardial biopsies). Some centers routinely insert a PAFC at this stage, while others prefer to rely solely on the transesophageal echocardiogram (TEE). TEE can provide valuable functional data throughout the transplant process, while a PAFC will need to be withdrawn during cardiectomy of the native heart. In either case, a PAFC can be safely passed after the donor heart has been implanted and cardiopulmonary bypass has been discontinued.

Surgery

Surgical planning should begin at the time of listing. Special consideration is needed for those with adult congenital heart disease (ACHD), those undergoing redo surgery, and those with VADs. ACHD patients may have abnormal venous connections, surgically modified atrial chambers, collateral vessels, and surgical shunts; these should be defined by cardiac magnetic resonance imaging or, for those with electrical devices, CT angiography. Data from previous echocardiograms and cardiac catheter procedures should also be reviewed for anatomical as well as functional information. Patients who have undergone prior surgery should have their previous operative and postoperative records reviewed. In VAD patients it is important to have a clear understanding of the location of the device and the position of the inflow and outflow connections. A preoperative CT scan can be invaluable, especially if the device has been implanted at another institution (Fig. 51.2). In redo and VAD cases, the transplant coordinator should be aware of the need for an earlier transfer to the operating room to allow extra time to open the patient and prepare for the arrival of the donor heart. In the OR, preparations should be made so that cardiopulmonary bypass can be established quickly via the femoral approach in case the patient develops hemodynamic instability or sternal opening leads to complications.

Prior to implantation the donor heart should be inspected for any damage sustained during retrieval and for the presence of a persistent foramen ovale (PFO), which, if present, should be closed to eliminate the risk of right to left shunting if right ventricular dysfunction should complicate the postoperative course.

There are two main techniques for orthotopic transplantation of the heart (Fig. 51.3). The original method, developed by Lower and Shumway, used anastomoses between the atria of the donor heart and remnants of the corresponding atria of the recipient heart.[81] An alternative method of total heart replacement uses four separate venous anastomoses for the superior vena cava, inferior vena cava, and left and right pulmonary veins.[82] This technique may have physiologic advantages by avoiding distortion of atrial geometry, reducing AV-valve regurgitation, and minimizing the frequency of atrial arrhythmia and sinus node dysfunction. It is particularly valuable for patients who have undergone previous "corrective" surgery for ACHD (such as Mustard's procedure or a modified Fontan operation) and in those with valvular heart disease and extreme enlargement of the native atria. A hybrid operation in which the SVC and IVC are anastomosed separately but a composite left atrium is still constructed has also been described.[83] However, the traditional Lower

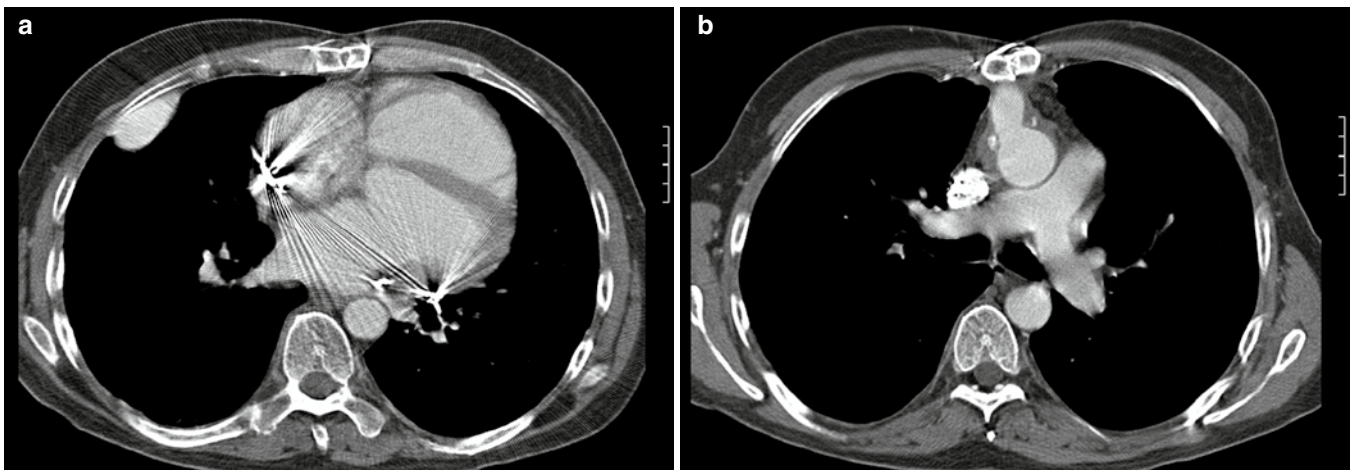

FIG. 51.2. Pre-transplant CT scan of a patient with a Jarvik LVAD. (**a**) Mid-thoracic level demonstrating the outflow graft in right pleural space adjacent to chest wall. (**b**) Insertion of outflow graft into the aorta demonstrating that the graft lies immediately behind the sternum at this level and so is at risk during sternal reopening.

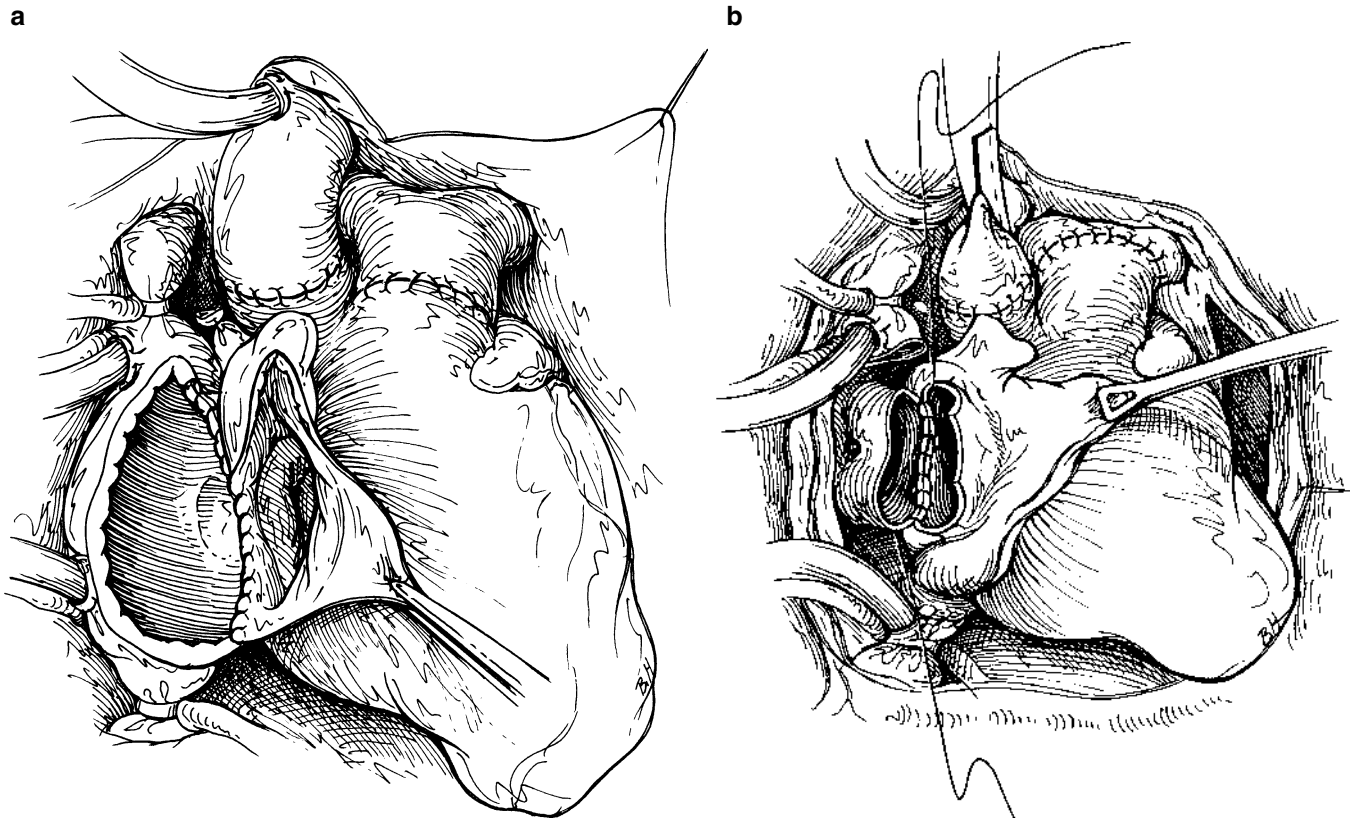

FIG. 51.3. Surgical techniques for orthotopic heart transplantation. (**a**) Original Lower and Shumway operation using anastomoses between corresponding donor and recipient atria. (**b**) The alternative method of "total" cardiac transplantation. Reprinted from Banner NR, Khaghani A, Fitzgerald M, et al. The expanding role of cardiac transplantation. In: Unger F, editor. Assisted circulation III. Chapter 40. Berlin: Springer; 1989. p. 448–467 with kind permission of Springer Science and Business Media.

and Shumway operation has the advantage of simplicity, speed of implantation, and it avoids the occasional problems that can arise with venous anastomoses when the heart has been totally replaced.

Many surgeons favor the use of repeated infusion of blood-based cardioplegia during the implant procedure in an attempt to prevent further ischemic injury.[84] However, as with organ transportation, there is not enough data to make a firm recommendation about the method that should be used.

Intraoperative transesophageal echo (TEE) is essential to monitor de-airing at the end of bypass, monitor cardiac function, and to help detect complications. Technical problems are uncommon during orthotopic heart transplantation but anastomotic complications may occur. For example, stenosis at a caval anastomosis will cause venous hypertension and compromise cardiac output, while narrowing of the pulmonary artery anastomosis or torsion of the pulmonary artery may lead to right ventricular failure[85,86] (Fig. 51.4).

In patients known to have pulmonary hypertension before surgery, nitric oxide should be started prophylactically while the patient is separated from cardiopulmonary bypass and continued during the early postoperative period.[87,88]

Where a first-generation VAD has been placed in a pre- or intra-peritoneal position, it may be advantageous to disconnect the inflow and outflow from the heart and the aorta at the time of transplantation and then leave the pump chamber in situ. The pump can then be removed semi-electively once hemodynamic stability has been assured. This allows the explant to be done in conjunction with a specialist abdominal surgeon and in the most favorable clinical circumstances.

Bleeding may be a problem in patients who have undergone multiple previous operations and particularly in those who have undergone surgery for complex congenital heart disease.[89] Meticulous surgical technique is of primary importance, but adjunctive therapy can be used to improve hemostasis. The thromboelastogram is a useful measure of coagulopathy in the operating room. It can provide rapid assessment of clot formation, platelet function, and the presence of fibrinolysis.[90] Aprotinin, a serine protease inhibitor with antifibrinolytic and anti-inflammatory properties, can reduce perioperative blood loss.[91,92] However, aprotinin should be used selectively based on clinical need and the results of thromboelastography because there is evidence that its use may be associated with an increased risk of thromboembolic complications and renal failure.[93,94]

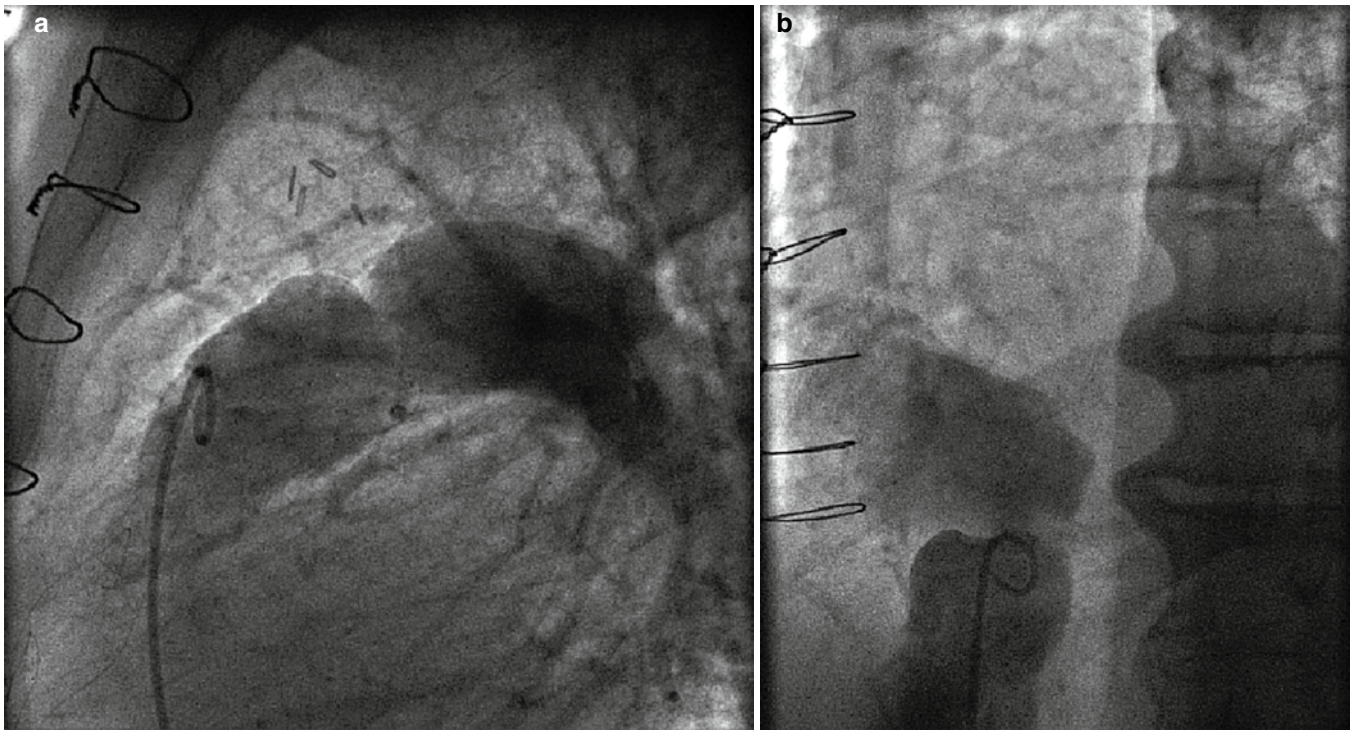

FIG. 51.4. Technical complications of heart transplantation. (**a**) Angiogram taken in a lateral projection demonstrating stenosis at a pulmonary anastomosis (systolic pressure gradient of 35 mmHg). (**b**) Angiogram demonstrating stenosis at an IVC anastomosis.

Postoperative Care

A period of supportive bypass is used following coronary reperfusion to allow cardiac function to recover. Management following separation from cardiopulmonary bypass is largely determined by the initial function of the heart. When the transplanted heart is performing well, the patient is returned to the ICU with only low doses of inotropes being administered. The overall management plan is similar to that used with patients after coronary bypass surgery, but with the additional concerns of pharmacologic immunosuppression together with prophylaxis against infection. Postoperative sedation is induced using propofol, and morphine is used for analgesia. The patient can be extubated after rewarming with a forced warm-air blanket system (e.g., the Bair Hugger®). Patient-controlled analgesia may be helpful for the conscious patient after extubation.

Patient transfer and the initial period in the ICU are of critical importance. Good communication between the operative and intensive care teams can be facilitated by systematic recording of therapeutic targets and utilizing preprinted postoperative orders sheets (Fig. 51.5). All team members must understand general principles of post-transplant management, including the need to avoid volume overloading and thereby precipitating right ventricular dysfunction, as well as being able to recognize the various hemodynamic scenarios that could evolve during the early postoperative period.

Assessment of Cardiac Function

Cardiac performance becomes apparent during separation from cardiopulmonary bypass. However, the full effect of any graft injury caused by brain death in the donor or during organ preservation may not be fully apparent for some hours. Therefore, full hemodynamic monitoring is essential in the initial postoperative period. A chest radiograph should be performed as soon as practicable to check the position of each catheter and so ensure that representative pressures are being recorded from each site. A PAFC is used to provide continuous monitoring of pulmonary artery pressure and mixed venous oxygen saturation (S_VO_2)[95] as well as intermittently estimating the LA pressure from the pulmonary occlusion pressure. Alternatively, a left atrial line may be placed so that left and right atrial pressures can be monitored simultaneously. Adverse trends in the serum lactate and in urine output may provide evidence of an evolving hemodynamic problem. Transesophageal echocardiography is used to monitor left and right ventricular systolic function and to detect complications.[96,97] The TEE findings must be interpreted in the light of the filling pressures (diastolic performance), the inotropic therapy being used, and arterial pressure (LV afterload). The management of patients with graft dysfunction is considered below.

Orthotopic Cardiac Transplant
OR to ICU transfer information and post-transplant orders

Surgeon:
Anaesthetist:
Intensivist:

Name:
DOB:
Hospital No.:
Transfer to ICU date/time: 21-40 June 1 2007
Orders valid until: 08-00 June 2 2007

ICU Resident:
Surgical Resident:
Transplant Resident:

Date June 1 2007		Time	HR Rhythm	CVP mmHg	PAP mmHg	PCWP or LAP mmHg	ABP mmHg	PA Sat %	CI L/min/m^2	Blood gas pH pO_2 pCO_2 kPa	Urine Vol ml/hr	Lactate mmol
Prior to Transfer		21-20	100 A Pace	10	35/20 M27	15	106/60 M75	65	2.8	pH7.4 PO2 12.0 pCO2 4.3	60	3.5
On arrival in ICU		21-40	100 A Pace	12	40/23 M32	19	100/60 M73	63	2.6	7.4 12.3 4.0	n.a.	2.0
Target Range	Min		100	10		15	M70	60	2.5	pH 7.3-7.45 pO2 >11.0 pCO2 3.7-4.5	≥60	≤2.5
	Max		120	15		20	M85					

DDD pacing Y/N Yes Rate: 100 min^{-1} Long AV delay allowing intrinsic conduction Inhaled NO **Y/N** Yes **Conc.:** 10 **ppm**

TOE Findings on Transfer to ICU: Good overall LV systolic function but septal hypokinesis, no significant MR Moderate RV systolic function with mild TR [looked better after starting Nitric Oxide]. No pericardial collection visible. Images downloaded to network.

See ICU chart for drugs and iv fluids, see Transplant chart for immunosuppression (page Transplant Resident to complete orders)
PAGE BOTH CARDIAC SURGICAL AND ICU RESIDENTS IMMEDIATELY IF TARGETS ARE NOT BEING ACHIEVED

FIG. 51.5. Example of a post-transplant communication and orders sheet.

Immunosuppression and Allograft Rejection

Immunosuppressive therapy can be divided into three components: induction therapy, maintenance immunosuppression, and treatment of rejection.

Induction Therapy

The use of induction therapy using an anti-T-cell antibody remains controversial, and the ISHLT Registry indicates that only half of the heart transplant centers use such therapy.[98] The available agents are compared in Table 51.2. The potential benefits of induction therapy include lower rates of acute rejection, host hyporesponsiveness to alloantigen, renal sparing by allowing delayed introduction of cyclosporine or tacrolimus, and a "safety period" early after transplantation when there may be absorption issues with oral immunosuppressive agents.[99] Post hoc analysis of trials conducted for other purposes suggests that induction therapy may be beneficial[100,101]; however, there is concern related to the potential adverse effects from nonspecific over-immunosuppression, such as increased risk of infection[102] or malignancy.[103,104]

TABLE 51.2. Comparison of induction agents.

	Polyclonal ATG	Muromonab CD3	Basiliximab	Daclizumab
Lymphocyte activation and cytokine release	Y	Y	N	N
Lymphocyte depletion	Y	N	N	N
Action specific to activated cells	N	N	Y	Y
Antibody type	Polyclonal rabbit or horse	Monoclonal mouse	Chimeric monoclonal human – mouse	Humanized monoclonal

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Studies comparing the mouse monoclonal antibody monomurab-CD3 (OKT3) with the polyclonal rabbit antithymocyte globulin (RATG) have shown similar efficacy to delay the time to first acute rejection, but different adverse effects.[105–107]

OKT3 resulted in higher incidence of viral infections (in particular cytomegalovirus) and a post-treatment rebound increased rejection and increased frequency of post-transplant lymphoproliferative disorder (PTLD); whereas polyclonal antibody therapy increased the risk of bacterial infections and was associated with a lower risk of PTLD.

The use of OKT3 has decreased while the use of the newer IL-2 receptor antibodies, basiliximab and daclizumab, has increased[98]—both agents have been used successfully as prophylaxis against acute rejection after renal transplantation.[108,109] One randomized trial that evaluated the safety, tolerability, and pharmacokinetics of basiliximab in cardiac transplantation showed no statistically significant difference in the time to first acute rejection, adverse events, or infections compared with placebo.[110] Another retrospective study compared basiliximab with RATG in 48 heart transplant patients and found that RATG was more effective for preventing acute rejection while the two agents had a similar safety profile.[111] A large-scale multicenter clinical trial compared the effect of induction of daclizumab with placebo in 434 heart transplant recipients receiving triple therapy with cyclosporine, mycophenolate, and corticosteroids. The primary end point was a composite of moderate or severe cellular rejection, hemodynamically significant graft dysfunction, a second transplantation, or death or loss to follow-up within 6 months. The daclizumab group had a lower incidence of the composite endpoint and a longer time to reach the endpoint compared with the placebo group; overall mortality was not significantly different but infection-related deaths were more common in the daclizumab subgroup that had also received cytolytic therapy.[112]

Maintenance Immunosuppression

The calcineurin inhibitors (CNIs) cyclosporine and tacrolimus form the mainstay of current maintenance immunosuppression protocols, and are traditionally used in combination with an antiproliferative agent (e.g., mycophenolate or azathioprine) and corticosteroids.[9,113] Such "triple" therapy can be used alone or in combination with a period of induction therapy. These can be directly combined ("quadruple therapy") or can be used to delay the introduction of a CNI ("sequential therapy"). Sequential therapy may reduce the incidence of perioperative renal failure by avoiding the renal toxicity of CNIs immediately after surgery.

The introduction of cyclosporine in the 1980s improved the results of cardiac transplantation to the point where it became accepted as a standard therapy for advanced heart failure.[114] Tacrolimus has a completely different molecular structure to cyclosporine, yet it has the same principle mechanism of action, namely inhibiting the phosphatase calcineurin that plays a key role in the early phase of T-cell activation.[115] Two recent clinical trials in heart transplantation have showed that tacrolimus reduced the rate of acute rejection, compared with cyclosporine microemulsion (Neoral), when both were used in combination with azathioprine or mycophenolate and corticosteroids, although there was no difference in patient or graft survival.[116,117]

The CNIs both cause dose-limiting nephrotoxicity, but there are some differences in their other side effects.[115,118] Both are substrates for the cytochrome P450 (CP450-3A) family of enzymes and P-glycoprotein (Pgp) transport system; hence pharmacokinetic drug interactions occur with other drugs that interact with (induce or inhibit) these proteins.[113,115,119] Thus, monitoring of CNI blood levels and renal function is essential during therapy, especially when there is concomitant treatment with other drugs that can cause such interaction.

Mycophenolate mofetil (MMF) is a prodrug; its active metabolite, mycophenolic acid (MPA), is a noncompetitive inhibitor of inosine monophosphate dehydrogenase, which is the rate-limiting enzyme in the de novo pathway for purine synthesis. Unlike most other cells, activated lymphocytes lack a purine salvage pathway and are dependent on de novo purine synthesis. Hence, MMF has a more selective effect on T- and B-cells than azathioprine, which interferes with multiple steps in purine metabolism. A large randomized clinical trial performed in heart transplantation found that, in the treatment-received analysis, MMF reduced mortality and graft loss at 1 year compared with azathioprine in patients also receiving cyclosporine and corticosteroids; this benefit persisted at 3 years.[120,121]

Corticosteroids are the third component of most immunosuppression regimens. They are administered intraoperatively, and continued first intravenously (methylprednisolone) and then orally (as prednisolone or prednisone). The greatest risk of acute rejection occurs within the first few months after transplantation. To reduce the risk of long-term steroid side effects, most physicians gradually taper the dose of corticosteroids with increasing time after transplantation and some actively try to discontinue steroid therapy.[122] In addition, the target levels of cyclosporine/tacrolimus are gradually reduced in an attempt to minimize the risks of chronic CNI nephrotoxicity.[115]

Cardiac allograft vasculopathy (CAV) is the main cause of late allograft failure. Some degree of CAV affects 32% of patients 5 years after their transplant.[123] The target-of-rapamycin (TOR) inhibitors, sirolimus and everolimus, reduce the incidence of acute rejection when compared with azathioprine and have been shown to have long-term efficacy against CAV when used together with cyclosporine and corticosteroids.[124–126]; However, MMF has also been shown to have activity against CAV,[127] and neither of the TOR-inhibitors has been compared head-to-head with MMF.

The TOR inhibitors appear to impair surgical wound healing when used de novo post transplantation and also enhance the nephrotoxicity of the CNIs.[124] Sirolimus has been used in CNI-withdrawal protocols together with MMF to minimize nephrotoxicity in a number of studies in heart transplantation.[128–130] However, CNI withdrawal remains controversial because of

the results of the cardiac "Save The Nephron" (STN) study, where sirolimus was used as a substitute for CNI therapy at 3 months after heart transplantation; this trial was terminated early as a result of an unexpected increased incidence of acute rejection in the sirolimus group.[131]

Adjunctive statin therapy has been shown to improve survival and reduce the risk of serious rejection and CAV after heart transplantation.[132–136]

Rejection

Allograft rejection is an important cause of cardiac dysfunction and patient death. Rejection is classified according to its mechanism and timing (Table 51.3).[137] With current immunosuppressive regimens, rejection is uncommon in the first 2 weeks after transplantation unless there has been a deviation from the immunosuppressive regimen or the patient was HLA sensitized. However, patients who have developed postoperative complications and have required prolonged hospitalization may experience an episode of acute rejection before discharge.

The endomyocardial biopsy was introduced by Philip Caves in 1973 and remains the gold standard for the diagnosis of acute cellular rejection (ACR).[138,139] Specimens are obtained from the right ventricular aspect of the interventricular septum via either a jugular or femoral venous approach. The procedure can be done using either a steerable bioptome or a flexible bioptome introduced via a guiding sheath under either fluoroscopic or echocardiographic control (Fig. 51.6). Most institutions perform between 10 and 15 routine surveillance endomyocardial biopsies in the first year after transplantation.[112,116,117,121] Serious complications are rare, but include tamponade, coronary septal branch to right ventricular fistulae, tricuspid regurgitation, myocardial infarction, and infection.

The diagnosis of acute cellular rejection is based on the detection of a lymphocytic infiltrate in the endomyocardial biopsy.[140] In 2004, the International Society of Heart and Lung Transplantation revised the standardized histopathological grading system for acute rejection. The current grading system has introduced immunopathological criteria for the biopsy diagnosis of antibody-mediated rejection (AMR)[141] (Table 51.4). Active research is being undertaken to develop noninvasive diagnostic methods, but these have not yet reached the point where biopsies can be eliminated.[142,143]

Antibody-mediated rejection (AMR) is less common than cellular rejection and can be more difficult to diagnose but may result in significant allograft dysfunction. HLA antibodies typically occur in patients with prior allosensitization due to blood transfusion, pregnancy, prior transplantation, or ventricular assist device implantation.[144] Hyperacute rejection, a

Table 51.3. Classification of rejection.

	Mechanism	Comment
Hyperacute	Preformed donor-specific antibody	Avoided by • Ensuring donor is ABO-compatible with recipient • Pre-transplant screening for anti-HLA antibodies • Performing prospective HLA cross-match if anti-HLA antibodies are present
Acute cellular	Initiated by helper T-cells	Current immunosuppression protocols provide more effective prophylaxis. Diagnosis usually based on surveillance endomyocardial biopsy. Break through cellular rejection treated with corticosteroids and, if necessary, antithymocyte globulin or muromonab-CD3
Acute humoral	Donor-specific anti-HLA antibodies (preexisting or acquired post-transplant)	Often presents as acute graft dysfunction without evidence of cellular rejection. Diagnostic criteria not clearly established. Treatment not standardized but requires antibody removal (by plasmapheresis or immunoadsorption) and inhibition of its resynthesis (intravenous polyspecific immunoglobulin, cyclophosphamide, mycophenolate, rituximab)
Chronic	Multifactorial	Involves both alloimmune and non-alloimmune mechanisms. Predominantly affects the coronary arteries of the allograft; cardiac allograft vasculopathy (CAV)

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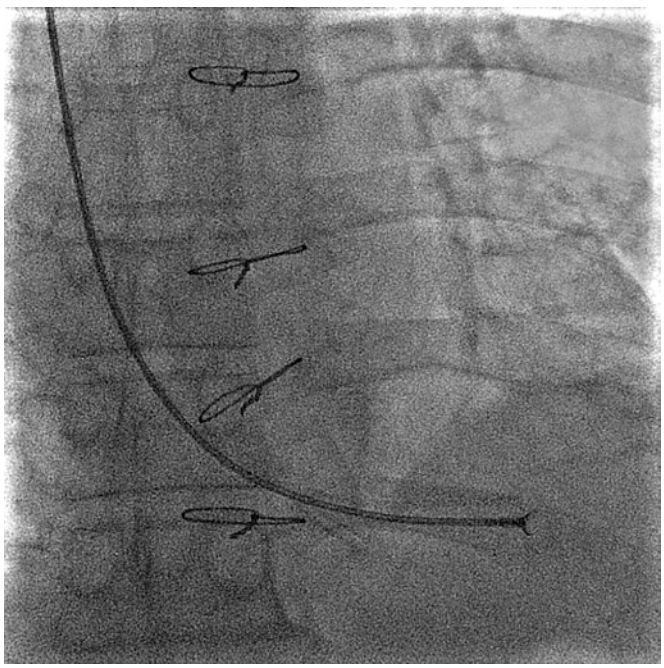

Fig. 51.6. Transvenous endomyocardial biopsy. The bioptome has been introduced via the right internal jugular vein and advanced under fluoroscopic control through the tricuspid valve to reach the right ventricular aspect of the interventricular septum.

Table 51.4. Revised (2004) ISHLT endomyocardial biopsy grading system.

Cellular rejection grade	Description
Grade 0	No rejection
Grade 1 R (*mild*)	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage
Grade 2 R (*moderate*)	Two or more foci of infiltrate with associated myocyte damage
Grade 3 R (*severe*)	Diffuse often polymorphous infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis
Humoral rejection grade	**Description**
AMR 0	Negative for acute antibody-mediated rejection No histological or immunopathological features of AMR
AMR 1	Positive for AMR Histologic features of AMR Positive immunofluorescence or immunoperoxidase staining for AMR (e.g., positive CD68, C4d)

R revised (to distinguish from the 1990 grading system); *AMR* antibody-mediated rejection.

form of AMR due to preformed anti-donor antibody, can be avoided by ensuring ABO blood group compatibility of the allograft, screening potential recipients for HLA antibodies before transplantation, and performing a prospective HLA crossmatch in those with HLA antibodies.[19,72] AMR may also be seen later after transplantation when a patient develops de novo donor-specific HLA antibody.

Treatment of acute cellular rejection is determined by the histological grade of the biopsy, the patient's clinical and hemodynamic condition, current immunosuppression, and history of prior rejection. Mild cellular rejection (ISHLT grade 1R) with no evidence of allograft dysfunction does not warrant treatment. Higher rejection grades (2R or 3R), are treated with intravenous methylprednisolone over 3 days or high dose oral prednisolone, this is followed by corticosteroids tapered over 7–14 days.[144] Episodes resistant to steroid therapy or associated with hemodynamic compromise are treated with either a polyclonal antithymocyte globulin (ATG) or muromonab-CD3 (OKT3) in combination with corticosteroids. Recurrent cellular rejection episodes may warrant a change in maintenance immunosuppression (Fig. 51.7).

Antibody-mediated rejection is usually treated by antibody removal using immunoadsorption or plasmapheresis together with high doses of polyspecific immunoglobulin, rituximab, or cyclophosphamide.[145,146]

Cardiac allograft vasculopathy (CAV) is the main form of "chronic rejection" after heart transplantation and is a late complication. CAV is usually diagnosed by surveillance coronary angiography or by intravascular ultrasound. Late acute allograft rejection has been recognized as a risk factor for the development of CAV.[147,148] Treatment includes all the secondary measures for conventional coronary vascular disease as well as optimizing immunosuppressive therapy. The proliferation signal inhibitors, also known as target-of-rapamycin (TOR) inhibitors, sirolimus (rapamycin) and everolimus, have been shown to slow down the progression of cardiac allograft vasculopathy when used in combination with cyclosporine.[124,125] Focal proximal stenosis can be treated by percutaneous coronary intervention or occasionally by coronary artery bypass grafting. However, CAV is often diffused and affects smaller branch vessels, thereby precluding revascularization. In cases where coronary intervention is not feasible, cardiac re-transplantation may be considered[149] (Fig. 51.8).

Specific Postoperative Problems

Hypotension and Low Cardiac Output

Hypotension due to a low cardiac output must be distinguished from that caused by vasodilatation as part of a systemic inflammatory syndrome, which may be seen in patients who were critically ill before surgery or where there has been preoperative infection (seen typically in a patient receiving VAD support pre-transplant). The differential diagnosis and key diagnostic features are addressed in Tables 51.5–51.7. Clinical examination is frequently unreliable in the postoperative period, and the distinction must be made using the PAFC to measure both cardiac output and S_VO_2. Assessment of the cause of hypotension or low cardiac output must be done quickly and corrective measures taken before secondary organ dysfunction progresses to renal, hepatic, or multiorgan failure. Failure to achieve an adequate cardiac output and other physiologic targets mandates immediate investigation including, when necessary, surgical reexploration. When the problem is due to primary graft dysfunction, temporary mechanical circulatory support may be required.

Whenever possible, treatment should be aimed at the specific mechanisms, and escalation of the level of inotropic support without a critical evaluation of the underlying problems must be avoided. Overfilling the patient can precipitate or exacerbate RV failure. Clinical assessment should be combined with the hemodynamic measurements from the PAFC and findings from the TEE examination to reach a specific diagnosis. The differential diagnosis of low cardiac output includes hemorrhage and hypovolemia, cardiac tamponade, failure of the donor right ventricle, and biventricular failure (Tables 51.6 and 51.7). The hemodynamic findings should

Fig. 51.7. (continued) vessels, indicative of a mixed cellular and antibody-mediated process (H&E, original magnification × 250). The immunohistochemical findings in antibody-mediated rejection should be supported by the finding of donor-specific HLA antibodies in peripheral blood: (**e**) capillary deposition of C4d throughout the biopsy (Streptavidin–biotin, C4d (Biomedica), original magnification × 250) (**f**) intravascular macrophages demonstrated by CD68 immunostaining (Streptavidin-Biotin, CD68 (Dako), original magnification × 250).

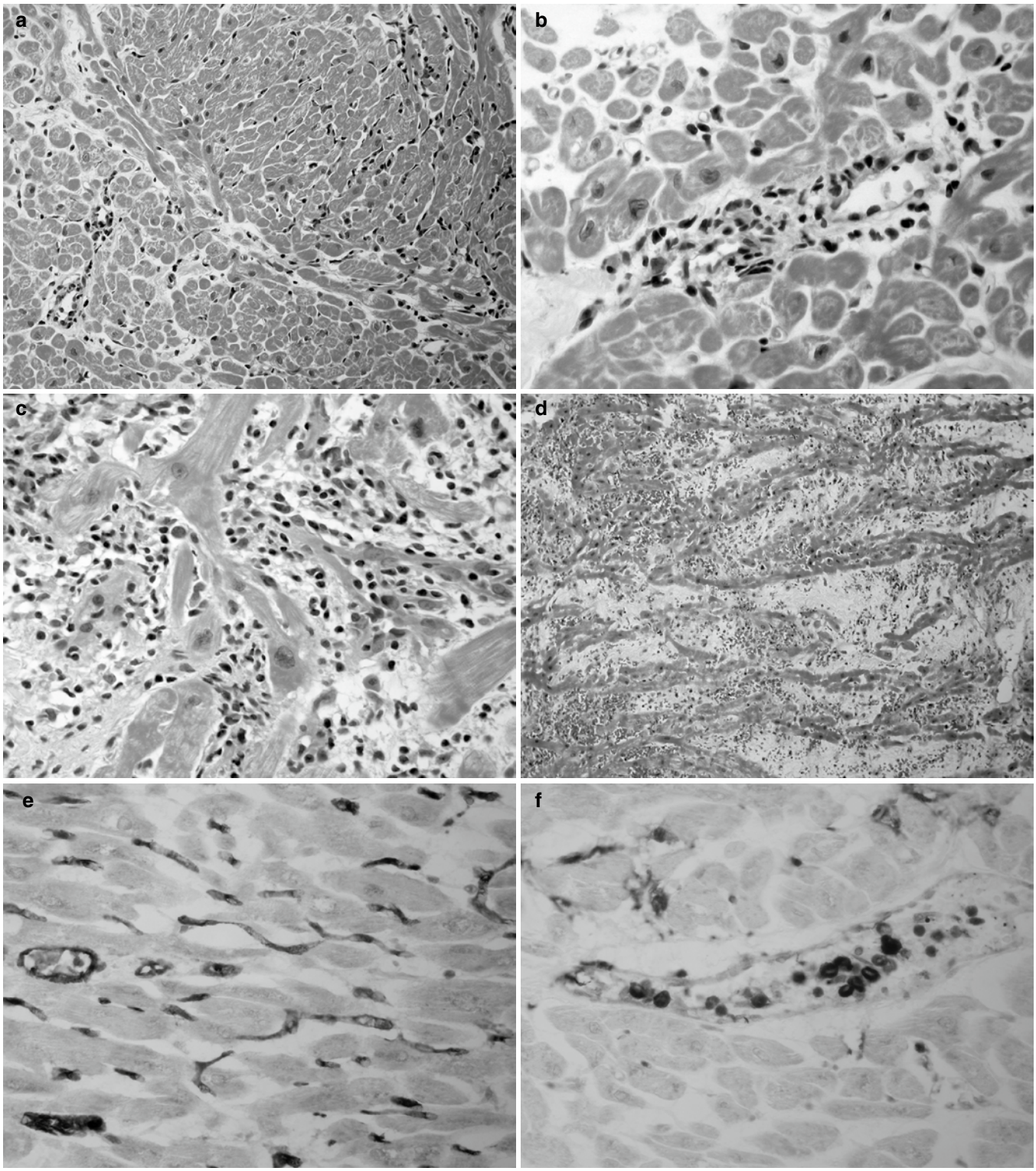

FIG. 51.7. Histology demonstrating the 2004 ISHLT grading system for endomyocardial biopsies. (**a**) Grade 1R mild cellular rejection appears as a sparse perivascular (*lower left corner*) and diffuse interstitial (*right half* of picture) T-lymphocytic infiltrate (Hematoxylin–Eosin, original magnification × 50). (**b**) At higher magnification, the perivascular lymphocytic infiltrate is seen, with lymphocytes traversing the vessel wall (endothelialitis) (H&E, original magnification × 250). (**c**) In grade 2R moderate cellular rejection, the infiltrate is much more dense, spreading the myocytes apart, and often associated with myocytolysis, seen here to the left of the frame (H&E, original magnification × 400). (**d**) In this frame of grade 3R severe cellular rejection there is interstitial edema and hemorrhage splaying the myocytes apart. There is often a mixed infiltrate of lymphocytes, macrophages, neutrophils, and plasma cells with fibrinoid necrosis of

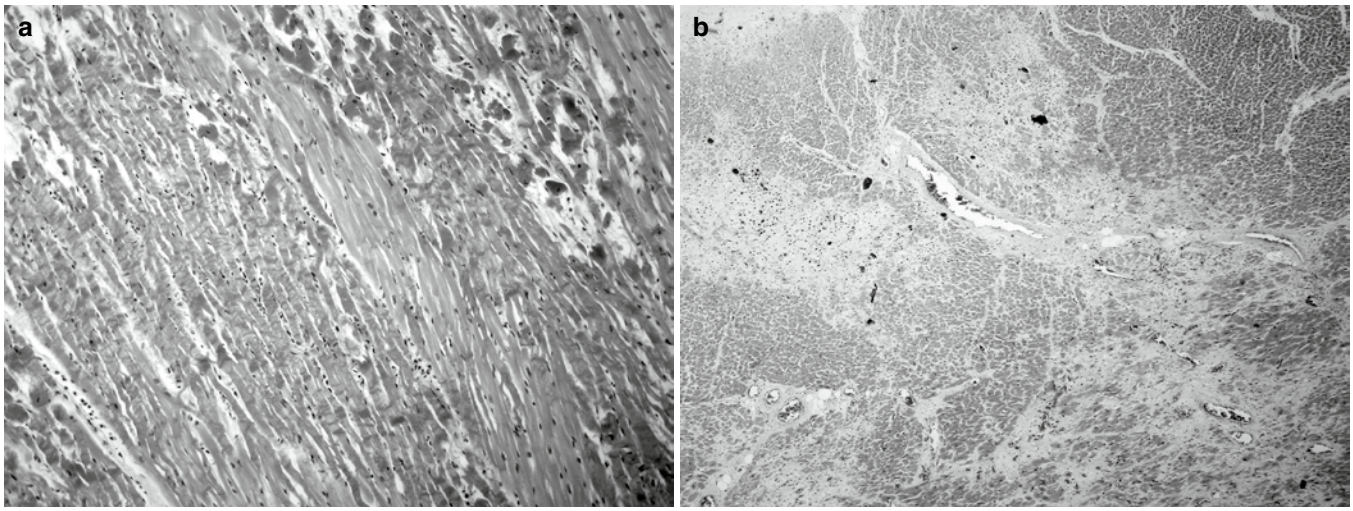

FIG. 51.8. Immediate and long-term effects of perioperative myocardial ischemia. (**a**) Myocardial histology from a heart with primary graft failure. Virtually all the myocardium in this frame is necrotic apart from a band of intact myocardium running diagonally from *top* to *bottom* of the frame. The patient was transplanted for dilated cardiomyopathy and was re-transplanted 2 days later because of primary graft failure necessitating circulatory support (Levitronix BiVAD) (H&E, original magnification × 100). (**b**) Extensive myocardial replacement fibrosis in a patient with previous primary graft dysfunction who had a stormy post-transplant course, but who eventually recovered but was left with LV diastolic dysfunction (H&E, original magnification × 25).

TABLE 51.5. Differential diagnosis of postoperative right ventricular failure.

Increased recipient pulmonary vascular resistance
RV ischemia-reperfusion injury
RV injury caused by donor brain death
Torsion of pulmonary artery or stenosis at PA anastomosis
Air embolism to the right coronary artery
As part of biventricular primary graft dysfunction (with RV failure initially masking LV dysvfunction)
Pseudo RV failure: raised venous pressure cause by stenosis at SVC or IVC anastomosis

TABLE 51.6. Differential diagnosis of postoperative biventricular failure.

Differential diagnosis of post-transplant biventricular failure/"primary" graft dysfunction
Ischemia-reperfusion injury especially following prolonged ischemic time
Myocardial injury caused by donor brain death
Myocardial protection compromised by donor coronary disease
Technical failure of myocardial protection
Hyperacute antibody-mediated rejection

be interpreted as trends as well as absolute values and in the light of the response to therapy that has already been given. Sometimes combinations of factors are present with an overlap of diagnostic features; frequent reevaluation is necessary until cardiac output and organ perfusion are adequate. Where the diagnosis is unclear or the patient fails to respond rapidly to treatment based on the hemodynamic and TOE data, early surgical reexploration should be undertaken to exclude occult cardiac tamponade and to clarify the nature of the problem. Hyperacute rejection must always be excluded.

Acute Renal Failure

Transplant patients who develop acute renal failure (ARF) that is severe enough to require renal replacement therapy have a worse prognosis.[150] The etiology of ARF is usually multifactorial.[151] In the case of heart transplantation, patients with heart failure come to surgery with renal function that is already impaired, usually as the result of low cardiac output and the effects of heart failure therapy. Some also have structural renal changes of glomerulosclerosis and atherosclerosis.[152] Cardiopulmonary bypass adds further stress to the kidney. Cyclosporine and tacrolimus can cause acute nephrotoxicity by vasoconstricting the renal vessels,[115] although this effect can be reduced by controlling drug levels. The use of other nephrotoxic drugs such as aminoglycosides should be avoided whenever possible. However, poor early function of the cardiac allograft resulting in inadequate cardiac output and the necessitating use of vasoconstrictor inotropes are frequently the major factors contributing to postoperative renal failure. Renal failure can often be prevented by early intervention to correct hemodynamic problems.

Once oliguric renal failure has occurred, one of the best signs of adequate cardiac output (urine flow) is lost, and, therefore, invasive monitoring with a PAFC will continue to be necessary until the cardiac output is satisfactory and stable. If renal failure occurs, continuous veno-venous hemofiltration, which is less likely to provoke hemodynamic instability

Table 51.7. Differential diagnosis of hypotension and the low cardiac output state. In all cases hyperacute rejection should be excluded.

Cause	Diagnostic indicators	Management strategy
Low CO (CI < 2.5 l/min/m² and low S_vO_2)		
Hypovolemia	Low CVP and LAP Excessive variation in systolic blood pressure with ventilatory cycle Empty hypercontractile RV and LV on TEE Surgical bleeding	Usually transient improvement when patient tilted head-down Colloid or blood bolus in increments of 2–4 ml/kg with continuous monitoring and assessment. Must avoid overfilling (always aim to keep CVP≤16 mmHg) If bleeding continues consider pro-coagulants and blood products as guided by blood count, clotting profile, fibrinogen levels and thromboelastogram Early surgical reexploration is usually indicated
Acute RV failure (see Table 51.5)	High CVP Low LAP Dilated hypo-contractile RV Normal LV systolic function and LV may appear empty on TEE	Use short-acting vasodilators, preferably specific for pulmonary circulation: 1. High F_IO_2 with moderate hyperventilation 2. Nitric oxide 3. Inodilators; e.g., milrinone or isoprenaline 4. Other pulmonary vasodilators; e.g., Prostaglandin E_2, epoprostenol (prostacyclin), GTN Inotropic support for RV Consider RVAD
Acute biventricular failure (see Table 51.6)	High CVP High LA filling pressure Typically poorly contracting, stiff, thick-walled LV and dilated poorly contractile RV on TEE	Increase inotropes; e.g., epinephrine/dobutamine Inodilators ± norepinephrine Place IABP Keep heart rate ≥ 100 bpm – Atrial pacing – Isoprenaline Consider biventricular VAD support
Cardiac tamponade	In a classic case: Progressively increasing CVP Decreasing systolic blood pressure with excessive variation with ventilatory cycle Heavy bleeding followed by "dry" (clotted) surgical drains TEE may show RA/RV diastolic collapse, cavity distortion or a pericardial collection Note that "atypical" presentations frequently occur caused by localized clots in the pericardial space	Surgery to relieve tamponade and stem hemorrhage Where the diagnosis is uncertain, surgical reexploration should be done at an early stage Usually immediate hemodynamic improvement once chest open
Hypotension due to low SVR and normal/high but "inadequate" CO		
Systemic inflammatory response (SIRS)	Critically ill patient before surgery or prolonged cardiopulmonary bypass time Dynamic RV and LV on TEE	Fluid to optimize CVP and LAP Cautious use of vasoconstrictors to increase SVR towards normal (norepinephrine/vasopressin)
Systemic infection	Dynamic RV and LV on TEE Pyrexia Raised inflammatory markers Preoperative infection (e.g., VAD related)	Fluid to optimize CVP and LA filling pressures Cautious use of vasoconstrictors (norepinephrine/vasopressin) Antimicrobial therapy
Iatrogenic vasodilatation	CVP and LAP normal or low Dynamic RV and LV on TEE Excessive use of vasodilators or inodilators (accumulation in renal failure)	Reduce or stop inodilators/vasodilators Cautious use of norepinephrine

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than intermittent hemodialysis, is preferred.[153] Renal recovery depends on establishing adequate cardiac output and avoiding repeated episodes of hypotension.[154]

Renal failure will alter the pharmacokinetics of many drugs and therefore appropriate dose adjustments must be made. Most immunosuppressive agents are metabolized in the liver, although their metabolites may accumulate in ARF.[113] Type III phosphodiesterase inhibitors such as milrinone will accumulate in ARF and may cause excessive vasodilatation.

Bradycardia and Arrhythmia

Bradycardia is common in the early postoperative period. The most common rhythms are sinus bradycardia or a junctional escape rhythm due to sinus node dysfunction.[155] Heart block is less frequent. In patients who have undergone transplantation using the biatrial technique, the surface ECG normally shows two sets of P waves (donor and recipient). Therefore, care must be taken to ensure that the dissociated P waves are of the donor and not recipient origin before diagnosing complete heart block.

Bradycardia is usually poorly tolerated because of impaired diastolic function in the newly transplanted heart. Temporary epicardial pacing wires should be placed on the right atrium and right ventricle during surgery so that the heart rate can then be controlled by dual chamber pacing while maintaining normal atrioventricular synchrony. Optimum hemodynamics are usually obtained at a heart rate of 90–110 bpm. Alternatively, sinus bradycardia usually can be treated with an infusion of isoprenaline or theophylline.[156]

Most patients return to sinus rhythm with an adequate heart rate within the first few days of surgery. When bradycardia persists beyond the second postoperative week, permanent pacing is required to facilitate rehabilitation of the patient and hospital discharge, although many patients eventually recover a normal rhythm and are not dependent on the pacemaker long-term.[157,158] Implanting a dual-chamber rate-adaptive pacemaker (DDDR) system provides maximum flexibility for future programming. If chronoscopic incompetence persists, the patient can be provided with rate-adaptive pacing during exercise.

Atrial arrhythmia (flutter or fibrillation) is common after transplantation. Although there is some association between these arrhythmias and acute rejection, most episodes are not related to rejection.[159]

Pharmacologic management of arrhythmia in patients who have undergone heart transplantation is similar to that in non-transplant patients, with the exceptions that the transplanted heart is supersensitive to adenosine and that digoxin is less effective because of vagal denervation.[160–162] Some calcium channel blockers (e.g., diltiazem) affect cyclosporine metabolism.[115]

Infection

Infection is one of the most serious complications of transplantation and one of the more common causes of mortality.[2] The risk of infection is highest in the early months after surgery.[163] In the early period after surgery, bacterial and fungal pathogens are most common, whereas more than 1 month after surgery opportunistic pathogens become more prevalent.[164] Surgery and intensive care breach mucosal barriers and expose the patient to nosocomial pathogens, while pharmacologic immunosuppression attenuates the host response to infection. Preventive measures include preoperative vaccination, removing catheters and drains as early as possible, avoiding unnecessary instrumentation, use of tunneled lines if prolonged intravenous access becomes necessary, and the use of prophylactic antimicrobial agents in the immediate postoperative period.[164] Management of the hospital environment must include screening new admissions for antibiotic-resistant organisms, isolation of individuals with potentially transmissible infection, and education of staff about infection control procedures. Tertiary heart failure centers are seeing an increased number of patients colonized with resistant organisms; contributory factors include prolonged hospitalization, invasive therapies including mechanical circulatory support, and multiple courses of antimicrobial therapy.

Heart transplant patients can be nursed in beds available to routine cardiac surgery patients, and special isolation procedures are not essential.[165] Antibiotic prophylaxis should be achieved with drugs that do not interfere with cyclosporine metabolism or cause added nephrotoxicity. The choice of drugs must be tailored to the pattern of organisms and drug resistance, seen in the individual unit and will need to be changed periodically. In the authors' institution, routine heart transplants receive amoxicillin/clavolanate, while those colonized with methicillin-resistant *Staphylococcus aureus* receive teicoplanin and ciprofloxacin. Patients transplanted after VAD support receive antibiotics guided by previous cultures or, if no positive cultures have been obtained, are treated with teicoplanin and Piperacillin/Tazobactam (particularly to cover resistant staphylococci and pseudomonas species). Routine antibiotic prophylaxis should be administered for 48 h. Low-dose co-trimoxazole prophylaxis is administered long-term to prevent *Pneumocystis jiroveci* (formerly *P. carinii*) pneumonia.[166] Patients who receive an organ from a *Toxoplasma*-seropositive donor and who are themselves seronegative should receive specific prophylaxis with co-trimoxazole or pyrimethamine.[167,168]

Cytomegalovirus (CMV) is the most common opportunistic pathogen encountered after heart transplantation. Infection can be acquired from the graft (or blood products) or caused by reactivation of a latent infection in a seropositive recipient. The introduction of valganciclovir, which is a pro-drug of gancyclovir that, in turn, is highly active against CMV, has provided an effective means of prophylaxis against this infection.[169] The authors' current approach is to provide prophylaxis to all at-risk patients for the first 3 months after transplantation and again after any period of intensified immunosuppression.

The management of infections caused by conventional bacterial pathogens is similar to that in other post-cardiac surgical patients, but nephrotoxic drugs and those that interact with CNI and TOR-inhibitor metabolism should be avoided whenever possible. When interactions cannot be avoided, close monitoring of immunosuppressant levels and the adjustment of the dose used are essential.[113] The management of opportunistic infections is outside the scope of this chapter, but it has been reviewed elsewhere.[164]

Long-Term Results

The overall survival rate 1-year after heart transplantation reported by the Registry of the International Society for Heart and Lung Transplantation is 81.2%.[2] Beyond the first year, the mortality rate is 3.4% annually. The overall patient half-time is currently 9.9 years. For patients transplanted between 1999 and 2004, 1-year actuarial survival was 84.9% and 5-year survival 72.1%; 10-year survival for patients transplanted between 1994 and 1998 was 51.3%. The 10-year actuarial survival for patients transplanted since 1995 at the authors' center is 62%.

Causes of late death include cardiac allograft vasculopathy or "chronic rejection," infection, malignancy, late-onset of acute rejection, and chronic kidney disease related to long-term therapy with cyclosporine or tacrolimus.[2] Some patients require therapy for other medical complications including new-onset diabetes, dyslipidemia, and post-transplant hypertension. Nevertheless, most patients have a far better survival and quality of life after transplantation than can be achieved by the current medical therapy for advanced heart failure.

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Postoperative Care of the Lung-Transplant Patient

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The early postoperative care in the management of the lung-transplant patient has significantly changed over the past two decades. The advances in donor preservation, improved surgical techniques, better understanding of immunosuppression and nosocomial infection along with multidisciplinary care have contributed to these changes. Although management of the lung-transplant patient is similar in many aspects to that of a critically ill postsurgical patient, care of some of these patients is challenging, and a multidisciplinary team familiar with their care makes a difference. With this approach, the postoperative mortality rate is kept below 10% and the morbidity is minimized in many centers. Preoperative recipient preparation plays a key role in postoperative management and cannot be taken lightly. There are no major randomized clinical trials to draw conclusions or provide guidelines; therefore, the recommendations are made from large-volume lung-transplant centers and personal experiences, as well as experiences with major thoracic surgical procedures. This chapter summarizes the early postoperative management of patients undergoing isolated lung transplantation.

Patient Characteristics and Preoperative Preparation

Many different patients with end-stage lung diseases benefit from lung transplantation[1] and each may pose a specific problem in the postoperative care of the patient. As all patients presenting themselves for transplantation have a long period of disability as a result of their underlying end-stage lung disease, a majority of patients are malnourished because of either poor intake or lack of activity, are deconditioned, and have various psychosocial problems. Prior to placing a patient on the transplant list, it is important to identify and address these issues. Appropriate treatment of preexisting medical, nutritional, and psychosocial conditions is necessary and has an impact in the early and late outcome following transplantation.[2,3] Updated guidelines developed by the international lung-transplant community are currently available to select patients for lung transplantation.[4]

Lung-Transplant Patient Care Team

Patients undergoing lung transplantation require a team of caregivers who are committed, familiar with the protocols, and able to ensure ongoing communication among team members. The team members include transplant coordinators, a transplant pulmonologist, a transplant surgeon, an anesthesiologist, a pain management team, a critical care specialist, ICU nurses, an infectious disease specialist, a pharmacologist, a physical therapist, an occupational therapist, a nutritionist, and a social worker. Clinical pathways are developed addressing complete patient care with incorporation of immunosuppressive and infection prophylaxis protocols[5] (Table 52.1). Despite clinical pathways, regular team meetings to discuss the daily care of the patient facilitate efficient and timely interventions and improve postoperative care.

Respiratory Management

Despite advances in the donor management and preservation of the lung, primary-graft dysfunction is not uncommon following lung transplantation.[6] In most cases, however, the degree of dysfunction is minor to moderate and reversible, and therefore does not progress to graft failure. The incidence of primary-graft dysfunction has been reported between 11 and 57%.[7] When there is primary-graft failure, extracorporeal mem-

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Table 52.1. Outline of clinical pathway framework.

	Preoperative	DOS	POD 1	POD 2	POD 3	POD 4	POD 5	POD 6	POD 7
Location	ICU/private room	ICU single room	ICU single room	private room	private room	private room	private room	private room	private room
Intermediate progression to discharge	Pre-op completed. States expected LOS and post-op activities via clinical path	States expectations for DOS. Discharge planner	States expectations for POD 1. Discharge planner	States expectations for POD 2. Discharge planner	States expectations POD 3. Discharge planner	Pulmonary rehabilitation, discharge planner	Self care in med card, spirometry, exercise prescription	Self care in med card, spirometry, Exercise Prescription	D/C from hospital
Medications/ IVs	Immunosuppressant, antibiotics, DVT prophylaxis	Immunosuppressant, post-op ATB, DVT and other prophylaxis	Immunosuppressant, post-op ATB, DVT and other prophylaxis	Immunosuppressant, post-op ATB, DVT and other prophylaxis	Immunosuppressant, post-op ATB, DVT and other prophylaxis	→	→	→	D/C heparin Meds per POD 3
Tests/diagnostic	CXR Blood draws	CXR Blood draws	CXR Blood draws	CXR Blood draws	CXR Blood draws	CXR Blood draws	CXR Blood draws	CXR Blood draws	CXR Blood draws
Treatments/ interventions	H&P in chart, VS on chart, consents Pre-op teaching enforced	ICU protocol, isolation protocol, Intervention per post-op protocol	ICU protocol, isolation protocol, intervention per post-op protocol	HDU protocol, isolation protocol, intervention per post-op protocol	HDU protocol, isolation protocol, intervention per post-op protocol	→	→	→	D/C from hospital
Activity	Bed rest with BRP	BR until extubation, PT/OT Evaluation	Ambulation protocol per PT/OT	Ambulation protocol per PT/OT	Progressive ambulation per PT/OT	→	→	→	→
Nutrition	NPO	NPO until extubated clear 12 h after	Advance diet as tolerated	Regular diet, assess tolerance	Regular diet, assess tolerance	Regular diet, assess tolerance	Regular diet, assess tolerance	Regular diet, assess tolerance	Regular diet, assess tolerance
Patient/family education	Review surgery, medications, bedside spirometry, C&DB, critical pathway, introduction to ICU, education materials	Instruction about extubation, post-op meds, pulmonary toilet Pain management Physical therapy goals	Pulmonary toilet, medications, spirometer/ FEV1, infection control, PT Education materials	Pulmonary toilet, medications, spirometer/ FEV1, infection control, PT Education materials	Pulmonary toilet, medications, spirometry, rehab. Infection control, transplant diet education	Pulmonary toilet, medications, spirometry, rehab. Infection control, transplant diet education	Pulmonary toilet, medications, spirometry, rehab. Infection control, transplant diet education	Post D/C procedures review, pill box D/C education materials, exercise prescription	Verbalize understanding of medical f/u, therapy, able to fill out daily log, fill pill box

brane oxygenation (ECMO) may be required. Early institution of ECMO has been shown to be more successful than later.[8–10] When the graft dysfunction is mild to moderate, the same management strategies are used as are used in patients with significant lung injury.

Ventilation

Ventilatory management is determined by the type of lung transplant the patient received: single or bilateral. In patients with bilateral lung transplant, ventilation would be aimed at minimizing barotrauma by using low inflation volumes and moderate levels of positive end-expiratory pressure (PEEP, less than 10 cm water). In patients with single lung transplant, the pathophysiology of the remaining native lung will influence ventilatory strategy. Significant air trapping and auto PEEP are not uncommon in patients with emphysema. Low ventilatory volumes, adequate expiratory time, and avoidance of excessive PEEP will help to prevent air trapping and significant hemodynamic instability in these patients. Positioning patients with the allograft side up and providing bronchodilator therapy are useful strategies in patients with a single lung transplant. Very rarely, isolated lung ventilation with a double lumen tube is necessary to effectively ventilate when there is significant graft dysfunction. Surgical intervention, such as volume reduction and pneumonectomy, has been reported in some cases of single lung transplant patients to facilitate postoperative recovery.

Inhaled nitric oxide (NO) through the ventilator has been shown to reduce reperfusion injury in experimental models clinically, when used as prophylaxis. Its usefulness in established graft dysfunction is controversial. Selective use of inhaled NO in the perioperative period in patients with preexisting pulmonary hypertension is not uncommon. The aim of the inhaled NO use is to reduce pulmonary artery pressures during the operation and immediately afterward, thereby assisting the right ventricular function.

Noninvasive Ventilation

Noninvasive ventilation is useful in selected patients whose graft function is good and for whom the primary concern is suboptimal respiratory effort and not retention of secretions. If the patient is unable to clear secretions, the noninvasive ventilation may worsen the situation by drying out the secretion in the bronchial tree. Noninvasive ventilation is most often useful in patients where phrenic nerve dysfunction is suspected or who are debilitated preoperatively with very poor muscle mass.

As a rule, aggressive weaning off the ventilator is practiced following lung transplantation to prevent nosocomial infection and promote early rehabilitation. Sedation should be monitored carefully and used sparingly. It is advisable to use short-acting agents while the patient is intubated. The majority of the patients are extubated within the first 24 h after transplantation. After extubation, the use of epidural analgesia is encouraged along with the avoidance of narcotics and benzodiazepines (unless the patient was on these medications preoperatively).

The concern that ventilation, either invasive or noninvasive, and endotracheal suctioning is hazardous and may disrupt bronchial anastomosis is unfounded.

Bronchial Hygiene

Aggressive bronchial hygiene is necessary to prevent collapse and development of pneumonia in these patients. While patients are intubated, soft-suction catheters should be used to clear secretions; this suctioning should be performed routinely. Once the patient is extubated, incentive spirometry, chest physiotherapy, and ambulation are necessary to promote clearance of bronchial secretions. In patients who are debilitated and are retaining secretions, the authors have used mini-tracheostomy" to facilitate removal of the secretions with a soft-tip 10 French catheter. Alternatively, patients will require repeat bronchoscopic suction of secretions. When a patient fails a trial of extubation, early tracheostomy facilitates rapid weaning, assists in effective management of secretions, and promotes early physical rehabilitation.

Hypercapnia

Chronic hypercapnia is not uncommon in patients with end-stage lung disease, particularly those with cystic fibrosis and emphysema. It frequently takes several days for these patients to reset their respiratory center in order to maintain a normal blood carbon dioxide level following lung transplantation. It is important not to ventilate these patients to normocapnic levels postoperatively. The aim in these patients would be to wean ventilation at a level of hypercapnia falling somewhere between the preoperative hypercapnia level and the normocapnic levels. A trial of continuous positive airway pressure while maintaining sound mental status should be used as a guideline to accept the level of hypercapnia prior to extubation.

Hemodynamic Management

Patients considered for lung transplant undergo a detailed cardiac evaluation and are excluded as candidates for isolated lung transplantation if they have uncorrectable or severe cardiac disease. If the cardiac pathology is severe with end-stage lung disease, the patient would be a potential candidate for combined heart and lung transplantation. Isolated coronary artery disease alone is not a contraindication for lung transplantation. These patients would be candidates for pre-transplantation, percutaneous revascularization, or simultaneous surgical revascularization.[11,12] Correctable cardiac lesions such as atrial septal defect (ASD) or simple ventricular septal defect (VSD) are repaired during

lung transplantation and would not be a major issue in the postoperative period.

Pulmonary Hypertension

Patients with primary or secondary pulmonary hypertension will have varying degrees of right ventricular dysfunction, but this improves with successful lung transplantation. Perioperative use of inhaled NO or other pulmonary vasodilator therapy is not uncommon and is certainly useful in reducing postoperative pulmonary hypertension, fluctuations in pulmonary artery pressures, and hemodynamic instability.

Systemic Hypotension

The most common hemodynamic disturbance following lung transplantation is hypotension and supraventricular tachyarrhythmia. The practice of keeping these patients in a relative hypovolemic state makes them susceptible to hypotension if there is any degree of vasodilation. However, overzealous restriction of fluid is another cause of systemic hypotension. It is important to maintain adequate intravascular volume in order to maintain adequate cardiac output as well as urine output. The fluid therapy is aimed at maintaining low or low-normal cardiac filling pressures. It is, however, not necessary to monitor pulmonary artery wedge pressures in all patients; monitoring of right atrial filling pressures is most often adequate. Since the lymphatic drainage is interrupted from the lung allograft following transplantation, any capillary leak into the lung parenchyma will be cleared less efficiently. It has been shown that fluid restriction in patients with lung injury promotes an early recovery.[13] This may be an important factor to consider during the postoperative period, because the majority of the lung grafts suffer some degree of reperfusion injury. Systemic vasodilation, whether it is produced by medications or sympathetic blockade as a result of an epidural or release of cytokines, is best treated with vasoconstriction using intravenous short-acting alpha-agonists rather than by volume. Phenylephrine is the drug of choice in the treatment of systemic vasodilation in these patients. Vasopressin is an effective systemic vasoconstrictor, but it also appears to cause profound bronchial vasoconstriction and may cause bronchial ischemia, adversely affecting anastomotic healing.

Supraventricular Arrhythmias

The incidence of supraventricular arrhythmias is not uncommon following lung transplantation.[14] The most common arrhythmias are supraventricular tachycardia and atrial fibrillation. Many programs take preventive measures for atrial fibrillation in the postoperative period, which can reduce the incidence of this complication but are unlikely to prevent it completely. The effects and complications caused by atrial fibrillation are systemic hypotension and systemic embolization, perhaps made worse by the fresh suture line on the left atrium. Although amiodarone is generally avoided because of its effects on the lung, the authors have used amiodarone in patients who are resistant to or unsuitable for treatment with calcium channel blockers or beta blockers. Anticoagulation will be necessary as used in other patients with atrial fibrillation, and the biopsy schedules need to be considered. Patients are preferentially treated with short-acting agents (usually enoxaparin) in the postoperative period. It is important to check clotting studies prior to transbronchial biopsy or endobronchial intervention, as uncontrollable bronchial hemorrhage is fatal.

Diagnosis and Management of Early Surgical Complications

Bleeding

Bleeding is an uncommon surgical complication now compared to the early days of lung transplantation. This improvement is a result of refinement in surgical techniques as well as the judicious use of pharmacological agents such as aprotinin and blood products. The patients at high risk are those with extensive pleural adhesions, large and extensive mediastinal collateral vessels, and connective tissue disorders with secondary pulmonary hypertension. Patients with right heart failure and congested liver or patients on chronic anticoagulation medication are particularly susceptible, and correction of coagulation defect is necessary in these patients. If a patient persists with significant blood loss (>100 cc/h) for 4–6 h, the patient needs to return to the operating room unless there is evidence of significant coagulation abnormalities.

Bronchial Anastomotic Complications

The dreaded complication of complete bronchial anastomotic dehiscence is rarely seen now, but stenosis at the anastomotic site is not that uncommon, being reported between 5 and 25% of the anastomoses. This complication is usually delayed for several weeks following transplantation.[15] In the presence of anastomotic site infection or significant donor bronchial ischemia, minor bronchial dehiscence may present as early as 1–2 weeks following surgery.

Vascular Anastomotic Complications

Vascular complications are infrequently reported, and their real incidence may be higher than suggested in the literature. The venous complication if severe enough can present, in a few hours following transplantation, as acute graft dysfunction. This presents as rapidly progressing pulmonary edema, with diffuse, dense infiltrate of the affected lung or lobe. It is potentially fatal and diagnosis requires a high index of suspicion. Transesophageal echocardiogram is helpful to confirm the diagnosis. Surgical correction is required if the condition

is a result of anastomotic narrowing due to surgical technique. Thrombus formation at the anastomotic site can also cause venous obstruction, which is insidious in origin and progressive. Thrombolytic agents have been successfully used in these circumstances. Arterial anastomotic stenosis presents as hypoxemia, usually associated with exercise. This should be suspected if there is no other reason for hypoxemia. Pulmonary angiogram is used for diagnosis and catheter-based interventions, including stent placement, has been successfully employed.

Axial Torsion

Lobar or lung torsion on its axis is a rare complication and if not corrected immediately will result in necrosis of the lobe or lung. Complete opacification is noted on the chest radiograph and bronchoscopic examination is confirmatory.

Pain Management

Patients undergoing thoracic surgery require adequate pain relief to allow deep breathing and coughing and to facilitate early ambulation. In lung-transplant patients this becomes crucial as they are chronically debilitated and they will be unable to clear secretions effectively or prevent atelectasis and pneumonia without effective pain relief. Thoracic epidural analgesia is effective in providing pain relief without causing sedation. The placement of a thoracic epidural catheter preoperatively provides effective pain relief while avoiding systemic narcotic and sedative hypnotics. The catheter is used until the patient is ready to be discharged or until the fifth postoperative day, whichever is longer. Nonsteroidal anti-inflammatory drugs (NSAIDs) are avoided because of the potential interactions with other nephrotoxic agents, particularly calcineurin inhibitors. Transitioning to oral pain medication is monitored carefully prior to discharge from the hospital.

Immunosuppression

Immunosuppression after lung transplantation includes three major categories of immunosuppressive agents: calcineurin inhibitors (tacrolimus, cyclosporin A), antimetabolites (azathioprine, mycophenolate mofetil), and corticosteroids. In addition, approximately 45% of lung-transplant patients receive induction therapy after surgery. The calcineurin inhibitors are administered within hours after transplantation and may be given either intravenously or sublingually (tacrolimus). In general, tacrolimus is dosed at 0.05–0.1 mg/kg over 24 h by continuous infusion and may also be given sublingually at a dose of 0.03 mg/kg twice daily. Target tacrolimus trough levels range between 10 and 20 ng/ml in the first 6 months after transplantation, followed by levels of about 10 ng/ml thereafter. Cyclosporine is administered at a rate of 3 mg/kg over 24 h with target trough levels between 350 and 450 ng/ml in the first month, between 300 and 350 ng/ml during the first year, and between 200 and 300 ng/ml thereafter. Both tacrolimus and cyclosporine are available in oral forms and should be given orally after extubation. Although current data have not shown a superiority of one calcineurin inhibitor over another, there has been an increasing use of tacrolimus in lung-transplant patients as a result of reports of improved pulmonary function and possibly a reduction in the incidence of bronchiolitis obliterans syndrome with this agent.[16,17]

Antimetabolites (either azathioprine or mycophenolate mofetil) are the second immunosuppressive medications that are used in lung-transplant recipients. The first dose may be initially administered prior to implantation of the lung allograft. Azathioprine is dosed at 2 mg/kg daily and can be administered either intravenously or orally. Mycophenolate mofetil is dosed orally at 2–3 g in daily divided doses. In general, antimetabolites may be associated with myelosuppression and gastrointestinal distress, and doses may be adjusted based on these side effects. Two randomized, multicenter studies have shown no difference in acute rejection or survival between these two agents.[18,19]

Corticosteroids have been the mainstay of immunosuppression since the advent of successful lung transplantation in the 1980s. Many centers administer the first dose of methylprednisolone (between 500 and 1,000 mg intravenously) preoperatively. Subsequent doses of corticosteroids range between 0.5 and 1 mg/kg during the first few weeks after transplantation. In general, corticosteroids are tapered to the equivalent of 5–10 mg of prednisone daily by 3–6 months after transplantation.

The role of induction therapy in lung transplantation has yet to be defined. Several types of induction therapy are currently being used in lung transplantation, including the interleukin-2 receptor antagonists (daclizumab, basiliximab), the polyclonal agents (ATGAM, thymoglobulin), and the monoclonal antibody (OKT3). Several reports have suggested that induction therapies may reduce the incidence of acute rejection during the first 6 months after lung transplantation. However, longer-term outcomes, including prevention of chronic rejection or improving survival, have not been associated with the use of induction therapy after lung transplantation.[20–22]

Infection Prophylaxis

Infections remain a major source of morbidity and mortality after lung transplantation. Prophylaxis against bacterial, viral, and fungal organisms usually starts immediately postoperatively in lung-transplant recipients. Initial antibiotic prophylaxis should be directed toward adequate anaerobic coverage and tailored towards any positive donor or recipient culture detected prior to transplantation. These antibiotics are usually continued for 3–14 days post-transplant, depending on the individual transplant center's protocol. Lung-transplant recipients with septic lung disease (cystic fibrosis, bronchiectasis), who may be colonized with resistant organisms, often receive

two synergistic antibiotics based on prior sensitivities during this time period.

Viral prophylaxis is most commonly targeted against cytomegalovirus (CMV). Aggressive prophylactic therapy is directed towards this organism because of its high virulence and association with mortality in the lung-transplant population. Lung-transplant recipients with either donor or recipient serology that is positive for CMV usually receive prophylactic therapy with valganciclovir for anywhere between 3 months and throughout the entire life. CMV-negative lung-transplant recipients who received a CMV-positive donor lung may receive CMV immunoglobulin in addition to their current valganciclovir therapy. Unfortunately, while valganciclovir prophylaxis decreases the incidence of CMV infection during the time of administration, prophylaxis does not completely prevent the development of CMV infection, especially after prophylaxis therapy is discontinued. The optimal duration and type of therapy are still a matter of debate. Acyclovir and its derivatives are given to CMV-negative lung-transplant recipients who receive CMV-negative donor lungs in order to prevent the development of herpes infections.

Fungal prophylaxis varies among the different transplant centers depending on prior colonization, mechanical airway complications, and environmental factors. Some centers provide general fungal prophylaxis while others consider preemptive therapy depending on surveillance bronchoscopy findings. Lung-transplant recipients are at increased risk of developing *Aspergillus spp.* colonization of the airways leading to anastomotic infections and ulcerative tracheobronchitis. Itraconazole (or other azole substitutes) and inhaled amphotericin B are the most common fungal prophylactic agents that are currently used. The azoles will increase the levels of the calcineurin inhibitors (cyclosporine and tacrolimus) such that the doses of these immunosuppressive medications should be decreased by at least one-third of their original dose. Calcineurin levels should be checked approximately 1 week after starting an azole. Of note, voriconazole and sirolimus should not be used together because of the significant rise in sirolimus levels.

Early Medical Complications and Management

The following are the medical complications that may occur within the first few months after lung transplantation.

Pulmonary Complications

Several pulmonary complications may occur within the first few weeks after lung transplantation. One of the most common is pneumonia. Post lung-transplant pneumonias are frequently caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*. As a result, all lung-transplant recipients are placed on broad-spectrum antibiotics, which are often tailored to donor and recipient sputum cultures.

Other pulmonary complications after lung transplantation include primary graft dysfunction (PGD) and acute rejection. Unfortunately, both of these complications are often present with nonspecific findings, including shortness of breath, cough, low-grade fevers, and nonspecific infiltrates on chest radiograph that may mimic acute pneumonia. It is important, therefore, to distinguish these diagnoses with early bronchoscopy, with transbronchial biopsy, and with bronchoalveolar lavage samples. It is estimated that PGD occurs in up to 60% of lung-transplant recipients and is characterized by worsening hypoxemia with bilateral radiographic infiltrates in the absence of infection or acute rejection within the first 72 h after lung transplantation. The primary treatment for PGD is supportive care with supplemental oxygenation and diuresis.[23,24]

Finally, there appears to be a higher incidence of thromboembolic disease in lung-transplant recipients. This may be due to prior lung disease, pulmonary arterial anastomoses, and postsurgical risk factors. Several studies have cited an incidence of pulmonary embolism between 12 and 22% in lung-transplant recipients. The majority of these events occur within the first few months after transplantation, most commonly in the lung allograft.[25,26] A high level of vigilance should be maintained to make this diagnosis and appropriately treat these patients in a timely manner.

Gastrointestinal Complications

Gastrointestinal complications are common after lung transplantation. Gastroesophageal reflux disease (GERD), which is often present in lung-transplant candidates prior to transplantation, usually worsens after transplantation. This is multifactorial and caused by underlying lung disease, vagal nerve injury, and immunosuppressive medications affecting the lower esophageal sphincter and gastric motility. Recent evidence has linked GERD with the development of bronchiolitis obliterans syndrome (BOS).[27] Therefore, aggressive therapy, including proton pump inhibitors and promotility agents, is strongly recommended in this population. Some recent evidence indicates that early fundoplication surgery may improve pulmonary function in patients who have developed BOS.[28]

Other gastrointestinal complications include the development of gastroparesis, adynamic ileus, or intestinal obstruction. Often, narcotic medications, dehydration, and the calcineurin inhibitors may predispose to the development of this condition. Cystic fibrosis patients are at increased risk for developing bowel obstruction because of distal intestinal obstruction syndrome (DIOS) and should be given GoLYTELY® (polyethylene glycol and electrolytes for colonic lavage) routinely after transplantation. In addition, all lung-transplant patients should be placed on a stool softener. Regular, careful assessment of the patient is necessary to prevent DIOS in this patient population.

Renal Complications

Most lung-transplant recipients will develop some degree of renal failure after lung transplantation. The calcineurin inhibitors have been found to be nephrotoxic by decreasing renal blood flow, decreasing glomerular filtration rate, and, ultimately, decreasing creatinine clearance. Fluid management should be very carefully titrated immediately post-transplantation, with special attention to the delicate balance of maintaining adequate renal perfusion without increasing interstitial and alveolar edema. This requires increased attention to fluid balance on a daily basis after lung transplantation.

Neurological and Psychological Complications

Lung-transplant recipients may develop neurological or psychological complications, or both, after the transplant surgery. Several medications, including the calcineurin inhibitors and corticosteroids, have been associated with the presence of seizures, tremors, strokes, neuropathies, and headaches. In the early postoperative state, these medications may also cause psychosis, delirium, and coma-like states. Occasionally, exchanging one calcineurin inhibitor for the other one may alleviate the symptoms. However, treatment is largely supportive and patients occasionally recover.[29] Anxiety, depression, and sleep disorders may also occur early after transplantation. These disorders are often treated with sleep medications, anxiolytic agents, and antidepressants as patients begin to regain their independence and return to an acceptable lifestyle.

Patient and Family Education

The patient and the patient's support personnel – usually the immediate family – need to understand the process of the transplantation and the importance of the postoperative medication as well as the surveillance schedules. The immediate and long-term outcome is significantly impaired when there is lack of such understanding; therefore, patient and family education, which starts in the pre-transplant period, needs to be reinforced in the immediate postoperative phase before the patient is discharged from the hospital.

Lung transplantation is an effective treatment in selected patients with end-stage lung disease. Seventy-six percent 1-year and 49% 5-year survival following lung transplantation is reported by the registry of the International Society of Heart and Lung Transplantation. The main causes of early morbidity and mortality are primary graft failure and infection. Acute rejection is responsible for less than 5% of early mortality. The main cause of late mortality is bronchiolitis obliterans or "chronic rejection." A significant group of patients surviving long-term require treatment for hypertension, diabetes, and hyperlipidemia. Mild to moderate renal dysfunction is not uncommon at 5- and 10-year follow-up. Most patients achieve significant improvement in their quality of life and length of life following transplantation compared to improvement following any medical therapy currently available for their medical condition.[1]

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53
Postoperative Care of the Liver-Transplant Patient

Philip A. Berry, Hector Vilca Melendez, and Julia A. Wendon

Introduction

Liver transplantation (LT) is performed to improve life expectancy and quality of life in patients with advanced chronic liver disease (CLD), and to save life in the context of acute liver failure (ALF). These two groups of patients differ significantly in terms of mean age, prior comorbidity, and degree of extra-hepatic organ dysfunction, requiring substantially different approaches to supportive care. Common aspects of care are those directed at the transplanted organ itself, with regard to monitoring and recognition of early dysfunction, initiation of immunosuppression, and management of surgical complications. Close liaison with the multidisciplinary team, which will include the intensivist, transplant surgeon, transplant hepatologist, anesthesiologist, and radiologist, is required.

Preoperative Physiological Profiles and Approaches to Optimization

Chronic Liver Disease

With an increasing imbalance between organ demand and supply, waiting times before surgery have become extended and complications of cirrhosis more challenging. Cardiorespiratory dysfunction in the form of portopulmonary hypertension, right ventricular dysfunction, alcoholic cardiomyopathy, coincident coronary vascular disease, and hepatopulmonary syndrome may create anesthetic and early postoperative problems. Preoperative hyponatremia due to secondary hyperaldosteronism and/or diuretic therapy may be associated with postoperative neurological and infectious complications, and may preclude surgery if too severe (e.g., <125/L).[1,2] Although these complications should have been recognized, delineated, and optimized during work-up for LT, abnormalities can evolve in the time between assessment and surgery. Pulmonary hypertension, for instance, can develop in as little as 5 months.[3]

Acute Liver Failure

The life-threatening sequelae of ALF are refractory vasodilatory shock and intracranial hypertension (ICH) with tentorial herniation. Lactic acidosis, acute renal failure, coagulopathy (including disseminated intravascular coagulation), and sepsis also represent particular problems. Preoperative optimization will usually require invasive cardiovascular monitoring, fluid resuscitation, vasopressor support, continuous renal replacement therapy (RRT), platelet/coagulation support, cerebral monitoring in grade 3 or 4 coma, and in some cases, intracranial pressure monitoring. The decision to commence intracranial pressure monitoring will be taken on an individual basis depending on the degree of clinical suspicion that raised intracranial pressure (ICP) is present or evolving. Factors favoring this decision are young age, markedly raised arterial ammonia (>150 mmol/L), neurological signs such as clonus, pupillary hyporesponsiveness, or dilatation, and the combination of hypertension and bradycardia. A recent analysis of 58 patients in whom intracranial monitoring was undertaken reported radiological evidence of intracranial bleeding in 10%. In two cases, bleeding was felt to have contributed to the patients' deaths.[4] Measures to reduce the risk of raised ICP, and to treat it once suspected, are summarized in Table 53.1. ICH remains a critical issue in the early posttransplant period and may be particularly relevant if immediate graft function is suboptimal.

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TABLE 53.1. Management of patients at risk of intracranial hypertension.

- Sedation: propofol, which reduces metabolic demands in the brain and may reduce ICP, is the favored agent (50–150 mg/h), co-administered with opiate
- Posture: positioning the head in the midline, with the angle of the body 20° from horizontal
- Normocapnia [pCO_2 4.5–5 kPa]
- Body temperature: normothermia
- Avoidance of stimulation

If pupillary abnormalities (progressive dilation, or dilation with sluggish reaction to light) or other neurological signs evolve, or intracranial pressure exceeds 25 mmHg, and tentorial herniation appears imminent, specific measures can be employed:

- Mannitol: 0.5 g/kg boluses may be administered and repeated, but serum osmolarity should be monitored so that 320 mosm/L is not exceeded. To prevent fluid overload a 500 mL diuresis (or negative balance if being hemofiltered) should be obtained
- Hypernatremia: serum sodium in the range 145–155 mmol/L has been shown to have a beneficial effect on ICP. This target can be achieved with continuous central infusion of 3.0% sodium chloride (NaCl), with regular monitoring. A slow bolus of 20 mL 3.0% NaCl may also be administered for possible surges in ICP
- Hypothermia: a core temperature of 32–33°C, achieved with active cooling, can bring about prolonged reductions in ICP if raised pressure persists despite the above management strategies
- Indomethacin: 25 mg IV bolus
- Hyperventilation: short-term reductions in ICP are seen secondary to induced hypocapnia; however, this strategy is most appropriate if cerebral hyperemia is indicated by high jugular bulb saturations

Overview of Surgical Techniques

The method of organ implantation may have significant consequences in terms of posttransplant care. The conventional method involves removal of the native liver together with a short section of the inferior vena cava (IVC) above and below the organ, followed by implantation of the equivalent anatomy ("caval interposition") from the donor (Fig. 53.1). The "piggyback" method, in which a cuff of the donor's IVC with the donor liver draining into it through the three hepatic veins is piggybacked onto the recipient's IVC, avoids cross clamping and transection of the recipient's IVC. "Split liver" grafts are used when it is felt that the donor organ is of sufficient size to provide liver tissue to two patients. The lobe is implanted conventionally; however, a cut surface remains that may bleed or leak bile (Fig. 53.2). Another technique, employed in ALF when it is projected that the insult to the native liver will abate and regeneration occur effectively (e.g., acetaminophen toxicity), is to implant a whole or partial graft as an "auxiliary" adjacent to the native liver. Ongoing necrosis of the native liver with release of cytokines and toxins can promote an ongoing inflammatory response. If a straightforward "duct-to-duct" biliary anastomosis is not possible (for instance in patients with primary sclerosing cholangitis [PSC], or those receiving auxiliary transplants), a hepaticojejunostomy and Roux-en-Y jejunal loop may be formed.

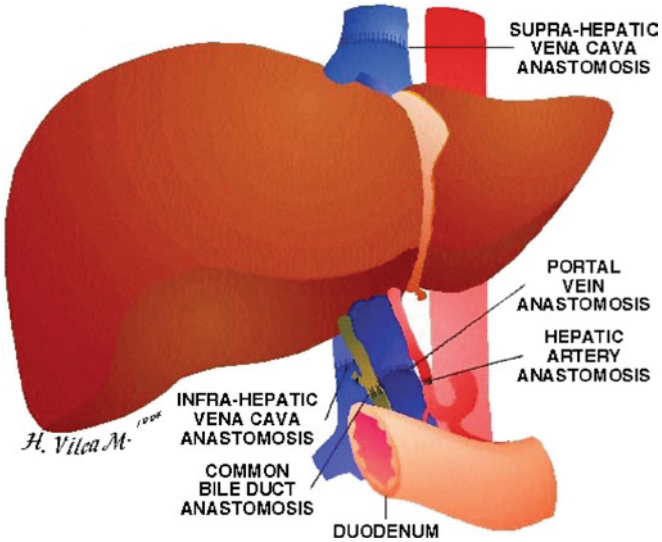

FIG. 53.1. Major vessels and anastomoses utilized on conventional liver transplantation.

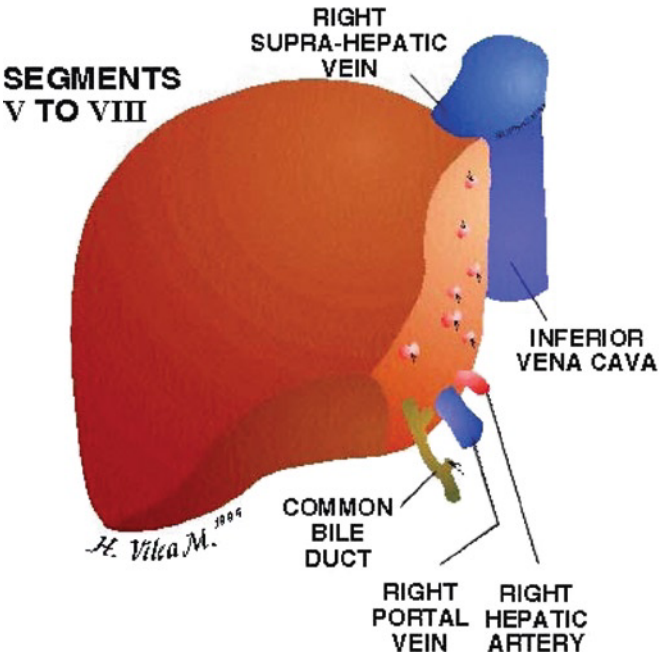

FIG. 53.2. Right liver segments used in "split" liver transplantation.

This intestinal anastomosis requires rest from feeding for up to 5 days postoperatively. In the case of a donor–recipient mismatch in bile duct diameter, or if the anastomosis is difficult, a T-tube may be inserted at the site of the anastomosis, its stem draining bile into a drain through the abdominal wall. Complex or suboptimal arterial anatomy may lead the surgeon to improvise arterial conduits from donor blood vessels (e.g., iliac), and knowledge of this will permit appropriate vascular investigations postoperatively.

Physiological Challenges During Surgery

Conventional LT involves several major physiological challenges beyond those usually associated with major abdominal surgery. These are encompassed in the three phases of LT, namely, hepatectomy, anhepatic phase, and reperfusion. During these phases the portal vein and IVC will be clamped, with consequent reduction in venous return to the heart, and de-clamped following implantation, which is associated with further cardiovascular disturbance due to recovery of pre-load and release of vasoactive substances from the donor organ. Additionally, there will be variable blood loss in the context of coagulopathy with the potential for major transfusion. The proximity of the liver and its venous drainage to the right atrium can lead to surgical interventions and complications above the diaphragm. Major hemodynamic variations are associated with poor outcome.[5]

The decision to employ veno-venous bypass is weighed by pros (reduction in hemodynamic disturbances during portal and caval clamping) and cons (extended operation time, extended anhepatic period, cannulation site complications), the patient's functional status, and the proposed implantation technique. The piggyback technique, in avoiding caval interruption, obviates the need for veno-venous bypass.

Immediate Postoperative Care

Electively transplanted CLD patients returning from the operating theater (OT) may be entirely stable, without the requirement of cardiovascular support, high inspired oxygen fraction or ventilatory support, renal support, or specific neurological therapy. If graft function proves satisfactory and there are no early surgical complications, such patients can be rapidly weaned from sedation and ventilation, extubated, and discharged to the general ward within 48 h. Management of the ALF and complicated CLD liver transplant patient will be divided into systems.

Cardiovascular

Hypotension requiring vasopressor support (e.g., norepinephrine) during surgery, typically following reperfusion of the graft, will in many cases prove transient. More severe degrees of cardiovascular instability require investigation into the possibility of previously unrecognized cardiac dysfunction, or the evolution of a new ischemic event. In the previously cirrhotic patient, right heart dysfunction in the context of pulmonary artery hypertension may need to be excluded (Fig. 53.3a, b). This requires pulmonary artery catheter insertion, which can provide pulmonary artery pressure (PAP), right ventricular end diastolic volume index (RVEDVI), and calculated right ventricular stroke work index (RVSWI). Pulmonary hypertension can be separated from right heart dysfunction by calculation of the trans-pulmonary gradient.

Mild (>25 mmHg) and severe (>35 mmHg) elevations in mean PAP in the absence of intrinsic pulmonary disease are likely to represent portopulmonary hypertension. Preoperative treatment with pulmonary artery vasodilators, such as intravenous prostaglandin E2 (epoprostenol), have achieved sufficient reductions in PAP to allow surgery[6]; however, published series in postoperative management are lacking. Nebulized or intravenous epoprostenol, the phosphodiesterase inhibitor

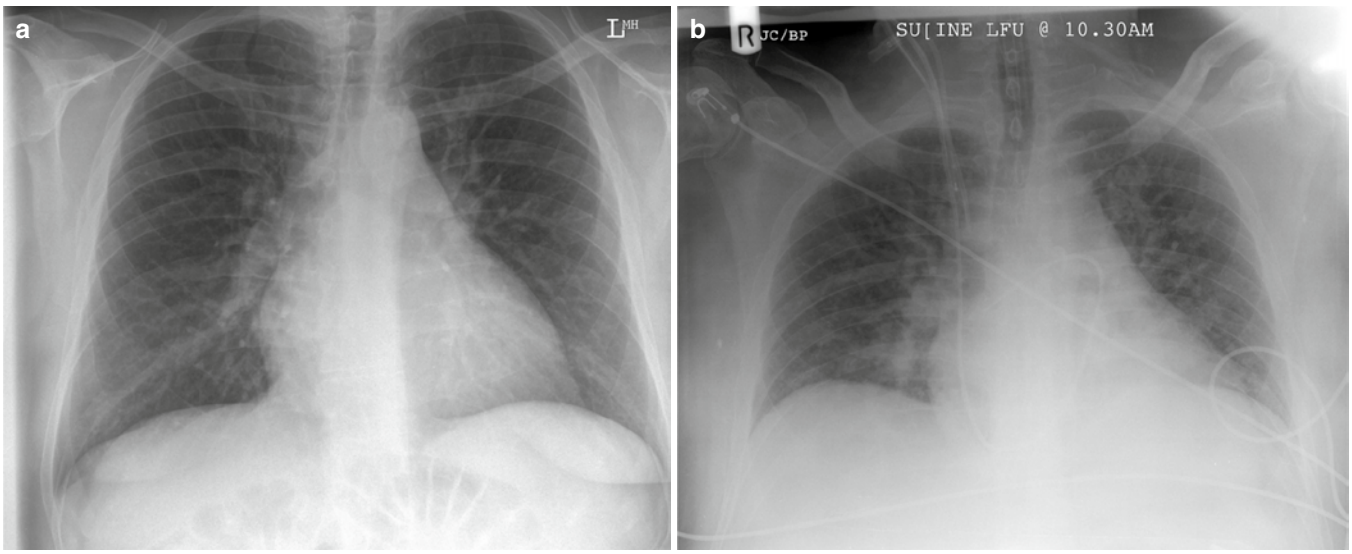

FIG. 53.3. (**a**) Pre-orthotopic liver transplantation (OLT) chest X-ray reported as normal in a man with end stage cirrhosis. There is pulmonary artery enlargement, indicating probable porto-pulmonary hypertension. (**b**) By 48 h post-OLT the patient was hypoxic and vasopressor- and inotrope-dependent. Pulmonary artery pressures via the Swan–Ganz catheter were 74/29 mmHg, and despite aggressive treatment with nebulized prostacyclin, bosentan, and sildenafil he succumbed due to cardiac failure 8 days later.

sildenafil, and the endothelin receptor antagonist bosentan have been used in this context.

Acute elevations in PAP and exacerbations in right ventriculo-arterial uncoupling occur during reperfusion. A hemodynamic study in patients with pulmonary artery (PA) hypertension demonstrated that although systolic ventricular function increased in response to the sudden change in pre-load, as per the Frank–Starling mechanism, afterload failed to decrease.[7] Use of dobutamine in this scenario demonstrated further increases in RVSWI and reductions in pulmonary afterload, with improved overall pulmonary hemodynamics.[8] Nevertheless, severe right ventricular dysfunction is associated with a poor prognosis.

Although most patients demonstrate high cardiac output with low peripheral resistance, global cardiac dysfunction is not uncommon in ALF, whether as a consequence of severe acidosis, or, in the case of acetaminophen, a direct toxic effect on the myocardium. Dobutamine is usually adequate in increasing cardiac output (CO); however, in more severe cases milrinone and levosimendan have been used. Evidence to support use of specific inotropes is lacking. Assessment of adrenal function by short Synacthen test and empirical hydrocortisone therapy is also indicated in the context of vasopressor or inotropic support, extrapolating from studies in acute hepatic dysfunction.[9]

Air embolism is a well-recognized complication of LT surgery. Air pockets within the donor portal venous anatomy may be mobilized during reperfusion,[10] air may enter during preparatory dissection of vessels within the recipient, and veno-venous bypass may itself result in this complication.[11] However, clinically significant volumes of air are unusual, and cardiovascular compromise will usually become apparent in the operating room (OR).

Respiratory

High inspired oxygen fraction on return from the OR may be a manifestation of cardiac (i.e., pulmonary hypertension and RV impairment – see above) or primary respiratory dysfunction. Examination of the respiratory system and chest radiograph may reveal pneumothorax, lobar collapse, or pulmonary interstitial edema. Accumulation of alveolar fluid may be due to volume overload, especially if a previously anuric but hemofiltered patient has undergone prolonged surgery without renal replacement. However, transfusion-related acute lung injury (TRALI) should be considered if blood products have been administered. Re-expansion pulmonary edema may also occur following intraoperative drainage of longstanding hepatic hydrothorax. Acute lung injury (ALI) progressing to acute respiratory distress syndrome (ARDS) is a complication of ALF, and may progress during and after LT. In patients with chronic liver disease, ALI/ARDS can also occur without any other identifiable precipitant, although this is unusual (Fig. 53.4). Covert respiratory tract sepsis, present prior to transplant, may progress in some patients. Pulmonary

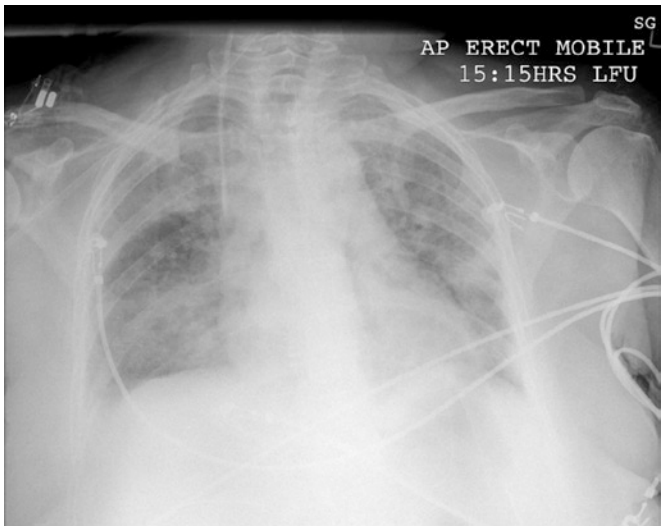

Fig. 53.4. Bilateral opacification 48 h after an uncomplicated elective OLT for primary biliary cirrhosis. ARDS developed and the patient died from respiratory failure despite excellent graft function.

infiltrates are common, seen in up to 44% of post-LT cases. In one study, pneumonia accounted for 38% of cases, pulmonary edema for 40%, and ARDS for 8%. Organisms isolated included methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Serratia marcescens*, and *Pneumocystis carinii*.[12]

There are no specifically favored ventilatory strategies post-LT; however, there are theoretical disadvantages in terms of liver blood flow with high positive end-expiratory pressure (PEEP).[13] This may limit venous return and lead to parenchymal congestion.[14] A recent human study found no impairment in systemic hemodynamics with short-term end-expiratory pressures up to 10 cmH_2O.[15]

Renal

RRT will often have been commenced prior to transplant in many ALF cases, and should be continued postoperatively. CLD patients with impaired creatinine clearance are at risk of further reductions in renal function in the context of cardiovascular instability and volume depletion, and 12% of all CLD may develop ARF after surgery,[16] the vast majority (>90%) of whom will regain function. Early RRT is favored if there appears to be a deteriorating trend in excretory function or sustained oligoanuria despite volume repletion and optimum perfusion pressure. Intraoperative administration of mannitol does not appear to preserve renal function.[17] Reno-protective immunosuppression strategies may be appropriate in cases of significantly impaired preoperative renal function, and these are discussed below.

Gastrointestinal

All patients should receive ulcer prophylaxis; this will normally be accomplished initially with proton pump inhibitors.

Enteral feeding can usually be commenced unless a new hepaticojejunostomy has been fashioned, or there are other surgical contraindications. If edema of intra-abdominal contents has developed, or a relatively large graft has been implanted in proportion to the size of the abdominal cavity (e.g., in small, female patients), primary closure of the abdomen may not be possible. In these cases the patient will be returned to the intensive care unit (ICU) with a dressing over the laparotomy. Closure will take place within 2–10 days according to the surgical assessment, and feeding is likely to be unaffected. Intra-abdominal pressure (IAP) should be monitored several times per day in all patients. Increased IAP (>25 mmHg) may occur in more than 30% of patients, and is associated with development of renal failure, prolonged ventilatory weaning, and death.[18] Further laparotomy may be considered if IAP rises, with formation of decompressive laparotomy.

Pancreatitis occasionally complicates ALF, and is a relative contraindication to urgent transplantation due to the high associated postoperative mortality. Clinical suspicion may be aroused during assessment by abdominal distension, raised IAP,[19] peritonism, and raised serum amylase. However, the systemic inflammatory response is common in both ALF and pancreatitis, and typical signs may be masked by sedation/paralysis.

Neurological

Fluctuations in cerebral perfusion pressure have been well reported during the first 10 h after surgery, putting the patient with ALF at risk for ICH in the immediate postoperative period.[20] Continued "fulminant care" is usually required while satisfactory graft function and the absence of suspicious neurological features are confirmed. If an intracranial pressure system has been inserted and raised pressures are detected, deep sedation strategies are required (and other pharmacological interventions if necessary) until the graft begins to exert a beneficial effect. Neurological dysfunction and risk of maintained surges of ICP will normally have reduced by 48 h. Focal signs in the context of acute or chronic liver failure should be aggressively investigated. The fear of complicating intracranial hemorrhage in the context of coagulopathy and/or thrombocytopenia and reduced level of consciousness may prompt consideration for computerized tomography (CT) scanning. Porto-systemic/hepatic encephalopathy in CLD patients can cause a multitude of signs, including asymmetrical clonus, hyper-reflexia, dysconjugate gaze, and pupillary dilatation. However, these are rarely seen in the post-transplant period. Subclinical seizures may occur in ALF,[21] and high index of suspicion should be maintained. CT may be indicated to exclude development of a focal lesion acting as an epileptiform focus. Other neurological complications in the early post-transplant period include central pontine myelinolysis (CPM) and paradoxical air embolism.[22] CPM, which typically occurs in cirrhotic patients who enter surgery with hyponatremia, results in quadriplegia and brain stem signs, and requires magnetic resonance imaging (MRI) to confirm the diagnosis.

Hematological

Patients often receive large volumes of platelets, fresh frozen plasma (FFP), and cryoprecipitate during surgery; and problems with hemostasis in the surgical field will mandate further transfusion on return to the ICU. However, coagulation indices represent a sensitive and early marker of graft function, so it is preferable to withhold further plasma, in the absence of bleeding, in order to gauge synthetic function in the first early period (see assessment of graft function). Full coagulation assessment with laboratory parameters and thromboelastography should be undertaken regularly in those with evidence of bleeding. The administration of FFP and cryoprecipitate should be discussed with the surgical team.

Antimicrobial Prophylaxis

Bacterial infection post-LT is common, with gram-negative organisms predominating in recent years.[23] Bacteremia may be present in up to 21% of donors, and this may result in transmission.[24] Piperacillin–tazobactam (Tazocin®) was shown to be more effective in preventing infection than ciprofloxacin and amoxicillin in a randomized controlled trial (RCT) involving 217 LT cases.[25] Invasive fungal infection (candidiasis, cryptococcosis, or aspergillosis most frequently) complicates 4–11% of LT patients,[26,27] the median time to diagnosis being 17 days post-LT.[28] Interventions to reduce the risk of oral candidiasis are normally undertaken. Fluconazole interacts with tacrolimus and increases serum levels, so close monitoring of tacrolimus levels is required if fluconazole is started or the dose increased. A recent randomized trial demonstrated a marked reduction in the incidence of infection post-LT (to 3%) with the introduction of a lactic acid bacteria and fiber enteral supplement.[29]

ALF is a profoundly immunosuppressing condition, bacterial infection being identified in 60% of cases in one large study.[30] Fungal sepsis (usually candida species) has been reported in more than 30%.[31] The respiratory tract was identified as the source of sepsis in approximately 50%. Broad antibacterial and antifungal microbial prophylaxis would normally be commenced at the time of listing in the case of ALF, and continued as clinically and microbiologically indicated in the post-transplant period (e.g., piperacillin–tazobactam 4.5 g IV t.d.s., fluconazole 200 mg IV o.d.). Patients whose clinical course is complicated by bowel perforation, or in whom infected bile collections have developed (e.g., ischemic cholangiopathy complicating hepatic artery thrombosis), will need antifungal coverage (e.g., amphotericin 1 mg – 3 mg/kg daily).

Graft Failure and Dysfunction

The major ischemic/anoxic insult suffered by a graft during removal and transportation results in a degree of hepatocellular dysfunction. A large number of mediators, including

reactive oxygen intermediates, are released resulting in a final pathway of neutrophil-mediated hepatic injury.[32] The reported incidence of clinically apparent graft dysfunction is up to 7%. Although donor factors such as advanced age, cardiovascular compromise prior to harvesting, raised body mass index, significant hepatic steatosis, and cold ischemia time are associated with reduced or delayed function, predicting graft dysfunction on an individual basis is very difficult.[33] A recent multivariate analysis indentified steatosis and non-cranioencephalic trauma as the only predictive factors.[34]

Clinical Picture

Definitions of primary graft non-function (PNF) and primary graft dysfunction (PGD) have been published (Table 53.2); however, in practice a combination of factors including extra-hepatic organ dysfunction will lead clinicians to suspect that the transplanted liver is not functioning well. The patient transplanted electively for CLD or urgently for ALF with a non-functioning graft will resemble a patient with ALF; worsening lactic acidosis, coagulopathy, and tendency to hypoglycemia will be observed. Cardiovascular instability and renal failure may ensue. Although worsening encephalopathy will not be detected in the sedated patient, ICH will not improve. Bile production will be absent, but cannot be assessed unless a T-tube is in situ. PNF requires early recognition as the only recourse is to re-list and offer a further transplant.

PGD manifests the same features but to a lesser degree. Extra-hepatic organ function can remain stable, but lactate may rise, measures of coagulation may appear to deteriorate rather than improve, and level of consciousness may remain subnormal even if the patient was lucid (in the case of CLD) before anesthesia.

A rarer explanation for apparent poor graft function is "small-for-size syndrome" (SFSS), in which the mass of hepatocytes is unable to cope with the excretory, metabolic, and synthetic demands of the body. This becomes apparent later than PGD, at day 4–5. SFSS has become more common as the splitting of donor organs and the use of living-related segments has become established.[35] Radiological studies have suggested that a graft-to-recipient body weight ratio of ≥0.8% is required to avoid the syndrome. The patient will display features of liver insufficiency, in particular progressive cholestasis, ascites formation, and coagulopathy.[36] Graft dysfunction may also be caused or exacerbated by right heart failure or high vasopressor therapy.

Table 53.2. Definitions of primary graft dysfunction and failure.

Ploeg et al.		
Primary dysfunction		
AST > 2,000 U/L	Day 2–7	
Prothrombin time >16 s		
Primary non-function		
Death or re-transplantation	Day 1–7	
Gonzales et al.		
Cumulative score	7–9: severe graft dysfunction	
	5 or 6: moderate graft dysfunction	
	3 or 4: good graft function	
Parameter	Assigned value	
ALT (U/L)		
<1,000	1	
1,000–2,500	2	
>2,500	3	
Bile output (mL/24 h)		
>100	1	
40–100	2	First 72 h
<40	3	
Prothrombin activity (%)		
>60	1	
>60 while receiving FFP	2	
<60 destpite receiving FFP	3	

Management of PGD

In the absence of PNF (for which the patient will require re-transplantation), or of hepatic artery thrombosis (HAT), therapy is directed at reducing the oxidative stress associated with ischemia/reperfusion, and improving microvascular perfusion. Infusion of prostaglandin E2 (epoprostenol), a potent vasodilator, has been shown in two RCTs to improve morbidity; however, the incidence of PNF/PGD was not altered.[37,38] Numerous case studies and uncontrolled series have described reversal of PGD with its use, and it is commonly utilized in this situation. The evidence base for *N*-acetylcysteine infusion is less well established. Benefits attributed to its anti-oxidative properties have been described.[39,40] It can be infused at 150 mg/kg per day.

Immunosuppression

Immunosuppressive strategies will vary according to the policy at individual centers, and a full review of current combinations is beyond the scope of this chapter. Problems with immunosuppression in the ICU relate to toxicity and opportunistic infection.

Tacrolimus-based immunosuppression was shown to have advantages over cyclosporin A in 1994[41] in terms of cellular rejection, and is the most common agent currently utilized. It is neurotoxic at high serum concentrations, and is an important cause of seizures in the early post-LT period; high trough levels will usually be found. It is nephrotoxic, and if the risk of postoperative renal failure appears significant caution is required. "Renal-sparing" induction agents may be used, allowing some delay before institution of calcineurin inhibitors. These include the humanized monoclonal IL-2 receptor blocking antibody daclizumab, antithymocyte globulin (ATG), and monoclonal anti-T-cell antibody (muromonab-CD3, or OKT3). Risks of ATG and OKT3 are an increased incidence of opportunistic infections (discussed below) and development of lymphoma. Drug interactions with tacrolimus are common, and are summarized in Table 53.3.

Table 53.3. Selected interaction with calcineurin inhibitors tacrolimus and cyclosporin A.

Increasing blood concentrations	Decreasing blood concentrations
Antifungal agents	*Anticonvulsants*
Fluconazole	Carbamazepine
Itraconazole	Phenytoin
Ketoconazole	Phenobarbital
Macrolide antibiotics	*Antibiotics*
Clarithromycin	Rifampin
Erythromycin	Rifabutin
Azithromycin	
Calcium channel blockers	*Others*
Diltiazem	Terbinafine
Verapamil	
Nifedipine	
Prokinetic agents	
Cisapride	
Metoclopramide	
Others	
Amiodarone	
Cimetidine	
Omeprazole	

Rejection

Acute cellular rejection (ACR) occurs in approximately 30% of recipients around 5–10 days post-LT. It is signified by acute elevations in transaminases and frequently fever. However, sepsis and ischemic insults (during episodes of shock) may also result in mild to moderate transaminase elevations, and differentiating these causes can be challenging. Pulsed methylprednisolone, the standard treatment of ACR, may represent a further challenge to the already immunosuppressed, possibly septic, ventilated patient. Liver biopsy, to confirm or exclude acute cellular rejection, is relatively contraindicated in patients in renal failure, because of the risk of bleeding. Management of early rises in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) requires detailed discussion with the multidisciplinary team (MDT), although a pragmatic approach may require empirical steroid therapy with broad spectrum antimicrobial coverage. Transjugular liver biopsy may also be considered, as the risk of hemorrhage is reduced. Steroid-resistant rejection will require specialized interventions, for example, the induction agents discussed above.

Other Early Graft-Related Considerations

The etiology of liver failure may mandate particular measures. ALF secondary to hepatitis B virus (HBV) is usually associated with complete viral clearance; however, passive anti-viral prophylaxis with pooled hepatitis B immunoglobulin is administered to bind free virus and reduce the risk of early graft viral infection. Regular serum hepatitis B surface antibody and HBV DNA levels are required to direct further dosing and antiviral therapy. Patients with cirrhosis secondary to HBV will have been taking effective antiviral agents, and viral replication at the time of LT should be undetectable. Nevertheless, passive immunization is essential. ALF secondary to other viral hepatitides such as Epstein–Barr virus (EBV), cytomegalovirus (CMV), or herpes simplex virus (HSV) will require specific antiviral coverage. Formal anticoagulation in veno-occlusive conditions such as Budd–Chiari syndrome will be indicated, and the timing of this requires close liaison with the surgical team, bearing in mind the risks of early bleeding.

Further Monitoring of the Graft

Laboratory Tests

Liver function tests should be performed on a daily basis. Transaminases will be raised during the first postoperative day; however, levels should fall exponentially thereafter. AST or ALT that does not fall according to this pattern is compatible with dysfunction. Coagulation indices should be monitored every 8–12 h during the first day, then daily. Development of a cholestatic profile is not uncommon, and may represent delayed function of the biliary transport mechanisms within the hepatocytes. A more sinister cause of cholestasis, in the patients transplanted for hepatitis B or C, is fibrosing cholestatic hepatitis (FCH), a rapidly progressive, destructive manifestation of early viral reinfection.

Imaging

An ultrasound should be performed routinely on the first and fifth days to ensure continued patency of the hepatic artery (HA), hepatic vein (HV), and portal vein (PV). If flow is not seen in the HA, CT angiography is usually required to delineate the vasculature. Should hepatic artery thrombosis (HAT) be confirmed (Fig. 53.5a, b), the usual approach is re-transplantation; however, interventional radiology may have a role in reperfusion (e.g., balloon dilatation, stenting, or regional thrombolysis) with reported success of 50–88%.[42,43] Reported inaccuracy of ultrasound scan (USS) in detecting HAT is 10%, and strong clinical suspicion (large elevations in AST/ALT, synthetic dysfunction) should prompt CT, MRI, or invasive angiography. Infarction of the graft without visible HA obstruction ("non-thrombotic infarction") can occur, resulting in graft failure.

Although lack of biliary dilatation on USS would suggest that mechanical obstruction to bile flow is not present, intrahepatic bile ducts in transplanted livers do not tend to distend. If early obstruction to bile flow is suspected, a functional investigation (such as a hydroxy iminodiacetic acid [HIDA] scan) may be required to demonstrate bile production and adequate flow through the biliary tree. In some centers this investigation is routine during the first 3 days.[44] Fibrosis and contraction of tissue at the biliary anastomosis may cause stricturing of the bile duct, although the incidence of this complication is now low (<5%) and should not become apparent in the early postoperative period. Bile leaks are of greater

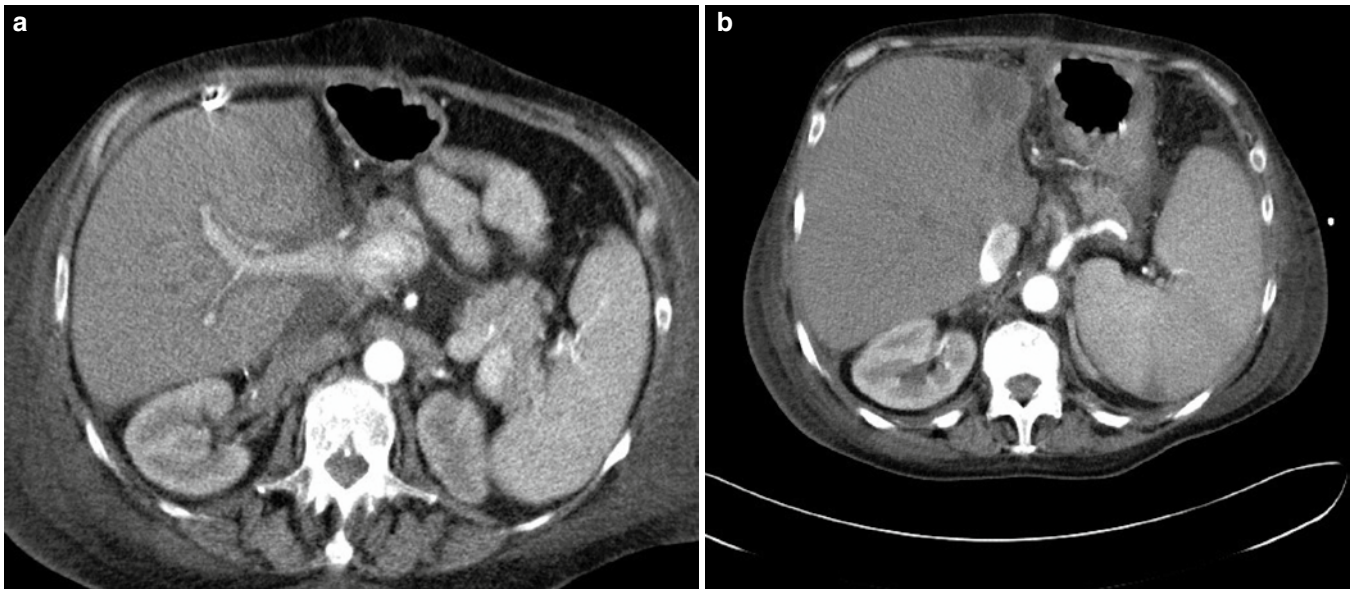

FIG. 53.5. (**a**) Arterial phase contrast enhanced CT scan of a right lobe split-liver graft demonstrating normal arterial and portal vein perfusion. (**b**) A further arterial phase contrast-enhanced scan of the same graft demonstrating proximal occlusion of the hepatic artery and an area of necrosis at the anterior right margin. The patient required re-transplantation.

immediate concern, their incidence being between 1% and 10%. Identification of an enlarging collection beneath the liver or near the porta will require diagnostic aspiration and drainage if a collection of bile is seen (biloma). Extended antibacterial and antifungal prophylaxis will be required, and formal surgical revision undertaken. Any biliary stricturing or leaking should result in interrogation of the arterial supply to ensure patency.

Postoperative Bleeding

Ten to fifteen percent of LT patients will need further laparotomy to investigate and manage abdominal hemorrhage. Sources of bleeding include injuries sustained to the donor liver during harvesting (lacerations to liver surface, untied small vessels around the gall bladder bed, or accessory veins draining into the vena cava), failure of hemostasis during removal of the diseased native liver, and failure to seal major vascular anastomoses.

Major bleeding may be signified by appearance of fresh blood in drains, although poor positioning of the drains and blockage during the initial period of hemostasis may result in retention of blood within the peritoneal cavity. Preexisting ascites and further ascites production post-LT may dilute the blood in the drains. Laparotomy may be indicated if there is hemodynamic instability or if transfusion requirement exceeds 4–6 U of blood/packed cells over a 24-h period; close consultation with the surgical team is required.

Late rupture of vascular anastomoses, with catastrophic bleeding, can occur in the context of postoperative intra-abdominal sepsis.

Days 1–7

Ventilatory Weaning and Decision to Perform Tracheostomy

In CLD patients, extubation can normally be achieved within 12–24 h of LT in the absence of important surgical or adverse cardiorespiratory complications. In ALF a longer recovery time is to be anticipated, although rapid global improvement, the absence of critical illness myopathy, and resolution of encephalopathy allow early extubation within the first week. Percutaneous or surgical tracheostomy will be required if prolonged ventilatory support is required. Significant graft dysfunction is independently associated with requirement for ongoing ventilation.[45] Complete diaphragmatic paralysis was found in 10 of 48 LT patients in one study, paralysis of the right diaphragm affecting another 11, with an associated prolongation in ventilation.[46]

Sepsis

Sepsis and septic shock are difficult to confirm in ALF due to its highly inflammatory and vasodilatory nature; however, progressive cardiovascular deterioration in the absence of primary cardiac dysfunction may represent uncontrolled infection. Vascular catheter-related infection is common, and old lines (>7 days) should be changed. Chest X-ray changes due to ALI are common in ALF and may not represent infection; however, tracheal aspirates and broncho-alveolar lavage will be useful in excluding resistant organisms not treated by first-line agents. Intra-abdominal sources of sepsis may include infected hematomas, collections related to

pancreatitis, and, rarely, intestinal ischemia seen in ALF or in association with severely raised IAP. CT scanning and/or laparotomy may be required.

The First Month

Specific complications encountered in the ICU after the first week include opportunistic infections and bone marrow dysfunction.

Early Opportunistic Infection

Opportunistic infections encountered during the first month include disseminated herpes simplex 1 or 2 and cytomegalovirus reactivation. HSV is a cause of early graft dysfunction, and usually requires detection by polymerase chain reaction (PCR) to prove the diagnosis. Patients without prior exposure (anti-CMV IgG negative pre-LT) who receive livers from CMV-exposed donors are at risk of primary CMV infection, and previously exposed patients may suffer reactivation. Blood should be sent for CMV DNA measurement on a weekly basis while in the ICU, and treatment with an antiviral agent (ganciclovir, valganciclovir) commenced if DNA is detected. CMV viremia may present with fever, a hepatitic LFT profile, deteriorating respiratory function with CXR infiltrates, or diarrhea.

Bone Marrow Dysfunction

Falling platelet, white blood cell, and hemoglobin counts are commonly seen in post-LT patients in the ICU. Thrombocytopenia may be heparin induced (HIT, type 1 and 2) requiring specific hematological investigation. Generalized bone marrow suppression is a well-established side effect of ganciclovir and valganciclovir. An important and possibly underrecognized cause of bone marrow dysfunction is acquired hemophagocytic lymphohistiocytosis (HLH), or reactive macrophage syndrome. Unregulated macrophage stimulation in the context of viral infection and/or immunosuppression results in auto-ingestion of cell lines, typically accompanied by the following clinical and laboratory features: fever, serous effusions and ascites, hepatosplenomegaly, skin rashes, hyperferritinemia, and hypertriglyceridemia. Diagnosis requires bone marrow examination; and treatment, although without a firm evidence base, comprises intravenous immunoglobulin and antiviral agents.

Outcomes

Despite counseling during assessment for LT, relatives of patients transplanted for cirrhosis may be surprised if the transplant operation does not appear to bring about rapid improvement in physical condition. Although liver function may be good, failure of other organs and systems in the postoperative period may result in prolonged ICU stays, survival from which cannot be guaranteed. A change of emphasis from liver disease to multiple organ dysfunction, with an attendant shift in expectation, must be achieved.

In ALF, where the time scale from diagnosis to surgery is far shorter and emotionally challenging to relatives, it is usual for the condition's severity and poor prognosis to have been emphasized before surgery. Perioperative and 3-month mortality rates are higher than in elective transplants, and multiple organ dysfunction, being a part of the ALF syndrome, will be anticipated.

Outcome studies in transplant patients have been shown that the requirement of mechanical ventilation, duration of mechanical ventilation, requirement for dialysis, development of pulmonary infiltrates, and ICU-related infections during the ICU stay are significantly associated with mortality. However, no discrepancy in postdischarge quality of life was found when survivors (82% in this study) were compared to those who did not require ICU. This observation may bring some comfort to relatives who fear that the patient, especially following tracheostomy and with evident global muscular weakness, will be wheelchair bound and dependent.[47]

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54
Postoperative Care of the Pancreas-Transplant Recipient

Shimul A. Shah and Rodney J. Taylor

Diabetes mellitus (DM) affects about 5% of the population and represents the eighth leading cause of death in the United States.[1] It is the leading cause of renal failure and blindness in adults and the most frequent, underlying disease leading to amputations.[2] Whole-organ pancreas transplantation is no longer an experimental procedure but a valid therapeutic option for patients with type I DM. For patients who are dependent on exogenous insulin for survival, the objectives of pancreas transplantation include insulin independence and normoglycemia, improvement in quality of life, and amelioration of secondary complications of DM.

The procedure has two important variants. It is indicated for patients with DM associated with chronic renal insufficiency as a simultaneous pancreas–kidney transplant (SPK) or as a pancreas after kidney transplant (PAK). It is also indicated in patients with uncontrollable insulin-dependent DM or documented metabolic complications without renal insufficiency as a pancreas transplant alone (PTA). SPK transplants are the most common type performed in the United States, representing 63% of all pancreas transplants in 2005.

A marked improvement in graft survival rates after pancreas transplantation has occurred in recent years. This can be attributed to improvements in immunosuppressive regimens and surgical techniques.[3–5] Unadjusted graft survival from 1996 to 2004 was highest after SPK transplantation with 1-, 3-, and 5-year rates of 85, 79, and 71%; conversely, graft survival rates after PAK and PTA at 1, 3, and 5 years were 79, 68, and 56% and 73, 58, and 53%, respectively (Fig. 54.1).[5,6]

The care of patients who have undergone pancreas transplantation in the surgical intensive care unit (SICU) is unique to other surgical patients. The general preoperative condition of these patients is commonly severely impaired due to their long-standing DM, which may lead to severe complications involving various organs and functions. These include nephropathy, blindness, myocardial infarction, neuropathy, gastroparesis, and peripheral vascular disease (Table 54.1).[7,8] Appropriate fluid and electrolyte resuscitation in addition to close monitoring of hemodynamic status and immunosuppression are essential to ensure favorable outcomes. This chapter reviews the evaluation and selection of the pancreas transplant recipient, the operative procedure, their immediate postoperative care, and potential complications.

Indications

Table 54.2 outlines the indications and options for pancreas transplantation. Candidates for SPK are type I diabetics with severe nephropathy leading to chronic renal insufficiency (creatinine clearance <20 ml/min) regardless of whether they are treated conservatively or with replacement therapy. Due to the high annual mortality rate of patients with type I DM waiting on the SPK waiting list (87 per 1,000 patient years) and the increasingly longer waiting times, it is now common for patients to first undergo a life-saving living donor kidney transplant (either living or deceased donor) followed by a PAK transplant.[5]

The indications for PTA are more restrictive. Specific listing criteria for patients for PTA include: (1) patients must have a diagnosis of type I DM confirmed by beta cell autoantibody or fasting C-peptide less than or equal to 110% of the

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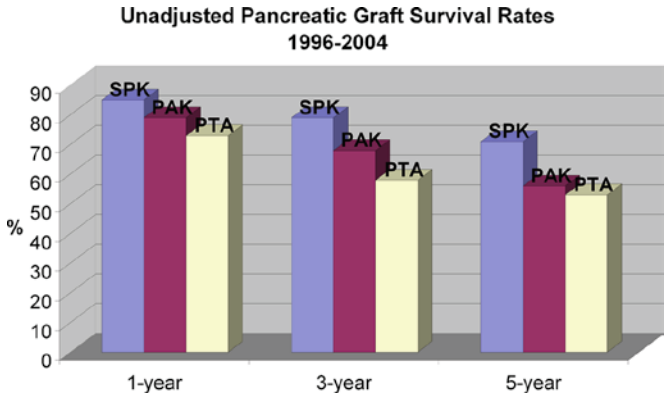

FIG. 54.1. Unadjusted 1-, 3- and 5-year pancreas graft survival by transplant type for transplants received 1999–2004. Data from the Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients.[5,6]

TABLE 54.1. Prevalence of complications of patients with onset of insulin dependent diabetes mellitus before age of 31.[7]

Complication	Cumulative prevalence
Visual impairment	14%
Blindness	16%
Renal failure	22%
Stroke	10%
Amputation	12%
Myocardial infarction	21%
Median survival after diagnosis	36 years
Median age at death	49 years

TABLE 54.2. Indications and options for pancreas transplantation.

Indications
Complications due to type I DM especially uremia
Brittle diabetics who fail maximal medical therapy
Successful completion of extensive pre-transplant evaluation
Options: uremic patients
Simultaneous pancreas/kidney transplant(SPK)
Pancreas after kidney transplant (PAK)
Options: non-uremic patients
Pancreas transplant alone (PTA)

laboratory's lower limit of normal, and with a concurrently obtained fasting glucose ≤225 mg/dl; (2) patients must have medically uncontrollable labile insulin-dependent DM with documented life-threatening metabolic complications that require hospitalization; (3) patients must have been optimally and intensively managed by an endocrinologist; or (4) patients have documented episodes of hypoglycemic unawareness.[5]

Evaluation and Recipient Selection

Potential recipients are referred to a transplant center and undergo a multidisciplinary evaluation performed by members of the transplant team including transplant surgeons, transplant nephrologists, endocrinologists, nurse coordinators, social workers, and financial counselors. Absolute contraindications to pancreas transplantation include active infection, and a recent or current history of malignancy. Morbid obesity (body mass index>40), advanced cardiovascular disease, advanced age (>60 years), and a history of poor compliance or substance abuse are relative contraindications (Table 54.3). For patients being evaluated for PTA, a 24-h creatinine clearance should be performed to confirm a clearance >60 ml/min. As their renal function deteriorates, patients with a reduced creatinine clearance (<60 ml/min) may be considered for SPK or for a kidney transplant with a PAK to follow.

TABLE 54.3. Exclusion criteria for transplantation.

Active malignancy or previous metastatic disease
Active infection
Substance abuse
Active psychosis
Lack of comprehension
Lack of financial/social support
Non-revascularizable cardiac disease
Severe peripheral vascular disease
Obesity (body mass index > 40)
Noncompliance

After a suitable candidate has been identified, an immunologic evaluation, cytomegalovirus, infectious disease profile, human leukocyte antigen (HLA) and ABO typing, panel reactive antibody screening, basic blood chemistries, complete blood count, chest x-ray, coagulation studies, and, if necessary, vascular studies are performed. Cardiac evaluation consists of electrocardiogram, echocardiogram stress test, and possible coronary catheterization. Due to the long waiting times for transplant, patients must be evaluated and updated annually to be sure they continue to be suitable candidates for transplantation. Given the high incidence of gastroparesis and peptic ulcer disease in this population, additional upper gastrointestinal (GI) series or endoscopy may be necessary, depending on symptoms. Patients with frequent foot infections or nonhealing ulcers may warrant complete assessment of the degree of peripheral vascular disease by a vascular surgeon and possible lower extremity arteriography. Any concern for patency or severe calcification of the iliac arteries should prompt a Doppler ultrasound or magnetic resonance arteriography (MRA).

Operative Technique

A successful pancreas transplant begins with appropriate donor selection (Table 54.4). All donor exclusion criteria are relative in terms of absolute or individual. Each candidate needs to be evaluated on that basis.

Backbench preparation of the donor pancreata requires construction of an iliac Y graft to the splenic and superior mesenteric artery as they emanate from the pancreas. Careful handling of the gland is a priority to reduce the

risk of pancreatitis after reperfusion. Once the patient is anesthetized, a large-bore Foley catheter, nasogastric tube, arterial line, and a central venous catheter are placed. A generous midline incision is made and a careful abdominal exploration is performed. For SPK transplantation, the authors prefer to transplant the kidney first in the left iliac fossa. The pancreas transplant, regardless of type, should be placed on the right side if available.[9] There are several different types of transplant techniques (Fig. 54.2). The external iliac artery and vein are dissected and mobilized. If the external iliac artery is heavily calcified and not amenable to an anastomosis, the graft can be placed more cephalad with the arterial anastomosis performed to the recipient's common iliac artery and the venous anastomosis to the inferior vena cava. Alternatively, the venous drainage can be linked to the recipient portal circulation via the superior mesenteric vein.[10] This technique is believed to be more physiologic and avoids systemic insulin delivery.[11,12] After the vascular anastomoses are completed, blood sugars should be closely monitored as serum glucose levels typically drop 50 mg/dl each hour. Dextrose solutions may be required to prevent hypoglycemia.

The duodenal segment is then prepared for anastomosis. The authors prefer an enteric anastomosis to a proximal loop jejunostomy; a Roux-en-Y jejunostomy is preferred at some centers to isolate the pancreatic secretions and reduce enteric contents from passing near the transplanted pancreas. If bladder drainage is preferred, the duodenal segment can be sewn to the bladder dome. Peripancreatic drains may be used in an attempt to reduce deep and superficial wound infections.[13]

Table 54.4. Deceased-donor criteria for pancreas transplantation.

Age: 10–45 years
Body mass index < 30
No history of glucose intolerance
No history of pancreatitis
No hemodynamic or ventilatory compromise
HLA match optimized for PAK or PTA

Table 54.5. Pancreas transplant hospital course.

Pre-op preparation
Operative procedure (4–6 h)
Hospital stay (7–12 days)
ICU routinely 1–2 days
Immunosuppression
Antibody induction
Calcineurin inhibition
Antimetabolite
Steroids (+/–)
Infection prophylaxis
Antiviral
Antibacterial
Anticoagulation perioperatively

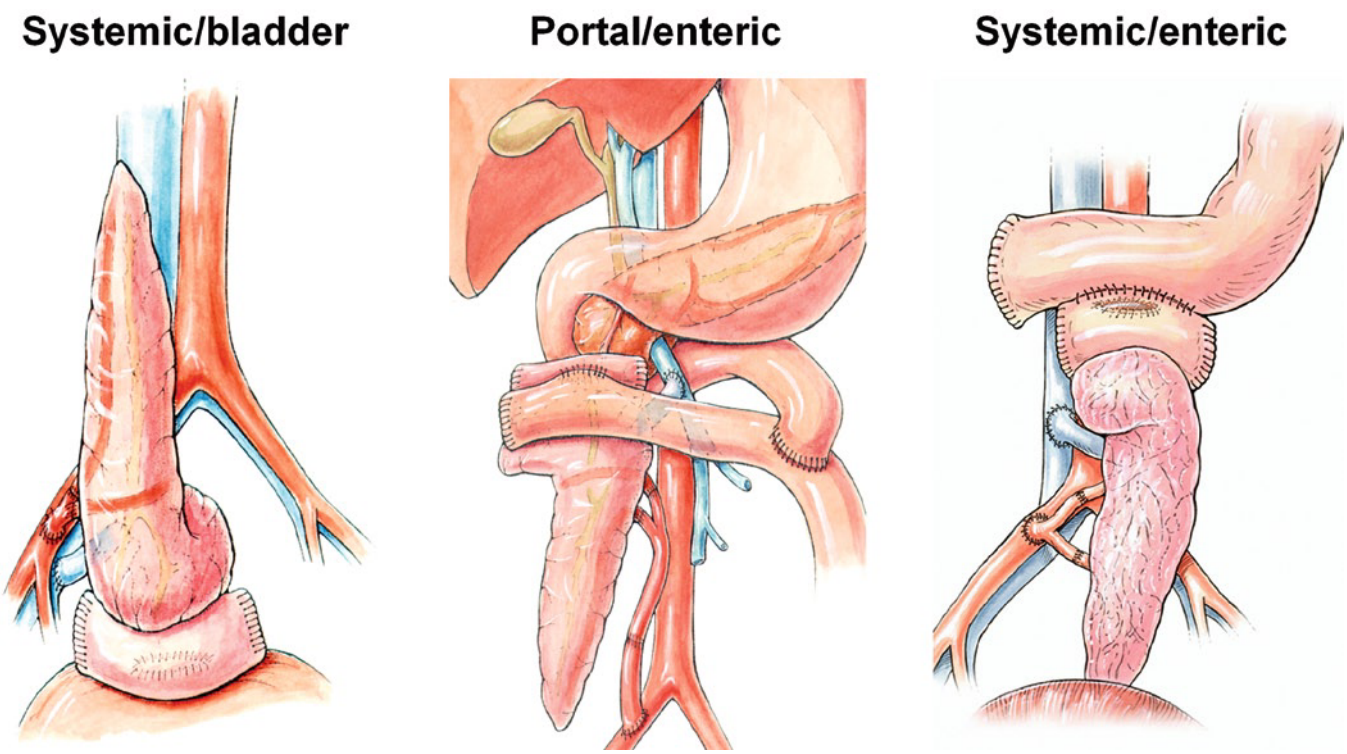

Fig. 54.2. Different techniques of pancreas transplantation.

Immunosuppression

The long-term success of organ transplantation is dependent on suppression of the immune system. Most immunosuppressive drugs are nonspecific, resulting in generalized immunosuppression, which places the recipient at increased risk of infection. Therefore, strict use of aseptic technique and surveillance of indwelling catheters are warranted in the SICU.

Immunosuppression is required indefinitely to achieve long-term graft survival. Chronic use makes recipients susceptible to opportunistic infections and cancer. The mainstay of any immunosuppressive protocol is to prevent graft rejection by blocking the immune response of the recipient. Current protocols for pancreas transplantation typically involve triple- or quadruple-drug therapy with use of an antibody induction agent, steroids, tacrolimus or cyclosporine (CsA), and mycophenolate mofetil (MMF) (Table 54.5).

Corticosteroids (methylprednisone or prednisone), the first immunosuppressive medications used in transplantation, are the mainstays of many immunosuppressive regimens. Corticosteroids are potent immunosuppressive and anti-inflammatory agents that inhibit the secretion of IL-1 by macrophages. Most protocols begin with a high-dose burst of steroid therapy given intraoperatively, followed by a stepwise dose reduction. Side effects of chronic corticosteroid use include impaired glucose tolerance, hypertension, weight gain due to sodium and fluid retention, peptic ulcer disease, Cushing's syndrome, and delayed wound healing. Due to these side effects, there has been increasing use of steroid-free regimens in pancreas transplantation.[5,14] The use of steroids in maintenance immunosuppression decreased to 65–71% of SPK or PAK patients, and only 52% of PTA recipients in 2005.[5]

Tacrolimus (FK506 or Prograf) is a macrolide antibiotic that inhibits IL-2 and cytotoxic T-cell generation. The IL-2 blockade is associated with a decreased response to class I and II antigens that are critical for rejection. Metabolism occurs primarily in the liver under the influence of cytochrome P450. Side effects include nephrotoxicity, neurotoxicity, hyperglycemia requiring insulin therapy, hyperkalemia, hypercholesterolemia, and alopecia. Patients with preexisting neurologic conditions, such as seizure disorders, appear more susceptible to neurotoxicity. The hyperglycemia, related to depletion of islet cells, appears to be reversible with dose reduction or cessation of tacrolimus.

Cyclosporine (CsA), first used in 1980, sparked the rapid expansion of organ transplantation due to the dramatic improvement in graft survival rates. CsA is similar to tacrolimus in mechanism, metabolism, and side effect profile. It has fallen out of favor recently; more than 85% of pancreas transplant recipients are currently maintained on tacrolimus.[5] This is due to a perceived superior efficacy, ease of clinical use, and patient compliance of tacrolimus over CsA.

Mycophenolate mofetil (MMF) is an antimetabolite that inhibits lymphocyte proliferation, thus inhibiting both cell-mediated and humoral immunity. Its relatively selective effect on lymphocyte activation allows it to be used in doses that are strongly inhibitory to lymphocytes without major side effects on other proliferating cells. Its major adverse effects include diarrhea, nausea, abdominal pain, and gastritis. More than 80% of current recipients have MMF in the maintenance regimen.[5]

The use of induction therapy has been shown to significantly improve pancreas graft survival rates. Anti-thymocyte globulin (ATG; Thymoglobulin) consists of polyclonal antibodies with a broad range of immunological effects and properties. They bind to cell surface receptors, thereby opsonizing lymphocytes for complement-mediated lysis or reticuloendothelial cell-dependant phagocytosis.[15,16] ATGs recognize most of the molecules involved in the T-cell activation cascade such as CD2, CD3, CD4, CD8, CD11a, CD18, CD25, HLA DR, and HLA class I. Although lymphocyte depletion constitutes the primary mechanism of the immunosuppressive effects of ATG, other mechanisms such as blocking of adhesion molecules and apoptosis induction are involved. The administration of ATG can result in a massive cytokine release characterized by high fever, chills, nausea, vomiting, flushing, and, rarely, anaphylaxis. The onset of the symptoms occurs most during the initial doses of ATG. It should be dosed for a total of 5–7 mg/kg usually administered over 7–10 days. ATG has been proven to be useful in pancreas and combined kidney–pancreas transplantation as induction therapy.[17,18]

Alemtuzumab (Campath-1H) is a monoclonal anti-CD52 antibody, which has been used off label in solid organ transplantation.[19] It has been primarily used as an induction agent at the time of transplantation; there is limited experience in its use to treat steroid-resistant rejection. Prolonged lymphocyte depletion can be expected following alemtuzumab treatment even with one dose of 30 mg intravenously or intramuscularly. The nature and kinetics of lymphocyte re-population depend on the maintenance immunosuppression being administered. In comparison with thymoglobulin, alemtuzumab offers significant practical benefits with lower cost, fewer side effects in administration, and no specific issues with intravenous access. While the majority of experience in solid organ transplantation has been in kidney transplantation, there is more limited experience in pancreas transplantation.[19]

Human monoclonal antibodies (daclizumab, Zenapax) bind to the IL-2 receptor on T lymphocytes and cause rapid depletion of these cells in the peripheral circulation. These agents are given intraoperatively and again on postoperative day 4. They are well tolerated and have minimal side effects. They are not associated with a cytokine release or an increased incidence of infection or malignancy.

Perioperative Care and Potential Complications

The perioperative period after pancreas transplantation demands a complete evaluation because of the comorbid

conditions linked with DM including coronary artery disease, hypertension, renal failure, autonomic and systemic neuropathy, and gastroparesis (Table 54.5). Because SPK patients have renal as well as pancreatic insufficiency at the time of surgery, postoperative complications are more common when compared to PTA or PAK recipients.[20,21] All patients should have central venous monitoring and an arterial line.

Postoperatively, strict glycemic control should be instituted with either a continuous insulin infusion or bolus insulin therapy if required[22]; hyperglycemia with serum glucose greater than 160 mg/dl should be avoided. Some patients may require dextrose in the setting of hyperinsulinemia, especially if the pancreas is systemically drained versus the portal system. Pancreatic grafts from older donors or with increased cold ischemic time may exhibit delayed graft function and therefore require initial insulin therapy for hyperglycemia.

Ischemic heart disease has been reported in up to 40% of pancreas transplant recipients.[7] Diabetic cardiomyopathy is a distinct entity that refers to a reduction in myocardial contractility without cardiomyopathy or coronary damage. If diagnosed preoperatively by echocardiography, a β1 agonist, such as dobutamine, may be necessary.[7,23] SPK recipients commonly need aggressive treatment of arterial hypertension, which may add to an increased cardiac risk in these patients.[20] On the other hand, hypotension must be avoided. Tight blood pressure control, with systolic blood pressure between 110 and 160 mmHg, is mandatory. The incidence of both silent and clinically overt cardiac ischemia is higher when DM is associated with renal disease requiring replacement therapy.[24]

Pancreas graft hypoperfusion can result in diminished flow leading to thrombosis; therefore, systolic blood pressure greater than 110 mmHg is critical. Crystalloid and colloid infusions should be used to optimize central venous pressure. Mannitol is recommended by some to decrease cellular edema and prevent graft thrombosis.[25] Hypotension may be the result of diabetic dysautonomy, aggressive renal replacement therapy, or rapid changes in the patient's position. Vasoactive medications may be necessary to correct the hemodynamic instability.

The most immediate and frequent complication is pancreatic graft thrombosis. There does appear to be a different coagulation profile between the SPK and PTA recipients. This is highlighted by a higher thrombosis rate in the PTA group. This may be explained by a uremic-related coagulopathy in SPK patients that protects them from thrombosis of the pancreatic graft, which is a low-flow organ.[26–28] The authors believe that systemic heparinization reduces this risk, especially in the PTA recipients.[29] Patients suffering decreased flow may present with fluctuating serum glucose levels, abdominal pain, or rising amylase and lipase levels. A CT angiogram should be performed urgently if suspicion of thrombosis exists and reexploration may be necessary to preserve the graft.

Hyperglycemia and the production of ketone bodies depress the immune system, making diabetics more susceptible to infection.[7] Infections after pancreas transplantation are quite common and may be either local or systemic. Local infections may necessitate graft removal[30]; intra-abdominal infections account for 15% of technical failures. Fungal infections are quite common (10% of cases) and require aggressive antifungal therapy, reduction in immunosuppression, and, in some cases, transplant pancreatectomy.[31] Fungal infections may induce more morbidity and graft loss than bacterial infections in these patients. The overall infection rate also appears to be higher in patients undergoing renal replacement therapy, regardless of type.[32]

The type of drainage used for the exocrine pancreas is important in determining leaks or complications specific to each technique. A duodenal cuff leak from the enteric anastomosis may be present with abdominal pain, leukocytosis, and fever. Due to immunosuppression, symptoms may vary widely. Leakage of pancreatic enzymes into the peritoneum initiates an inflammatory reaction to adjacent organs and the transplanted pancreas as well. Autodigestion of the gland and pancreatitis may occur. Prompt drainage and control of the leak is mandatory. Inability to obtain a controlled fistula may require graft pancreatectomy. Bladder drainage is associated with its own possible problems including bicarbonate losses and resultant metabolic acidosis, urinary tract infections, dehydration, reflux pancreatitis, and the development of urinary leaks if the bladder becomes over-distended.[33,34] Frequent urinary tract infections may require cystoscopy to rule out foreign bodies or stones in the bladder and a determination of bladder emptying and capacity. Patients with poor bladder function and recurrent urinary tract infections should be considered for enteric conversion.[35–38]

Other early post-surgical complications may include reexploration for bleeding, wound dehiscence, and small bowel obstruction from scar or an internal hernia. Patients commonly have significant gastroparesis and require nasogastric decompression for 2–3 days. Oral medications may not be absorbed initially; therefore, critical medications like MMF and Solu–Medrol are usually given intravenously until bowel function returns. The authors routinely start metoclopramide postoperatively to improve gastric emptying.

Systemic infections are most commonly caused by cytomegalovirus (CMV) or Epstein–Barr virus (EBV). Prophylaxis and CMV serology testing is effective in reducing the incidence of CMV infection.[39,40] The risk of post-transplant lymphoproliferative disorder (PTLD) after EBV infection is less than 2% in pancreas transplant recipients regardless of type.[41,42]

Acute rejection of the transplanted pancreas is rare in the initial postoperative period. SPK recipients can be monitored with the serum creatinine since the organs are usually from the same donor. For solitary pancreas recipients (PAK, PTA), serum creatinine cannot be used as a surrogate marker for rejection. In patients whose exocrine function was diverted with bladder drainage, urine amylase levels and cytology may be a reliable marker(s) of graft function.[43] For patients with enteric drainage, no such markers exist. Elevations in serum

amylase/lipase or serum glucose are often late markers of graft dysfunction. Due to the intraperitoneal placement of the graft, percutaneous pancreatic biopsy can be technically challenging. Treatment is often empiric and usually consists of steroids initially, but commonly requires ATG.

Conclusion

Pancreas transplantation continues to be an accepted therapy for the treatment of complications associated with type I DM. Although advances in surgical technique and immunosuppression have improved graft survival rates in the last 10 years, the intensive care management of patients in the perioperative period remains a vital part in achieving excellent outcomes for these unique surgical patients.

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Part XI
Additional Topics

55
Management of the Critically Ill Geriatric Patient

Paul E. Marik

People who are older than 65 years of age are the fastest growing segment of the US population.[1] By 2030 the population older than 65 years will double to approximately 70 million, and the fastest growing segment of the population, those older than 84 years, will triple.[1–3] Age is associated with an increasing prevalence of multiple diseases and disabilities. Age is also associated with a decline of the functional reserve of multiple organ systems and a progressive restriction in personal and social resources. It is, therefore, not surprising that elderly patients will utilize a disproportionate share of health care resources. It is estimated that by the year 2030, 55% of all health care expenses in the USA will be spent on caring for the elderly.[4] By virtue of having lived longer, increasing numbers of elderly patients (age >65 years) are being admitted to intensive care units (ICUs), with diagnoses ranging from exacerbations of chronic illnesses and new onset of catastrophic health problems to trauma caused by home-related incidents and injury-resultant accidents that have occurred outside of the home. Elderly patients currently account for 42–52% of ICU admissions and for almost 60% of all ICU days.[3,5–7] A disproportionate number of these ICU days is spent by elderly patients before their death. Forty percent of Medicare dependants are admitted to an ICU during their terminal illness, accounting for a quarter of all Medicare expenditure.[8,9] Clearly ICU utilization by the elderly will increase exponentially over the next three decades. With the current unitization patterns, a severe shortage of intensivists and ICU beds has therefore been predicted.[3] The reality of our aging society dictates that we must focus on how to best care for the elderly who develop critical illness.

This chapter will review (1) the physiological changes that occur with aging, particularly as they apply to critically ill patients; (2) the outcome of elderly patients admitted to the ICU, and prognostic factors that may aid in ICU admission decisions; and (3) management issues that pertain particularly to elderly, critically ill patients.

The Physiology of Aging

Aging is a process that converts healthy adults into frail ones, with diminished reserves in most physiologic systems and with an exponentially increasing vulnerability to most diseases and to death. At the cellular level, aging can be defined as a progressive deterioration of structure and function that occurs over time.[10] The factors that lead to primary aging are poorly understood; however, the interplay between genetics and oxidant damage is believed to play a major role.[10,11] The free radical theory of aging postulates that the production of intracellular reactive oxygen species is the major determinant of life span.[11] Numerous cell culture, invertebrate, and mammalian models that lend support to this hypothesis exist. Genetics has a powerful influence over lifespan, as indicated by the enormous differences among species. The rate of primary aging is probably determined by the effectiveness of mechanisms that act to maintain structural and functional integrity of cells and tissues. These include protecting DNA against free radical damage, repairing damaged DNA, and providing protection against the development of malignancies. Primary aging causes deterioration in cellular structure and function,

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independently of disease, in healthy individuals. Examples of the consequences of primary aging include declines in maximal oxygen uptake capacity, cardiovascular function, and in muscle mass and strength, as well as decreases in memory, reaction time, and elasticity of the lungs and skin.[10,11]

The changes in cardiopulmonary, renal, and immune function with aging have important implications for the critical care physician and will be briefly reviewed. Cardiovascular performance impacts on critical illness in the elderly in two ways. First, age is a major risk factor for cardiovascular disease, which accounts for over 40% of deaths in those aged 65 years and older.[12] Second, the effect of aging on cardiovascular structure and function has implications for hemodynamic support of the elderly. A substantial lack of cardiac reserve is noted by the age of 70. This lack of reserve may not affect the daily functioning of a "healthy" older individual, but when this same older person experiences physiological stress such as blood loss, hypoxia, sepsis, or volume depletion, the lack of reserve becomes apparent through cardiac dysfunction.

With aging there is a progressive decrease in the number of myocytes and an increase in myocardial collagen content.[13] Autonomic tissue is replaced by connective tissue and fat, while fibrosis causes conduction abnormalities through the intranodal tract and the His bundle. These changes contribute to the high incidence of sick sinus syndrome, atrial arrhythmias, and bundle branch blocks. Arterial distensibility – the major component of afterload – decreases with aging.[13,14] These changes result in a decrease in left ventricular ejection fraction with compensatory myocyte hypertrophy; consequently left ventricular mass index increases with aging.[14,15] Resting cardiac output is maintained despite the increased afterload imposed by the stiffening of the outflow tract. However, maximal heart rate, ejection fraction, and cardiac output decrease with aging. Left ventricular hypertrophy, together with increased myocardial collagen, results in an overall decline in ventricular compliance. Ventricular relaxation, which is more energy dependent than ventricular contraction and therefore more oxygen dependent, also becomes impaired with aging. Diastolic dysfunction is therefore common in the elderly, particularly in those patients with systemic hypertension.[14–17] Indeed, diastolic dysfunction is responsible for up to 50% of cases of heart failure in patients over the age of 80 years. In critically ill elderly patients, particularly those with coronary artery disease, hypoxemia may compound the preexistent diastolic dysfunction.

In younger persons, cardiac output is increased predominantly by increasing heart rate in response to adrenergic stimulation. With aging there is a relative "hyposympathetic state" in which the heart becomes less responsive to sympathetic stimulation, possibly secondary to declining receptor function. The aging heart, therefore, increases cardiac output predominantly by increasing ventricular filling (preload) and stroke volume rather than by an increase in heart rate. Because of the dependence of preload, even minor hypovolemia can result in significant cardiac compromise. The dependence on preload to maintain cardiac output is made even more important by the diastolic dysfunction associated with aging. However, due to decreased ventricular compliance, overzealous fluid resuscitation is likely to cause pulmonary edema. These changes dictate scrupulous management of the elderly patients' volume status. The reduction in left ventricular compliance results in a reduction of early diastolic ventricular filling and a compensatory increase in flow due to atrial contraction.[15,17] The contribution of left atrial systole to left ventricular filling increases with age[17] Atrial fibrillation is therefore poorly handed by elderly patients, particularly those with marked diastolic dysfunction.

The cardiac dysfunction with aging is compounded by the high incidence of cardiac disease, especially coronary artery disease, in the elderly. Coronary artery disease may go unrecognized in the elderly, as myocardial ischemia may present with nonspecific and atypical symptoms. In the Framingham Heart Study, myocardial infarction was unrecognized or silent in greater than 40% of patients over the age of 75 years.[18]

Declining respiratory function in the elderly is the result of changes in both the chest wall and the lung.[19,20] There is a progressive decrease in chest wall compliance caused by structural changes of kyphosis and vertebral collapse. There is a progressive decline in respiratory muscle strength resulting in a decline in maximal inspiratory and expiratory force by as much as 50%. In the lung, there is a loss of elasticity with collapse of the small airways and uneven alveolar ventilation with air trapping. Uneven alveolar ventilation leads to ventilation perfusion mismatch, which in turn causes a decline in arterial oxygen tension of approximately 0.3 mmHg/year from the age of 30 years. The control of ventilation is also affected by aging. Ventilatory response to hypoxia and hypercapnia fall by 50 and 40%, respectively. Elderly patients have a decreased respiratory reserve and may therefore decompensate faster than younger patients. Weaning from mechanical ventilation may be more prolonged in these patients. As a consequence of poor nutritional status, decreased T-cell function, a decline in mucociliary clearance, poor dentition with increased oropharyngeal colonization and swallow dysfunction, aspiration pneumonia is exceedingly common in elderly patients, particularly those admitted from acute and chronic care facilities.[21]

There is a marked decline in renal function with aging. This decline has important implications for the critical care physician. Between the ages of 25 and 85 years, approximately 40% of the nephrons become sclerotic. The remaining functional units hypertrophy in a compensatory manner. Sclerosis of the glomeruli is accompanied by atrophy of the afferent and efferent arterioles and a decrease in renal tubular cell number. Renal blood flow falls by approximately 50%. Functionally, there is a decline in the glomerular filtration rate (GFR) of approximately 45% by age 80 years. Serum creatinine, however, remains unchanged because there is a concomitant decrease in lean body mass and, thus a decrease in creatinine production. Estimates of GFR in the healthy aged can be made

from the serum creatinine by using the formula derived by Cockroft and Gault.[22] This formula must be used with caution in critically ill patients as the serum creatinine may be altered by factors other than the GFR, including numerous medications and increased muscle breakdown due to sepsis, trauma, protein catabolism, and immobility.

Renal tubular function declines with advancing age. The ability to conserve sodium and excrete hydrogen ions falls, resulting in diminished capacity to regulate fluid and acid–base balance. The aging kidney compensates poorly for non-renal losses of sodium and water. These changes are thought to be due to a decline in the activity of the renin–angiotensin system and a decreased end-organ responsiveness to antidiuretic hormone. Elderly patients are therefore at high risk of becoming dehydrated; this is compounded by the pre-load dependence of the heart for adequate cardiac output. The decreased GFR with aging has important implications in terms of drug dosing as most drugs are renally excreted, with the reduction in renal elimination falling in parallel with the drop in GFR. Therefore, the creatinine clearance (estimated or measured) should be used in dosage calculations for drugs that are renally eliminated.

Body composition and energy expenditure change with aging. There is an increase in body fat and a decrease in lean muscle mass by up to 40% at age 80 years. Accompanying this decline in muscle mass is an even greater decline in muscle strength caused by a selective loss of muscle fibers. The loss in muscle mass may be compounded by a poor intake of high-quality protein, which is especially common in the elderly. Daily energy expenditure decreases with age. Resting energy expenditure falls by as much as 15%. This decrease is primarily the result of the decrease in lean muscle mass and less physical activity. Following acute illness or injury, the increase in oxygen consumption and energy expenditure in patients over the age of 65 years is approximately 20–25% less than their younger counterparts.[23] These changes in body composition and energy expenditure have important implications with respect to nutritional support. Due to decreased muscle mass in the face of acute illness or even elective surgery, elderly patients may rapidly develop protein-energy malnutrition. Nutritional support should therefore begin within 24 h of admission to the ICU. However, due to their decreased body mass and lower energy expenditure, overfeeding of the elderly – with the sequelae of "stress hyperglycemia," fatty liver, and excess CO_2 production – should be avoided.

A progressive decline in the integrity of the immune system occurs with aging.[24–27] The age-related changes are most evident in the peripheral T cell pool, which shows signs of decreased reactivation to challenge with antigens.[26–28] Several studies have demonstrated that the secretion of IL-2 by T cells and the number of IL-2 receptors on T cells (IL-2R/CD25+) are reduced in elderly subjects.[29,30] Trebilcock and Ponnappan have provided evidence of an age-associated decline in the induction of NF-6 in activated T cells, which could explain the decreased production of both IL-2 and its receptor with aging.[31] These changes may explain the observation that elderly patients tend to have a less intense systemic inflammatory response to infection and to be less hyperdynamic when compared to younger patients. The age-related changes in the immune system, together with the increased burden of chronic disease, may explain the increased incidence of sepsis in the elderly. Martin and colleagues performed a longitudinal observational study using national hospital discharge data. In this study, elderly patients (>65 years) accounted for 12% of cohort, yet they accounted for 64.9% of the sepsis cases (relative risk of 13.1 compared to younger patients).[32] In addition, the case-fatality rate increased linearly with age, with age being an independent predictor of mortality.

Elderly patients are also at an increased risk of nosocomial infections. Pneumonia is particularly common in this group of patients; multiple factors contribute to the increased risk of pneumonia including an increased risk for aspiration due to swallow dysfunction, increased oro-pharyngeal colonization with potentially pathogenic organisms, weak cough, poor ambulation, and altered immune status.[33] Urinary tract infections, decubitus ulcers, and wound infections are also common. In a study of 3,254 trauma patients, 39% of patients older than 65 developed a nosocomial infection as compared to 17% of younger patients..[34] In this study, the mortality rate for elderly patients who had nosocomial infection was 28% compared with 5% for younger patients.

The Outcome of Elderly Patients Admitted to the ICU

With the projected exponential increase in the number of elderly patients and the increasing burden of chronic disease, how best should physicians select which patients are likely to derive the most benefit from admission to the ICU? The current guidelines of the Society of Critical Care Medicine state that "in general ICUs should be reserved for those patients with reversible medical conditions who have a reasonable prospect of substantial recovery."[35] Despite this recommendation, almost all patients with serious and life-threatening illnesses in the USA, regardless of their prognosis or prospect of recovery, are admitted to an ICU, unless the patient or his/her surrogate specifically declines ICU admission. It is, therefore, exceeding uncommon for intensivists in the USA to refuse ICU admission; if a bed is not immediately available, one is "made." This contrasts to the situation in most Western nations in which not all requests for an ICU bed are honored. Indeed, refusal of ICU admission is common, with a rate that varies from 24% to 46%.[36–40] Advanced age and poor functional status are reported to be the commonest reasons for ICU refusal.[36,37,39,40] In a study from France, Garrouste-Orgeas and colleagues reported an ICU refusal rate of 73.3% for octogenarians referred for ICU admission.[41] Sinuff and coworkers reviewed ten observational studies that evaluated rationing of ICU beds.[42] Age and severity of illness were associated

with ICU refusal, and patients denied ICU admission had an increased hospital mortality compared to those admitted to the ICU (odds ratio 3.04). In the report by Sinuff et al., only one of the studies was performed in the USA, and this study was related to a short-term nursing shortage during a 6-month period in 1981.[43]

Should age alone be used to limit admission to the ICU? In a survey of 600 American intensivists performed in 1988, 12% stated that advanced age alone should limit ICU admission while 43% considered age important in deciding admission to the ICU.[44] In order to address this question, one has to evaluate the outcome of elderly patients who are admitted to the ICU. Severity of illness and age appear to be important factors determining ICU survival.[45–48] In both the acute physiology and chronic health evaluation (APACHE) II and APACHE III disease severity and outcome predictive systems, increasing age was associated with a progressive increase in the risk of ICU death.[6,49] Nicholas et al. analyzed the influence of age on ICU survival from data collected on 792 admissions to eight ICUs in France.[47] These authors reported that ICU mortality increased progressively with age; for patients older than 65 years of age it was more than double than that of patients under 45 years (36.8% vs. 14.8%). Rellos reported an in-hospital mortality of 40% in patients 90 years or older admitted to an ICU, compared with 8.9% in those younger than 90 years of age.[50] However, ICU survival may not be the most appropriate end-point when evaluating the role of critical care, particularly in the elderly. The goal of critical care medicine is to restore patients to a level of functioning similar to that of their pre-admission status and to return patients back into the community from which they came. However, many ICU patients are discharged with persistent organ failure to subacute facilities, where they linger for months before ultimately dying. Therefore, post-discharge disposition and long-term survival (1–3 years) may be more important than hospital survival in evaluating the role of ICU admission.

Somme et al. reported an ICU survival rate for those below 75, 75–79, 80–84, and 85 years and older of 80, 68, 75 and 69% respectively.[51] However, most deaths occurred during the first 3 months following ICU discharge, with survival rates at 3 months for those 75–79, 80–84, and 85 years and older of 54, 56, and 51%, respectively. Similarly, Ridely and colleagues reported a 1-year survival of only 47% for patients aged 65 years or more compared to 83% for patients less than 35 years of age.[46] Chelluri and colleagues evaluated the long-term outcome of 97 elderly patients admitted to an ICU. The ICU survival was 79% for the cohort 65–74 years and 69% for those patients over the age of 75 years.[5] At 12 months, the survival rates were 42 and 37%, respectively. Dardaine et al. reported a 6-month survival post-ICU-discharge of 52% for a cohort of patients over the age of 70 years.[48] De Rooij reported the outcome of 578 octogenarians admitted to an ICU.[52] In this study, the ICU mortality of unplanned surgical and medical patients was 34 and 37%, respectively. The mortality 12 months after hospital discharge, including ICU and hospital mortality, was 62 and 69%. In this study, severity of illness at the time of admission was the most important factor determining ICU outcome, while long-term mortality was associated with base-line renal function. Rady and Johnson studied the demographics, comorbidities, and outcomes of a cohort of 900 octogenarians requiring ICU admission.[53] In this study, octogenarians represented 15% of ICU admissions. The interventions performed in the ICU, utilization of resources, the severity of illness, and length of hospital stay were similar for octogenarian and younger patients. However, the octogenarians had a higher hospital mortality (10% vs. 6%, $p<0.01$) and discharge to a subacute care facility (35% vs. 18%, $p<0.01$). On follow-up, octogenarian hospital survivors who were discharged to a subacute care facility had a higher mortality than hospital survivors discharged to home (31% vs. 17%). Preadmission comorbidities and severity of illness were independent predictors of hospital discharge to a subacute care facility. Those comorbidities associated with an increased likelihood of care dependency included degenerative brain disease, cerebrovascular disease, congestive cardiac failure, chronic pulmonary disease, diabetes mellitus, and malnutrition. Kaarlolo and colleagues assessed the long-term survival and quality of life of 882 elderly patients (>64 years of age) as compared to 1,827 controls (<65 years of age) admitted to a medical–surgical ICU.[54] The cumulative 3-year mortality rate among the elderly patients was 57% as compared to 40% in the control group ($p<0.05$). The majority (88%) of the elderly survivors assessed their present health status as good or satisfactory. Mattison and colleagues reported a 90-day mortality of 55% for a cohort of 123 nursing home residents who were admitted to an ICU.[55] In this study, impaired functional status prior to admission and severity of illness were independent predictors of outcome.

An analysis of the available data suggests that functional elderly patients have a favorable long-term outcome following ICU admission. This suggests that age alone should not be used in making ICU triage decisions. The decision to admit an elderly patient to an ICU should be based upon the patient's comorbidities, acuity of illness, and pre-hospital functional status, which includes quality of life and whether the patient was living independently or was admitted from a subacute/chronic health care facility. Simultaneously, it is imperative to determine the patient's preferences (or surrogate's best estimate of the patient's wishes) with regards to mechanical ventilation and other forms of life-sustaining treatment. For some elderly patients, physicians should provide the most peaceful and comfortable dying process and avoid admission to the ICU.

Trauma and the Elderly Patient

Geriatric patients are at high risk of traumatic injuries, particularly those patients with diminished functional status. Falls are the most common mechanism of injury in the elderly population and are responsible for significant morbidity, mortality, and

medical costs.[56–58] Pedestrian–motor vehicle injuries affect the elderly disproportionately and result in a higher mortality as compared with other age groups. Perdue and colleagues reported that trauma patients older than 65 years were 4.6 times more likely to die than younger patients.[59]

A number of factors contribute to the increased mortality of elderly patients after traumatic injuries, most notably their limited physiologic reserve together with the presence of comorbid cardiopulmonary disease. Elderly patients compensate poorly following blood loss due to limited chronotropic and inotropic reserve (hypoadrenergic state), diastolic dysfunction, and the inability of the kidney to conserve fluid. Many elderly patients are prescribed beta-blockers; these drugs further reduce the ability of the patient to compensate for decreased intravascular volume. In addition, elderly patients are frequently treated with Coumadin and/or antiplatelet drugs, which increase the propensity for uncontrolled hemorrhage.

Evidence suggests that many injured elderly patients are under-triaged despite the increased risk of death and complications. One possible cause of under-triage is the late presentation of physical findings indicating hypovolemia. Elderly patients who have severe injuries are best treated in trauma centers where the outcome is reported to be improved.[60]

Surgery and the Elderly

The operative mortality and incidence of postoperative complications are increased in elderly patients undergoing elective surgery.[61] It is not uncommon for elderly patients who appear fit and healthy (physiologic age less than chronologic age) to do poorly following elective surgery (the "knife" is the great equalizer). The decreased physiologic reserve and increased incidence of comorbidities probably accounts for this finding. Liu et al. reported an operative mortality of 4.6% and a postoperative complication rate of 25% in a cohort of octogenarians undergoing noncardiac surgery.[62] Elderly patients have a high incidence of protracted disabilities following major surgery. Lawrence and coworkers reported a high incidence of functional disabilities at 6 months following major abdominal surgery in a cohort of elderly patients.[63] In patients undergoing thoracic surgery, dependence for the performance of activities of daily living and impaired cognition were predictors of postoperative complications.[64] Postoperative delirium is common following surgery (see following section) and is associated with increased length of stay, morbidity, and mortality. The operative mortality and rate of postoperative complications are even higher in elderly patients undergoing emergency surgery, being reported in up to 49 and 68% of cases, respectively.[61,65–67]

Elective surgery must be considered very carefully in the elderly. Most randomized controlled trials comparing surgical to a more conservative approach were performed in patients less than 65 years of age. It is probably not appropriate to extrapolate the results of these trials to the elderly population. Coronary artery bypass surgery is frequently performed in the elderly with no evidence to support the benefit in this population of patients. Rady and Johnson compared the outcome from cardiac surgery in octogenarians compared to younger patients.[68] The octogenarians had a significantly higher incidence of postoperative complications and a significantly higher hospital mortality (13.5% vs. 1.3%, $p<0.001$) than the cohort of younger patients. Furthermore, significantly more octogenarians were discharged to a subacute/chronic health care facility than their younger counterparts (39.5% vs. 13%, $p<0.001$). This study demonstrated that only 47% of the octogenarians (all who were living at home and independent prior to surgery) were discharged to home after surgery and therefore potentially benefitted from undergoing coronary revascularization.

Over the last few years, geriatricians have developed an approach to care for the elderly called comprehensive geriatric assessment (CGA). CGA evaluates the comorbid illnesses, mental status, nutritional status, living circumstances, social support systems, and polypharmacy.[64,69] The goal of CGA is to provide information to the surgeon that will allow more accurate risk assessment for surgery. CGA will also allow for a proactive team-based approach to interventions, which will limit complications in those patients who undergo surgery.

Delirium in the Elderly

Delirium is common in elderly hospitalized patients and is a cause of significant morbidity.[70,71] Sleep deprivation, sepsis, hypoxemia, use of physical restraints, fluid and electrolyte imbalances, and metabolic and endocrine derangements have been implicated in the causation of delirium in these patients.[71] Drugs including digoxin, antihistaminics, opiates, antiparkinsonian medications, antipsychotics, antidepressants, and sedative–hypnotics can induce delirium, particularly in elderly patients. Marcantonio and colleagues reported that the use of meperidine and benzodiazepines were independently associated with the development of postoperative delirium in elderly patients after orthopedic surgery.[72] Pandharipande and colleagues reported that the use of lorazepam was independently associated with the development of delirium in ICU patients.[73] The high noise level, incessant monitor alarms, and bright lights in the ICU may contribute to the development of delirium in ICU patients. Preexistent cognitive or functional impairment is an important risk factor for the development of delirium in hospitalized patients. Using the Confusion Assessment Method (CAM) for the ICU (CAM-ICU), McNicoll et al. reported that 70.3% of elderly ICU patients developed delirium at some time during their hospitalization.[74,75] Delirium in ICU patients has been demonstrated to be an independent predictor of the length of hospital stay as well as ICU and 6-month mortality rates.[76–78]

Delirium is common following major surgery in elderly patients. Postoperative delirium is associated with an increased

mortality, a more frequent incidence of medical complications, and a prolonged hospital stay.[79] Preoperative cognitive dysfunction (dementia) is a strong predictor of postoperative delirium.[80] Postoperative delirium has an onset of approximately 24 h after surgery and generally resolves within a week. Delirium was reported to occur in 33% of elderly patients undergoing coronary artery bypass surgery (CABG).[81] Due to their advanced age, delirium is common following hip fracture repair, occurring in 28–65% of patients.[82–85] Transient postoperative delirium is associated with a poor long-term functional outcome.[82,83,86] Furthermore, some patents may progress into a long-term confusional state. Marcantonio et al. reported that 6% of patients remained delirious 6 months after hip fracture surgery.[83]

These data suggest that the prevention, early detection, and treatment of delirium should be important goals in the management of elderly ICU patients. Proactive geriatric consultation with a multicomponent interventional protocol has been demonstrated to reduce the incidence of delirium in hospitalized elderly patients.[85,87] Preoperative sleep deprivation may increase the risk of postoperative delirium.[80] Establishing a sleep–wake cycle, controlling noise pollution, morning bright light therapy, reorientation, and music therapy may be useful in the prevention and treatment of delirium in the ICU.[85,87] Poor postoperative pain control has been associated with the development of delirium.[88] Opiates (fentanyl or morphine) should therefore not be withheld in elderly patients in the fear of causing delirium. In patients in whom nonpharmacological agents fail to control the delirium, antipsychotic agents such as haloperidol or olanzapine should be considered.[89] Milbrandt et al. reported that the use of haloperidol within 2 days of the initiation of mechanical ventilation was associated with a lower hospital mortality.[90] The role of haloperidol in preventing delirium was not reported in this study. Kaneko and colleagues administered 5 mg haloperidol (or matching placebo) intravenously at night for 5 days postoperatively in 78 geriatric patients undergoing gastrointestinal surgery.[91] Postoperative delirium developed in 10.5% of the patients receiving haloperidol as compared to 32.% in the placebo group. Kalisvaart et al. performed a similar study in elderly patients undergoing hip surgery.[92] While the incidence of delirium was the same in both groups, the severity was worse and the duration of delirium significantly longer in the placebo group. In this study, low-dose haloperidol was used (0.5 mg PO three times daily); this may partly explain the difference in outcome between the two studies. Haloperidol and other "atypical" antipsychotics hold great promise for the prophylaxis of delirium in elderly patients undergoing surgery. Melatonin has been suggested to reset the internal circadian rhythm and sleep–wake cycle, and may have a role in the treatment and/or prevention of delirium in hospitalized elderly patients.[93]

Postoperative Cognitive Dysfunction

Transient postoperative cognitive dysfunction (POCD) is an acute and short-termed disorder of cognition, memory, and attention. An etiologic factor must be searched for in every patient, since POCD may be the first symptom of respiratory (hypoxemia) or cardiac complication, electrolyte disturbance, sepsis, or drug interactions. However, in most instances a specific cause cannot be identified, and may be related to the interaction between anesthesia and the alteration in neurotransmitters involved in the cognitive decline of aging. The prognosis of transient POCD is good in the majority of patients; however, prolonged POCD may occur. Prolonged POCD may last for months to years and is a cause of significant disability. The "long-term postoperative cognitive dysfunction in the elderly (ISPOCD1) study" was a prospective, multicenter study that investigated the incidence and causation of transient and prolonged POCD in elderly patients undergoing major noncardiac surgery.[94] POCD was present in 26% of patients 1 week after surgery and in 9.9% three months after surgery, compared with 3.4 and 2.8% of controls. Increasing age, duration of anesthesia, postoperative infections, and respiratory complications were risk factors for early POCD, but only age was a risk factor for prolonged POCD.

POCD is common after cardiac surgery in the elderly, with an incidence of up to 80% at discharge and 50% at 6 weeks.[81,95–98] Newman and colleagues reported that 42% of patients had neurocognitive decline that persisted for up to 5 years following CABG.[98] Knipp and colleagues performed neurocognitive testing and diffusion-weighted magnetic resonance imaging (MRI) on elderly patients undergoing coronary artery bypass surgery.[99] Transient postoperative decline in one or more domains of cognitive function was detected in all patients, with memory impairment persisting for months. New ischemic lesions were reported in 45% of patients; however, these lesions did not appear to account for the persistent neurocognitive decline. Cardiopulmonary bypass has been implicated as a cause of both short- and long-term POCD.[81,95–99]

Drug Dosing in the Elderly

Adverse drug reactions (ADRs) are common causes of complications in hospitalized elderly patients. Age has been shown to be an independent risk factor for ADRs.[100–102] Aging is associated with decreased renal and hepatic reserve with delayed renal and hepatic clearance of drugs. Renal function can be readily estimated from the serum creatinine level; however, this estimate is unreliable in the elderly because of the frequent loss of muscle mass secondary to age itself and aging-related conditions. Hypertension and type 2 diabetes mellitus are common in the elderly, and these patients are more likely to have concealed renal insufficiency, that is, renal insufficiency (decreased GFR) despite a normal serum creatinine. Using data on 11,687 hospitalized patients enrolled in the Gruppo Italiano di Farmacovigilanza nell'Anziano Study, Corsonello and colleagues reported that concealed renal insufficiency was present in 13.9% of patients (serum creatinine <1.2 mg/dl and estimated GFR of <60 ml/min/1.73 m^2).[101] In this study, both concealed and overt (serum creatinine >1.2 mg/dl

and estimated GFR of <60 ml/min/1.73 m^2) renal failure were associated with an increased risk of ADRs with water soluble drugs. Digitalis, angiotensin-converting enzyme inhibitors, and hypoglycemic drugs were most commonly associated with ADRs in these patients. Polypharmacy was also an independent predictor of ADRs. Excessive bleeding with the use of low molecular weight heparins (LMWH) is associated with a decreased GFR.[103–105] These data suggest that GFR should be estimated in all hospitalized elderly patients receiving drugs that are renally excreted; in critically ill elderly patients who are markedly catabolic or have large shifts of fluid, the GFR should be measured (not calculated). The dose of LMWH should be reduced in patients with mild renal insufficiency (CrCl 50–70 ml/min) and unfractionated heparin used in patients with a more marked decline in renal function (CrCl<50 ml/min).[103–105] Aminoglycoside antibiotics should be avoided in elderly patients with renal dysfunction, as both age and preexisting renal dysfunction are predictors of nephrotoxicity. Those patients in whom an aminoglycoside is indicated require careful dosage adjustments according to measured creatinine clearance and measured trough levels.[106,107] These patients should receive once-daily dosing and treatment limited to 8 days or less.[106,108] ACE inhibitors should be used cautiously in elderly patients, particularly those with deranged renal function. Due to the myriad of possible drug interactions, the medication list of all elderly patients should be "trimmed" as much as possible. Age, diabetes, and preexistent renal dysfunction are risk factors for the development of contrast-induced nephrotoxicity. As contrast studies are frequently performed in elderly ICU patients, preventative measures should always be undertaken; that is, pre-hydration, *N*-acetyl-cysteine, and avoidance of concomitant nephrotoxic drugs. Magnetic resonance imaging (MRI) and contrast MRI should be considered as an alternative to contrast computed tomography (CT) scans in high risk patients.

Conclusion

In conclusion, the management of critically ill elderly patients is a complex issue that involves an understanding of the changing demographics of our society as well as the physiology of aging. ICU admission decisions should not be based on age alone, but the interplay of the patient's baseline level of function and comorbidities, severity of illness, as well as the patient's preferences for life support. Elderly ICU patients are at a high risk for developing delirium, which independently increases morbidity and mortality. An aggressive approach is required to prevent and detect delirium, with early initiation of treatment. A comprehensive geriatric assessment with a multicomponent interventional protocol is recommended in all geriatric patients undergoing elective surgery. Adverse drug reactions are common in the elderly, mostly due to declining renal function and drug interactions. The critical care physician should consider this factor when prescribing medications for elderly patients.

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56
Alcohol Withdrawal in the Surgical Patient: Prevention and Treatment

Anja Heymann, Irit Nachtigall, Anton Goldmann, and Claudia Spies

Alcohol withdrawal syndrome (AWS) is a common condition seen in hospital practice consisting of symptoms and signs that typically develop in alcohol-dependent patients 6–24 h after the last drink.

Epidemiology and Clinical Relevance of Alcohol-Use Disorders

Alcohol is one of the most abused drugs throughout the world.[1] It is a factor in 50% of motor-vehicle accidents, burns, and crimes; and it is the fourth-leading cause of disability and health-care burden worldwide.[2]

In a national survey conducted in United Kingdom in 2002, 38% of male respondents and 23% of female respondents self-reported hazardous drinking on a typical drinking day. However, in hospitalized patients this figure is higher. Reports indicate that approximately 20% of hospitalized patients have an alcohol-use disorder (AUD); half of those patients are alcohol abusers and half are alcohol dependent.[2–4]

Alcohol influences many organ systems and promotes carcinogenesis.[1,4–8] More than 50% of patients with carcinoma of the gastrointestinal tract have AUD,[6] and AUD patients develop more infections, cardiopulmonary problems, and bleeding disorders than those who do not drink.[8–18] As a result, the intensive care unit (ICU) and hospital length of stays are significantly prolonged, complicated, and expensive.[9,11–14,19,20]

Many studies have been conducted to evaluate the relationship between trauma and alcoholism. Most show that almost half of all trauma beds are occupied by patients who were injured while under the influence of alcohol. The blood alcohol level correlates with the probability of death after trauma.[10]

Clinical Presentation

The most common features of AWS are tremulousness, sweating, nausea, vomiting, anxiety, productive-psychotic symptoms, agitation, tachycardia, and hypertension within 6–24 h after the last drink. Although AWS can occur predictably in those seeking abstinence, it may arise unexpectedly in an alcohol-dependent patient after being admitted to the hospital and in those patients who have abruptly decreased their amount of alcohol consumption but have continued to drink.

The most feared postoperative complication of AWS is the development of delirium tremens (DT). It may occur in up

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Table 56.1. Differential diagnosis of AWS and DT.

I	Infections	D	Deficiencies
W	Withdrawal	E	Endocrinopathies
A	Acute metabolic	A	Acute vascular events
T	Trauma	T	Toxins/drugs
C	CNS pathology	H	Heavy metals
H	Hypoxia		

Table 56.2. CAGE questionnaire ("CAGE" is an acronym formed by taking the first letter of key words from each of the following questions). Patients with a CAGE score >2 are considered chronic alcoholics.

Have you ever felt you should Cut down on your drinking?
Have other people Annoyed you by criticizing your drinking?
Have you ever felt Guilty about drinking?
Have you ever taken a drink in the morning to steady your nerves or get rid of a hangover (Eye opener)?

to 25% of postoperative alcohol-dependent patients, despite preventive treatment.[21–33] Delirium tremens is characterized by auditory and visual hallucinations, confusion, disorientation, impaired attention, and pronounced autonomic hyperactivity (fever, tachycardia, and diaphoresis) typically occurring 72–96 h after cessation of drinking.

According to the Diagnostic and Statistical Manual of Mental Disorders[23] and the International Classification of Diseases[24] criteria, only alcohol-dependent patients develop AWS and DT.

Differential Diagnosis

The differential diagnosis in ICU patients is often complex. Cognitive disorders and productive-psychotic symptoms such as hallucinations are difficult to recognize in tracheally intubated patients. Most patients in the ICU require prolonged analgesia and sedation. After sedation is reduced, the differential diagnosis includes a broad spectrum of common complications. It is most important to eliminate all possible underlying causes of delirium before the diagnosis of AWS is established.[34] Alcohol withdrawal syndrome can be associated with many different general medical conditions, each of which has characteristic physical examination and laboratory findings. It is most important to eliminate all possible underlying conditions. The mnemonic I WATCH DEATH includes the most important symptoms for the differential diagnosis of AWS and DT (Table 56.1).

The Pathophysiology of AWS

Chronic alcohol exposure exerts numerous pharmacological effects by means of interactions with various neurotransmitters and neuromodulators.[35,36] Because different neurotransmitter systems are affected,[37] it is not surprising to find that the pathophysiology of AWS is complex. The onset and spectrum of the various symptoms result from different transmitter systems, which differ in their vulnerability to the withdrawal of ethanol.[38] On the one hand, there is an increased activity of excitatory mechanisms; on the other, there is a decreased function of inhibitory systems.[37]

The main inhibitory neurotransmitter is gamma-aminobutyric acid (GABA), which acts through the GABA-alpha (GABA-A) neuroreceptor. One of the major excitatory neurotransmitters is glutamate, which acts through the *N*-methyl-D-aspartate (NMDA) receptor. Alcohol enhances the effect of GABA on GABA-A receptors. Chronic exposure to alcohol results in compensatory down-regulation of GABA-A receptors. Alcohol inhibits NMDA receptors, and chronic alcohol exposure results in up-regulation of these receptors. Abrupt cessation of alcohol exposure results in brain hyperexcitability because receptors previously inhibited by alcohol are no longer inhibited. Brain hyperexcitability may produce agitation and seizures.

Several studies have also shown that adrenergic hyperactivity and increased dopaminergic transmission occur in AWS. Adrenergic hyperactivity produces sympathetic symptoms and signs such as tachycardia and hypertension, whereas increased dopaminergic transmission is associated with the development of hallucinations.

Perioperative Assessment

A well-performed preoperative assessment can reduce the postoperative risk of AWS.[12] However, only 1–24% of surgical patients with AUD are diagnosed during clinical routines.[4,39] With an established diagnosis of alcohol dependence, an adequate prophylaxis can be initiated, and AWS can be prevented in up to 75% of patients.[12]

Although prophylaxis can significantly reduce morbidity,[40] preoperative abstinence can also decrease perioperative complications of alcohol dependence. Tønnesen et al.[41] were able to show that 1 month of preoperative abstinence significantly reduced postoperative morbidity in alcohol abusers admitted for colorectal surgery.

A precise preoperative assessment should include an alcoholism-related questionnaire, along with a routine patient history and physical examination. The CAGE[42] is a short, precise, and feasible four-item questionnaire (Table 56.2) that can be used to assess alcohol use. Patients with a CAGE score >2 are considered chronic alcoholics. Buchsbaum et al.[43] found a strong correlation between the CAGE results and the *Diagnostic and Statistical Manual of Mental Disorders* criteria for alcohol dependence.[23] An algorithm composed of an alcoholism-related questionnaire and laboratory markers can be used to enable the preoperative assessment of an AUD (Fig. 56.1).[9]

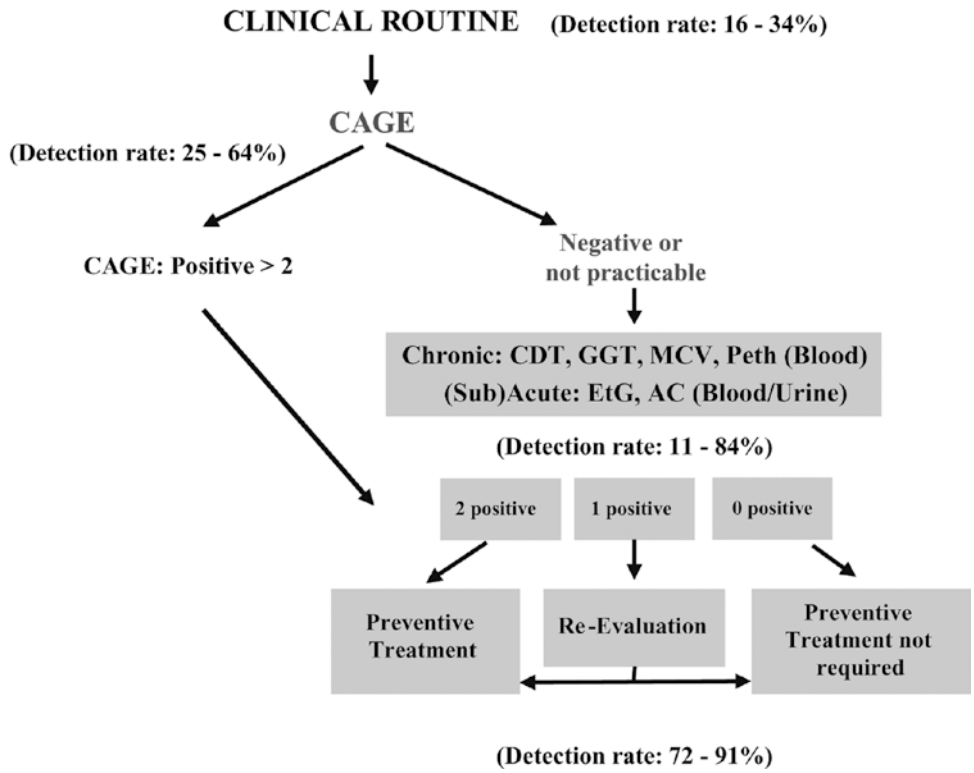


FIG. 56.1. Algorithm for recognizing alcohol misuse and strategy for treating surgical patients. *CAGE* cut down, annoyed, guilty, eye opener. *CDT* carbohydrate-deficient transferrin (normal range male <6%, female <5%). *MCV* mean corpuscular volume of the erythrocytes (normal range 84–98 fl). *GGT* gamma-glutamyl transferase (normal range male <55 U/l; female <38 U/l). *Peth*: phosphatidylethanol (chronic alcohol metabolite, detecting AUD; only increased in whole blood if chronic alcohol consumption is present for 2–3 weeks; determination not available in all institutions). *EtG* ethyl glucuronide (subacute alcohol metabolite, also increased after social alcohol intake, therefore detects only consumption but does not detect AUD; detectable in serum 8 h after consumption, in urine 80 h after consumption and hair if ethanol was consumed; determination not available in all institutions). *AC* alcohol concentration.

Diagnosis and Monitoring of Delirium

At present, two diagnostic tools have been validated for monitoring delirium in ICU patients: (1) the Confusion Assessment Method for the ICU (CAM-ICU)[25] (Table 56.3) is appropriate to detect agitated as well as hypoactive deliria; (2) the Delirium Detection Score (DDS)[27] (Table 56.4) is a modification of the clinical institute withdrawal assessment for alcohol, revised (CIWA-Ar) scale,[44] which has good validity with excellent sensitivity and specificity for delirium. In addition it has the ability to estimate the severity of delirium.

Prevention of AWS

Because of the importance of preventive treatment of AWS in AUD patients, prophylaxis should be considered in every patient with a history suspicious for alcohol misuse (see Fig. 56.1).

In contrast to psychiatric patients admitted for ethanol detoxification,[45] surgical patients can usually undergo prophylactic treatment (Table 56.6).[46–48] Withholding prophylaxis from alcohol-dependent patients increases postoperative complications and the duration of ICU treatment. Therefore, prophylactic treatment is required in ICU settings.[12]

Although different drugs are used in the prophylaxis of AWS, the best drug has not been determined. Spies et al.[47] studied a total of 197 alcohol-dependent patients admitted to the surgical intensive care unit following tumor resection. Patients were allocated randomly to one of the following regimens: flunitrazepam–clonidine, chlormethiazole–haloperidol, flunitrazepam–haloperidol, or ethanol. The authors did not find any advantage in any of the four regimens with respect to the primary outcome measures, but patients in the chlormethiazole–haloperidol group had a significantly increased incidence of tracheobronchitis.

An oral benzodiazepine is the best-studied drug for preventing AWS, particularly for lowering the risk of seizures (diazepam 2.5–10 mg, lorazepam 0.5–2 mg, or chlordiazepoxide 5–25 mg, PO every 6 h). An alternative for a benzodiazepine is an alpha-adrenergic agonist such as clonidine (clonidine PO or transdermal 0.1–0.3 mg/day).

The administration of intravenous ethanol as an alternative prophylactic agent is still used in many surgical ICUs.

Table 56.3. Confusion assessment method for the ICU (CAM-ICU).

I. Acute onset or fluctuating course
   A. Is there evidence of an acute change in mental status from the baseline?
   B. Or, did the behavior fluctuate during the past 24 hours?
II. Inattention
   Did the patient have difficulty focusing attention, as evidenced by a score of fewer than 8 correct answers on either the visual or the auditory components of the Attention Screening Examination (ASE)?
III. Disorganized thinking
   Is the patient's thinking disorganized or incoherent, as evidenced by incorrect answers to at least 3 of the 4 questions and inability to follow the commands?
   Questions
   Will a stone float on water?
   Are there fish in the sea?
   Does 1 pound weigh more than 2 pounds?
   Can you use a hammer to pound a nail?
   Commands
   Hold up this many fingers (examiner holds 2 fingers in front of the patient)
   Now do the same thing with the other hand (not showing the fingers again)
   Determine whether the patient's thinking is disorganized or incoherent
IV. Altered level of consciousness
   Is the patient's level of consciousness anything other than alert? For example, is the patient vigilant or in a stupor or coma?
   If I and II are present, or either III or IV is present, the patient has delirium

Table 56.4. Delirium Detection Score (DDS). The DDS is composed of several criteria: orientation, hallucination, agitation, anxiety, and paroxysmal sweating. For each criterion, 0, 1, 4, or 7 points can be allocated (Delirium = sum ≥ 8 points). Because the DDS is composed of several criteria, it is more suitable to be used with a symptom-guided therapy.

Item	Description	Scoring
Orientation	Oriented to time, place, and personal identity; able to concentrate	0
	Not sure about time and/or place; unable to concentrate	1
	Not oriented to time and/or place	4
	Not oriented to time, place, and personal identity	7
Hallucinations	Normal activity	0
	Mild hallucinations at times	1
	Permanent mild-to-moderate hallucinations	4
	Permanent, severe hallucinations	7
Agitation	Normal activity	0
	Slightly higher activity	1
	Moderate restlessness	4
	Severe restlessness	7
Anxiety	No anxiety when resting	0
	Slight anxiety	1
	Moderate anxiety at times	4
	Acute panic attacks	7
Paroxysmal Sweating	No sweating	0
	Sweating only on palms	1
	Beads on the forehead	4
	Severe sweating	7

Advocates of this therapy argue that ethanol provides effective prophylaxis against AWS without the excessive sedation observed with benzodiazepine therapy. Weinberg et al. have recently compared intravenous ethanol versus diazepam for alcohol-withdrawal prophylaxis in the trauma ICU and concluded that intravenous ethanol offers no advantage over diazepam with respect to efficacy or adverse sedative effects.[49] Because of the paucity of well-designed clinical trials, its inconsistent pharmacokinetic profile, narrow therapeutic window, and close monitoring requirement, intravenous alcohol should not be used routinely.

Treatment of AWS and DT

The treatment for AWS has been extensively studied. Benzodiazepines form the cornerstone of therapy, and clonidine, haloperidol, beta-blockers, and propofol have been shown to be useful as adjuncts. Patients being treated for major AWS should also receive thiamine and have serum electrolyte concentrations monitored.

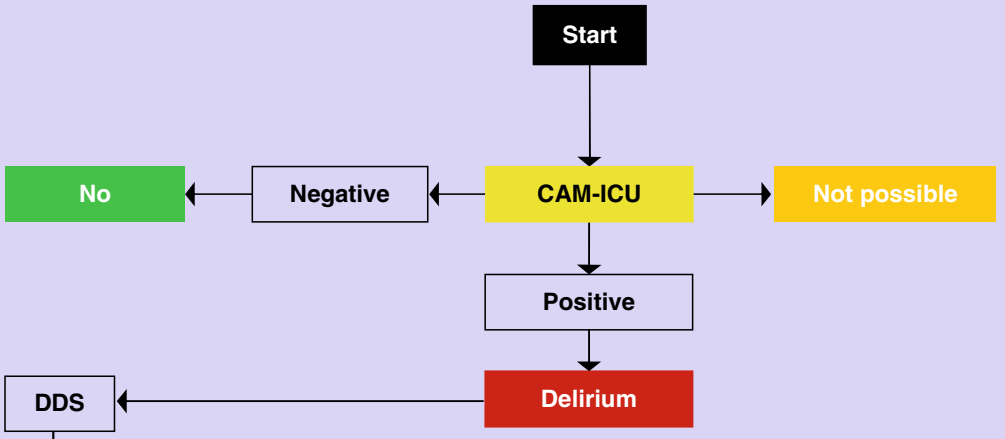
Although there has been extensive research on pharmacological interventions aimed at ameliorating withdrawal symptoms, the studies are widely dispersed in the medical literature, involve few subjects, and are often of uncertain methodological quality. Recommendations from authoritative sources vary widely, some advocating drugs that have never been tested in clinical trials or for approaches that result in the administration of unnecessary medication.[45,50] Most studies have failed to use an international scale to quantify AWS.[45,50] In some studies, even the differentiation among autonomic signs, hallucinations, and the delirious state is missing.[45,50] In many studies, too few patients were tested to be able to detect differences among regimens.[45,50] Notwithstanding, evidence-based practice guidelines have been developed for nonsurgical patients.[50]

Recent recommendations for treating AWS suggest a symptom-triggered approach based on a frequent objective assessment of the patient (Table 56.4). In the symptom-triggered approach, the patient receives medication only when symptoms exceed a threshold of severity, rather than on a fixed schedule. This approach is as effective as fixed-dose therapy, but requires significantly less medication. It does, however, require careful and frequent monitoring[51].

Benzodiazepines

Benzodiazepines are suitable drugs for treating AWS. The choice among different drugs should be guided by duration of action, rapidity of onset, and cost. Because withdrawal severity varies widely, and the amount of medication needed to control symptoms can also vary significantly, AWS cannot be adequately treated by a fixed standardized dose for all patients. Treatment should allow for a degree of individualization so that

TABLE 56.5. Symptom-oriented therapy of delirium in the ICU. If the patient has a positive CAM-ICU, delirium therapy should be started according to the DDS. Benzodiazepines are used for anxiety, haloperidol or risperidone for hallucinations, and α-2-agonists for autonomic symptoms and signs.



Hallucination				
≥1 point	Haloperidol	3 x 0.5 mg IV	Risperidone	2 x 0.25 mg PO
≥4 points	Haloperidol	3 x 1.5–2.5 mg IV	Risperidone	2 x 0.5 mg PO
≥7 points	Haloperidol	3 x 5 mg IV	Risperidone	2 x 1.0 mg PO
Anxiety				
≥1 point	Lorazepam	Titrate 0.25–0.5 mg IV	Midazolam	Titrate 1–2 mg IV
≥4 points	Lorazepam	Titrate 0.5–1.5 mg IV	Midazolam	Titrate 2–4 mg IV
≥7 points	Lorazepam	Titrate 1–2 mg IV	Midazolam	Titrate 4–5 mg IV
Agitation and vegetative symptoms				
≥1 point	Clonidine or Dexmedetomidine	Start 60 µg/h IV Start 0.1 µg/kg/h IV	Clonidine patch 0.1 mg/day	
≥4 points	Clonidine or Dexmedetomidine	Start 120 µg/h IV Start 0.3 µg/kg/h IV	Clonidine patch 0.2 mg/day	
≥7 points	Clonidine or Dexmedetomidine	Start 180 µg/h IV Start 0.5 µg/kg/h IV	Clonidine patch 0.3 mg/day	

TABLE 56.6. Prophylaxis and treatment for AWS/DT in surgical intensive care patients.[47,59]

Prophylaxis

Start with benzodiazepines (diazepam 2.5–10 mg, lorazepam 0.5–2 mg, or chlordiazepoxide 5–25 mg, PO every 6 h) or clonidine (PO or transdermal 0.1–0.3 mg/day)

Monitor patient every hour by DDS to maintain score <8 for 24 h

Therapy

Start with benzodiazepine (titrate lorazepam 0.25–2 mg IV or midazolam 1–5 mg IV)In case of psychosis, add haloperidol (3×0.5 mg – 5 mg IV) or risperidone (2×0.25 mg – 1 mg PO)

In case of vegetative symptoms, use clonidine (0.1–0.3 mg/day patch or 60–180 mg/h IV) or vdexmedetomidine (0.1–0.5 mg/kg IV

Do a symptom-oriented, bolus-titrated approach as needed[39]

Titrate medication immediately to decrease DDS to <8, then monitor patient every hour by DDS until score has been <8 for 24 h

Monitor electrolytes closely

Use propofol as rescue medication

patients can receive large amounts of medication rapidly if needed.[45,50–52] Individual treatment should be based on withdrawal severity as measured by withdrawal scales, comorbid illness, and history of withdrawal seizures. Trials comparing different benzodiazepines have demonstrated that all seem similarly effective in reducing signs and symptoms. Some evidence suggests that longer-acting drugs, such as diazepam, may be more effective in preventing seizures.[45] Few data are available on the comparative efficacy of benzodiazepines in reducing delirium.[53–56] Pharmacological and clinical experience suggests that longer-acting benzodiazepines can pose a risk of excess sedation in selected groups, including the elderly and those with marked liver disease.[53–56] Longer-acting benzodiazepines, however, contribute to an overall smoother withdrawal course with less breakthrough or fewer rebound symptoms.[53–56] Certain benzodiazepines have a higher risk of abuse, and the cost of these drugs varies considerably.[45]

Adjuvant Therapy

Clonidine, neuroleptic drugs, and beta-blockers may be used as adjunctive therapy but are not recommended as monotherapy because they reduce the seizure threshold.[45,51] In cases of withdrawal refractory to standard therapy, propofol can be used. To prevent Wernicke's encephalopathy, thiamine (vitamin B-1) should be administered to all patients with alcohol dependence at the initial examination.[45] Electrolytes should be replaced if their serum concentrations are low.

Clonidine is a central alpha-adrenergic agonist that has been shown to be as effective as chlordiazepoxide and more effective than placebo in treating the signs and symptoms of AWS.[53,54] Clonidine attenuates central sympathetic outflow and reduces plasma catecholamine levels, resulting in a decreased heart rate, reduced frequency of tremors, and less diaphoresis. It can produce hypotension and has no effect on delirium or seizures. Thus, it should only be used in conjunction with sedatives and hypnotics. Dexmedetomidine is a more selective alpha-2 agonist that is emerging as an alternate therapeutic agent in the management of AWS because of its efficacious and safe profile. Hypotension and bradycardia are its most significant side effects.[55]

Haloperidol is a butyrophenone derivative with antipsychotic properties that has been considered particularly effective in the management of agitation. Haloperidol can reduce AWS symptoms but can also reduce the seizure threshold, increasing the risk of withdrawal seizures. Because haloperidol has alpha-adrenergic blocking properties along with anticholinergic activity, it can produce hypotension and tachycardia. It also has the potential to increase the QT interval, leading to torsade de pointes, especially in patients with hypomagnesemia.[56]

Beta-blockers reduce autonomic manifestations of AWS and relieve most arrhythmias. Beta-blockers do not prevent the occurrence of seizures and should be used only in conjunction with benzodiazepines. Furthermore, delirium is a known side effect of beta-blockers, particularly those with good central nervous system penetration, such as propranolol. Contraindications include insulin-dependent diabetes, hypotension, pulmonary disease with bronchospasm, congestive heart failure, and second- or third-degree heart block.

Propofol has been suggested for control of agitation in cases of withdrawal refractory to standard therapy.[57–66] Although propofol is used extensively in the ICU for sedation, there is limited literature on its use for the control of severe alcohol withdrawal. There are several properties that make propofol an attractive drug in cases of severe alcohol withdrawal and DT. Propofol is easily titratable, and has a rapid metabolic clearance. Propofol activates the GABA-A receptor–chloride ionophore complex and inhibits the NMDA subtype of glutamate receptor while benzodiazepines are only active on GABA receptors.[65] Thus, it is hypothesized that the hypermetabolic state of severe withdrawal, not controlled with benzodiazepines, is the result of their lack of effect on the glutamate receptors.[57–66]

Thiamine deficiency is frequent in patients with AUD and can cause Wernicke encephalopathy, which is characterized as a triad of acute mental confusion, ataxia, and ophthalmoplegia. Korsakoff amnestic syndrome is a late neuropsychiatric manifestation of Wernicke encephalopathy with memory loss and confabulation; hence, the condition is referred to as Wernicke–Korsakoff syndrome or psychosis. The mechanism appears to be associated with the accumulation of pyruvate secondary to the lack of efficacy of pyruvate-dehydrogenase in the thiamine-deficient patients (Fig. 56.2). It is most often seen in alcoholics, but it can be seen in disorders linked with malnutrition and also in patients on long-term hemodialysis or with acquired immunodeficiency syndrome (AIDS). All patients with AWS should receive thiamine even in the absence of symptoms and signs of Wernicke encephalopathy. The dose of thiamine required to prevent or treat Wernicke encephalopathy may be as high as 300–400 mg given once a day parenterally. Thiamine should be given prior to the

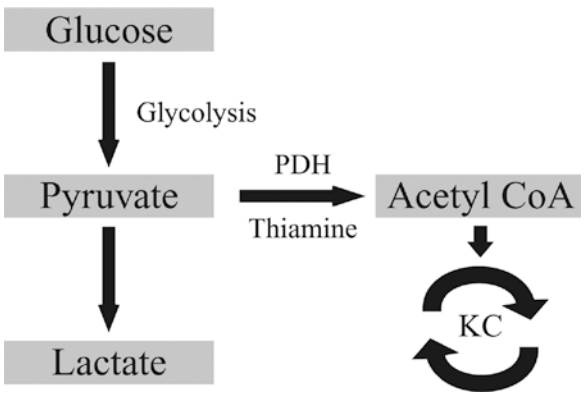


FIG. 56.2. There is a reduced efficacy of PDH in thiamine-deficient patients resulting in an accumulation of pyruvate.

intravenous administration of glucose solutions, because administering dextrose in a thiamine-deficient state can precipitate Wernicke encephalopathy.[45]

Electrolyte abnormalities such as hypophosphatemia, hypomagnesemia, hypocalcemia, and hypokalemia are common in patients with AUD. The mechanisms for the electrolyte depletion are multifactorial and the severity and clinical importance of these disorders depend largely on the quantity of alcohol ingested, the duration of drinking, and associated factors, such as malnutrition, chronic liver disease, and intercurrent illness. Patients with AWS should have their serum electrolyte concentrations measured and abnormalities corrected (see Chap. 40). Patients with Wernicke encephalopathy are frequently hypomagnesemic and should be treated empirically with parenteral magnesium sulfate, as they may be unresponsive to parenteral thiamine when their total magnesium stores are low.

Conclusion

The literature on AWS emphasizes the importance of performing a preoperative assessment in patients with a suspected AUD. Because these patients are difficult to diagnose and treat in surgical settings, a multimodal approach is highly recommended.[66] Alcohol withdrawal syndrome is usually preventable with adequate prophylaxis. If AWS develops after surgery or trauma, immediate therapy is required. Therefore, a monitoring tool to diagnose AWS and DT is mandatory. The symptoms of AWS and DT can be controlled using the combination of a benzodiazepine (in Europe known as chlormethiazole) with haloperidol or dexmedetomidine/clonidine. Propofol can be used in refractory cases of DT. The drug regimens must be individualized and symptom-oriented to treat hallucinations and autonomic signs. Dosages are generally increased compared to those in detoxification units. Patients treated for alcohol withdrawal should eventually be referred to alcohol dependence programs for long-term management.

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Ethics and the End-of-Life Care

Dan R. Thompson

Ethical Theory and Principles

The basis for much of what we find to be ethics rests in theory and principles. Although the terms *ethics* and *morality* represent the same concept and therefore are interchangeable, we generally use the term *ethics*. *Bioethics* is the common term for ethics in the biosciences, which includes medicine. The term *morality* seems to have a religious overtone. We will examine the concepts from a Western perspective, but ethical principles should truly be considered universal and not dependent on location. Although this might not necessarily be true, discussion of that issue is beyond the scope of this chapter. The study of bioethics is based on four simple concepts – autonomy, beneficence, justice, and nonmaleficence – that we will review briefly.[1,2]

Autonomy

The principle most commented upon today is respect for autonomy. This has a more important place in the United States than perhaps in other parts of the world. The long history of individual rights in the United States differs from the history of individual rights in other parts of the world where the concept of the community may have proportionally more weight.

Respect for autonomy implies that the individual should be self-determining and that we have an obligation to respect the right of an individual to make his or her own decisions. Conflicts occur when questions arise about the individual's rational ability or capacity to make decisions.

The word *autonomy* comes from the Greek *autos* ("self") and *nomos* ("rule," "governance," or "law").[3] Originally it referred to self-government or self-rule. The position of the individual has superseded the implications of society in modern thought. The US Constitution and United Nations Human Rights Charter include important examples of the concept. Beauchamp and Childress describe it as the "personal rule of the self that is free from both controlling interferences by others and from personal limitations that prevent meaningful choice, such as inadequate understanding."[4] The person who is not completely autonomous is by definition at least influenced, if not somewhat controlled, by others and has problems in independently making his or her own decisions. Two conditions define the concept of autonomy: independence from controlling influences or liberty; and the capacity to make the decision or agency. The concept implies a respect for persons and comes from the traditions of Immanuel Kant and other liberal political philosophies.[4]

In modern society, one could argue that the individual's right to autonomy may be, and perhaps should be, constrained by the rights of others and society. Public health issues are examples of this constraint. Beauchamp and Childress write, "The principle of respect for autonomy should be viewed as establishing a stalwart right of authority to control one's personal destiny, but not as the only source of moral obligations and rights."[4] We need to be aware of potential limits. We should reflect on four different principles to consider these limits: harm, paternalism, legal moralism, and welfare.

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With the principle of harm, we may limit the freedom of others when the exercise of their autonomy would result in the harm of another. Restricting the freedom of a murderer or a rapist is obvious. We may also limit the freedom of a physician who has no intention of harming another, but who by his or her incompetence may do so. We may restrict the freedom and autonomy of a physician in not allowing him or her to care for patients. In this case, autonomy may be appropriately overridden. The individual who by exercising autonomy may harm himself or herself may also have an ethical issue. In this case, the principle of paternalism may be considered.

There is an assumption that the autonomous action is immoral and therefore should be controlled and not be performed within the principle of legal moralism. The basis for the restriction of the autonomy of another is that the action is immoral. In the United States, deciding what is moral may be at times difficult to understand, and there will be questions about whether laws should be enacted to regulate morality. Examples include the use of alcohol or other drugs, divorce, birth control, and abortion. The legal restrictions are enacted into law based on an assumption of immorality.

With the welfare principle, it is considered appropriate to withhold individual autonomy when it benefits others, particularly society as a whole. It is a necessary condition that this does not require "serious" self-sacrifice in order for the welfare of others to be able to trump autonomy; it is akin to a little given up for the benefit of many. Mandatory organ donation at the time of death is an example of the welfare principle. Some philosophical positions would consider it appropriate to limit autonomy only from the standpoint of the harm principle.

Beneficence

Beneficence is not only the obligation to respect another's autonomy and not harm another (nonmaleficence), but also the obligation to contribute to the welfare of others. As professionals, we have a moral obligation to assist others. It is not simply enough to avoid harm. The principle of beneficence can be broken into two pieces: positive beneficence and utility beneficence. Positive beneficence requires that we provide benefits; utility beneficence requires that we balance the benefits and burdens in order to provide the best overall results. The cost must be considered as well as benefits and harms.

An obligation to provide benefits does not necessarily require great sacrifice and extreme altruism in every case. We do not have to put ourselves in a situation that is detrimental to us. The line between the obligatory and the moral ideal is unclear. As professionals, we have a relationship with our patients that may make the line more clear. The following general rules are important:

1. Protect and defend the rights of others.
2. Prevent harm to others.
3. Remove conditions that will cause harm to others.
4. Help persons with disabilities.
5. Rescue persons in danger.[3]

The biblical parable of the Good Samaritan is an example of beneficence. The Samaritan assisted a stranger when he was not required to do so; the interaction would have been considered uncomfortable during that era.[5]

Justice

Philosophers have used many terms to describe the concept of justice. These terms include *fairness*, *desert* (what is deserved), and *entitlement*. What is generally meant is the fair and equitable treatment of others. Standards of justice are important in order to protect those who have a rational claim and are therefore owed something in return. If we deny these claims, we commit an injustice.

It is common to think of justice only in the context of distributive justice. However, there are other types of justice, including criminal justice and rectificatory justice. Distributive justice means the fair and appropriate distribution based on a theory of social mutual aid. Distributive justice can be seen in taxation, property, resources, privileges, medical resources, welfare payments, and open opportunities. These issues formulate both benefits and burdens in a society. Criminal justice refers to punishment based on the law; rectificatory justice, a more legalistic concept, refers to compensation for breaches of trust in contracts and malpractice.

Nonmaleficence

The concept of *primum non nocere* ("first, do no harm") is thought to originate in the Hippocratic oath. The oath expresses an obligation of nonmaleficence in the line: "I will use treatment to help the sick according to my ability and judgment, but I will never use it to injure or wrong them." There is an important argument that nonmaleficence may be the most important principle for the physician. Refraining from inflicting harm on another may be more important than the other principles. Some feel that when two principles are in conflict, nonmaleficence should always take precedence. The physician will have to weigh the circumstances and vary the weight given each principle as appropriate.

Decision Making

When physicians have to make ethical decisions, it helps to have a method that will guide them in making those decisions. Organization in ethics may be as important as is organization in critical care.

The Four Boxes Concept

One of the easiest and most commonly accepted methods for decision making is the "four topics" or "four boxes" method, so called because some physicians divide a sheet of paper into four quadrants during development.

The concept of the four topics comes from Jonsen et al.'s *Clinical Ethics*.[6] Most physicians are familiar with the concept of the subjective, objective, assessment, and plan (SOAP) notes, and the division described works in a similar way. Divide the issue into four areas: (1) medical indications, (2) patient preferences, (3) quality of life, and (4) contextual features. Each area is correlated with one or more of the four ethical principles: respect for autonomy, beneficence, justice, and nonmaleficence. The format is one of a series of questions and a sorting out of the resulting information.

Medical Indications

Medical indications include those medical facts that are relevant to the ethical questions. What are the patient's medical problems and history? What are the goals of this treatment; are those goals obtainable; and is there a backup plan if the treatment plan does not work? Do these goals benefit the patient? What is the patient's prognosis? These are the issues most clinicians are use to facing, but they require a thorough assessment of the long-term outcome potential. This can be a hard process, as the information may not be well understood; however, it is a matter of understanding for everyone involved in the process. This group of questions is based on the principles of beneficence and nonmaleficence.

Patient Preferences

What are the patient's preferences and what is the patient's understanding? Frequently, the patient in the critical care unit cannot speak, but can communicate by lip reading and by using a set of questions that can be answered "yes" or "no." At other times, the patient can state his or her wishes. An assessment of the patient's capacity is important, remembering that capacity is task specific. "Capacity" is different from "competency," which is a legal term. This discussion requires that the patient have a good understanding of his or her condition, including the possibility that the condition may be able to be resolved. If the patient does not have the capacity to make decisions, the *surrogate,* or *proxy*, is the person who can appropriately speak on behalf of the patient. Has the patient expressed his or her wishes in the form of an advanced directive (AD) that instructs the surrogate or discussed those wishes with the surrogate in the past?

Advanced directives (AD) almost always have an "if … then" clause. The AD usually goes into effect when a certain situation is present – "*if* I am in a terminal condition" or "*if* I cannot reasonably be expected to regain consciousness," for instance. Are the conditions that are usually attached to the AD present? If they are, then the AD usually should be honored. At times the patient may appoint a surrogate to help carry out the instructions explicitly. The AD is only a guideline and is written to allow the proxy to act as he or she thinks is right under the circumstances. Generally, the surrogate is only to act if the situation does not match the "if … then" statement. If the situation does not match, does the AD give the surrogate the right to make decisions that are not elucidated in the document? Does the surrogate know the patient's wishes, or is the surrogate substituting his or her own wishes? Once a decision has been made, will or can the patient cooperate with the treatment plan? This part of the process is designed to respect the patient's choices of care to the extent possible. This group of questions is based on the principles of respect for the patient's autonomy.

Quality of Life

The concept of quality of life takes into account the past, present, and future. What was the patient's quality of life before the present illness? Can the patient return to his or her former quality of life or to a better quality of life, and what are the odds of this? An important consideration is that a restorative treatment plan may not be generally considered acceptable to everyone, including the patient. What will the patient's quality of life be if the goals of treatment can be accomplished? Does or would the patient find this quality of life to be acceptable? What factors in the patient's life may affect the decision? What issues may make the patient's condition and future quality of life likely to be undesirable? Has the patient thought about the limitations of therapy, withdrawal of therapy, or palliative therapy? Discussion of or thinking about these issues is often lacking or insufficient. Talking and thinking about these issues with the patient or surrogate can help to clarify the situation. This series of questions rests on the principles of beneficence, nonmaleficence, and respect for the patient's autonomy.

Contextual Features

Contextual features are those factors in the environment in which the patient exists and makes decisions that potentially affect the decisions. These include family relationships, relationships among health care providers, and even finances. Family support for both the patient and his or her spouse is frequently at the heart of the contextual features. The patient's or family's ethnic background and religious beliefs frequently come to the forefront in these areas, particularly in end-of-life issues.

The health care team may find issues of allocation of resources, confidentiality, and law that direct decisions; there may also be conflicts of interest among the health care providers and the institution. These issues need to be put into perspective. These questions highlight the principles of justice, loyalty, and fairness.

Resolution

At this point, the health care team should have enough information to be able to make a decision on what should happen in the given situation. The resolution should be acceptable to all the parties – patient, surrogate, and family – if possible. Sometimes this process can be done by the clinicians or social workers involved in the care of the patient; other times, an outsider such as the ethics consultant or members of the hospital's ethics committee may be able to help.[7] It is important to remember that (1) the resolution

needs to address what is clinically possible, and (2) the health care providers need to be ethically comfortable with actually carrying out the plan. When members of the health care team are not ethically comfortable with this process, they should be excused from participating. This is particularly important in issues of life support.

Foregoing Life-Sustaining Therapies

Discussion about the difference between withdrawing treatment (stopping established treatment) and withholding treatment (not starting treatment) has stirred controversy in both philosophical and religious theory. Many people believe there is a *prima facie* difference between withdrawing and withholding treatment; others do not. There is a sense that it is more difficult to stop therapy once started than to not start it at all. One is an act of commission; the other an act of omission. The feeling is that the act of withholding treatment is of a passive nature and that of withdrawing treatment is active.

The major religions differ to a certain extent on the issues of withholding versus withdrawing therapy. In Catholicism there is considered to be no difference between withholding and withdrawing therapy; whereas in Orthodox Judaism there is considered to be a difference between withholding and withdrawing therapy, and after therapy is started it cannot be withdrawn. At times, the actual nature of beliefs must be elucidated; at other times, misconceptions may need to be clarified. Clergy and ethics consultation may be of help.

This is a problem in a philosophical sense: If there is truly a difference between withholding and withdrawing therapy, then the health care team may be reluctant to initiate potentially efficacious treatment if they foresee a need to stop that treatment in the future (to do no harm). As a result, the patient might be denied beneficial treatment. In order to avoid this ethical dilemma, a proposed Israeli law suggests using ventilators with timers for critically ill patients in order to avoid breaking Jewish religious law that forbids any active human withdrawal of treatment that would result in death.[8] For example, a critically ill patient could be put on a ventilator that is set to run for a specific number of days and then automatically turns itself off. The medical team and patient's family would then have the option of turning the ventilator back on or letting it remain off so that the patient may experience a natural death.[8] In general, we tend to require a more considered rationale for withdrawing therapy than we do for withholding therapy because it seems to feel different.

Definitions

Extraordinary or Ordinary

We frequently discuss treatments as being ordinary or extraordinary, and understanding the history of the formulation of the concept can be helpful. Catholic moral theology is the basis for the concepts of ordinary treatment (and therefore obligatory) and extraordinary (therefore optional) treatments; the original notion revolved around the use of surgery before the availability of antisepsis. Refusal of treatment if it was without risk or if it would be clearly beneficial would be a form of suicide, which, by church law, is forbidden. Optional therapy (therapy that carries significant risk) is considered just that, not mandatory. There has been much discussion made of this topic.

Gerard Kelly, a Jesuit theologian, provides an excellent definition of ordinary and extraordinary means of treatment:

> Ordinary means are all medicine, treatments and operations that offer a reasonable hope of benefit and which can be obtained and used without excessive expense, pain or other inconvenience. Extraordinary means are all medicine, treatments and operations, that cannot be obtained or used without excessive expense, pain or other inconvenience or which, if used, would not offer a reasonable hope of benefit.[9]

Others have used the balance between benefit and burden to distinguish between ordinary and extraordinary. In this case, although there may be a benefit, if the burden is high, the treatment may be considered optional. Perhaps a better way to think about the moral concept is to consider not optional and obligatory, but rather the balance of the benefit and the burden to the patient. Not surprisingly, the meanings may differ from patient to patient and from physician to physician, as well as between physician and patient, and patient and family or surrogate. An explanation of the terminology can be helpful to everyone's understanding.

Autonomy

Capacity and Competency

We frequently discuss the competency of a patient to make decisions, but it is important to note that competency is really a legal term that is made by the courts. Capacity is what we frequently need to know in making these decisions. Capacity is task specific; that is, a person may have the ability to do some tasks but not others. A person may not be able to take care of his or her financial affairs or balance a checkbook but may be able to decide about medical care.

Physicians who know the patient should not have other physicians make these decisions. Familiarity with a patient is more important than the input of neurologists and psychiatrists acting as consultants.

Surrogate Decision Makers

In some cases, the patient may not have the capacity to make a decision. Patients with severe brain damage, coma, psychosis, or other mental-health impairments frequently have

lost their ability, at least temporarily, to give their consent or exercise their own autonomy. A person with any of these diagnoses may not necessarily lack capacity. The court has ruled that the diagnosis in itself is not the determining factor, but rather the patient's ability.[10] The nature of the patient's physical state is what has deprived him or her of capacity. The patient's moral status as an individual human being is intact, but the person is not able to exercise it. The patient still merits respect. Infants, children, and people with severe developmental disabilities do not have the capacity to exercise their autonomy, not because they have lost it but because they have never had it. In these cases, we usually have another person – a surrogate, or proxy – exercise the autonomy for the individual who is unable to do it.

"Surrogate" is the more common ethics term and "proxy" is the more common legal term. Within reason, both mean the same thing. We assume that the surrogate has the same rights as the patient to exercise the autonomy of the individual, particularly when legally designated. From an ethical standpoint, assuming that the surrogacy is accepted, the decision-making process should be no different than that of the individual exercising his or her own autonomy. In New York and other states, the proxy is legally defined. The legal issues are complex and will not be discussed here. However, the process adds a layer of responsibility onto the professional. Respect for the autonomy of an individual assumes that each can make a truly informed, voluntary choice, and the professional's responsibility is to protect the interests of the patient.

When a surrogate is making a decision, there can be a limit to the choices. A surrogate cannot exercise exactly the same powers as the patient he or she represents, in that the surrogate cannot reject truly beneficial treatments except in very unusual circumstances. The surrogate can take three different paths:

1. The surrogate may know the patient's wishes and exercise the patient's autonomy from a real knowledge of those wishes.
2. The surrogate may not know explicitly what the patient would do, but may know the patient well and be able to use that knowledge of the patient to make the decision.
3. The surrogate may use what is called the *substituted judgment principle* and do what a reasonable person would.

Alternatively the surrogate may be uncomfortable in making any decision to the point of ignoring the patient's wishes and making a decision based totally on the surrogate's own fears. The professional must not only respect the patient's autonomy as expressed by the surrogate but also protect those rights as long as founded. We usually error on the conservative side when the patient's wishes are not known. So there are real and assumed limitations on the exercise of a surrogate's autonomy on behalf of the patient. These limits differ from the informed, autonomous, and free exercise of the autonomy of an individual.

Appointed

When appointed by the patient, the surrogate usually has a document that explains his or her rights and the situation that allows the surrogate to exercise those rights. It is important that advanced directives, whether in appointing a surrogate or describing the individual's wishes, are always "if … then" statements. This means that there are conditions that have to be met before the instructions go into effect. At times, obtaining the document is problematic and due caution must be exercised in locating the latest document.

Family

When there is no patient-appointed surrogate, the physician turns to the family to exercise the patient's rights. Although this can be helpful, it can also be challenging. Family members frequently know the patient's wishes but may not have the same feelings. This may stem from different values or may be related to fear of loss of the patient in end-of-life situations. Understanding what the patient is willing to endure may be different from what the family thinks is appropriate.

Friends

When no family members are present or available, friends who know the patient well may be the appropriate choice to speak for the patient. Friends frequently will function within the same three situations that the legally appointed or family surrogate does.

Court-appointed

At times, the issue of a surrogate can be solved only by going to court. If the individual is a "ward of the state," the only way to make a medical decision is through the court or by someone appointed by law or through court verdict. At other times, there may be a conflict either between the caregivers and family or among members of the family, and the court must intervene. In general, the court is reluctant to intervene unless all other avenues have been explored, including the hospital ethics committee.

Bioethics Consultation

At times and usually before going to court, the ethics committee process should be used to try to make a medical decision. In most but not all cases, the court will side with the considered opinion of the committee. The ability of the committee will vary in their ease and timeliness in coming to a decision.[7]

If in the course of a patient's care an ethical question arises that may not be easily answered or if an impasse develops

between people involved in the care of the patient, how does one get help?

Differences between Services

Ethics committees in hospitals have variable abilities and expertise. At some institutions, there will be an ethics consultation service, which may be the ideal. Sometimes an individual will be able to answer the question promptly. Other times, it may be necessary to gather the committee, which will take more time but may be necessary or desirable in some cases.

Effective Use of the Ethics Consult

How then does one get the most out of the ethics consultation? Like most medical consults, explaining exactly what you want to know will help the consultants understand the issue. Frequently, the impasse is one that requires an outside individual who can support various parts of the team or family. At times, the support for members of the health care team and the debriefing of staff can be very valuable. At other times, mediation is necessary and is a skill that can be very important in resolving issues. Several good books on mediation are available that apply to ethics and perhaps the best is that of Dubler and Liebman.[11]

Special Problems

Artificial Nutrition and Hydration

The problem of withholding or withdrawing nutrition or hydration can be complex. There are not only the issues of the feelings of the patient and surrogate but also the issues of religious and legal aspects. A lot of emotion surrounds the decision to withhold or withdraw something thought to be as basic as nutrition or hydration. Some think it is cruel and uncomfortable. There is very good literature available addressing the controversy.[12,13] In general, the patient will not be uncomfortable with this process, as explained by Ganzini and colleagues in a study of hospice patients who voluntarily chose to refuse food and fluids. They "usually die a comfortable 'good death' within 2 weeks of stopping both."[12]

We cannot ethically withhold food and nutrition from those who can take it by mouth, but only in the situation of it being given by "artificial" means – i.e., feeding tube, G or J tube, or total parenteral nutrition. Clearly one must balance risk with benefit and assessment of benefit may be clearer when one accepts that the patient will not be uncomfortable.

Physicians and other health care professionals also must follow their own consciences and should not have to participate in treatments they find against their personal beliefs and ethics. Unfortunately, the fiduciary bond that professionals have with their patients can make this difficult or impossible.

Transfusion

Over recent years the transfusions of blood products has received particular attention. Transfusion can be very problematic when dealing with Jehovah's Witnesses. The religious basis for refusing transfusion was formulated 60 years ago and has undergone minor revisions. The changes reflect the issue of "disfellowshipping" the individual who accepts blood. Disfellowshipping involved shunning the individual and was an important control tool in the process. Now things are somewhat different:

Under recent changes in the policy of refusal of blood by Jehovah's Witnesses, members can remain silent about the medical treatment they receive and avoid religious punishment. Such freedom of conscience hinges on the integrity of medical confidentiality, which may not be adequate for Jehovah's Witnesses.[14]

In general, the patient or family will refuse the administration of red and white cells and platelets, but will permit the use on a conscience-basis of albumen and some other blood products. Physicians in many areas in the United States offer minimal-loss surgery and alternative treatment for these patients and may be available to offer advice to other caregivers.

In the past, committees from the church often made these decisions, but now the patient/member can make their own decisions and "not object to the administration." In this case, the patient/member may not necessarily be subjected to a religious determination of revocation of membership; rather, the patient/member effects that revocation by his or her own actions:

In June 2000, the Watchtower Society issued a directive stating that the organization would no longer disfellowship members who did not comply with the policy of refusal of blood. Its official statement to the media was that "if a baptized member of the faith willfully and without regret accepts blood transfusions, he indicates by his own actions that he no longer wishes to be one of Jehovah's Witnesses. The individual revokes his own membership by his own actions, rather than the congregation initiating this step. This represents a procedural change instituted in April 2000 in which the congregation no longer initiates the action to revoke membership in such cases."[14]

The important issue is one of discussion with the patient and then keeping the discussion confidential. Some patients will accept the transfusion as long as the family does not know about it. The physician should not expect that this would necessarily happen. The process of administering the transfusion in private and not discussing the issue with anyone but the patient must be clearly and rigidly followed in order to protect the patient's decision and privacy. Failure to protect confidence from family and church members may result in isolation for the remainder of the patient's life. The refusal should be allowed on the basis of the patient's autonomous choice of refusal of beneficial treatment. The physician must be cautious of others refusing for the patient who is awake,

particularly in view of the change in church position. Many patients carry cards or have signed documents that church members or family present. These should be handled the same way as any other advanced directive.

The issue with children is different. In most cases, the State will assume responsibility for the child and will order the transfusion and not permit the family to make the decision of refusal. But the issue will generally have to be taken to court. When there are disputes, the court may need to intervene even with adults. Some states, such as Pennsylvania, have systems that facilitate this action.

End-of-Life Care

Admission to the intensive care unit should be viewed as a trial. The goal of all who participate in the care of the critically ill or injured patient is survival of the patient. At times, the trial fails and the health care team needs to be prepared to shift from curing to comforting. Some refer to "comforting" as *caring*, but we all assume that we are caring all the time.[15] When the primary goal of critical care medicine changes from curing to comforting, things may feel different but end-of-life care is as important as the earlier curative component. Generally, most people will want to avoid death, and some physicians may actually feel that the death of a patient is a sign of failure. If death is the alternative, many patients who have little hope for a cure will pay a high price to continue the struggle to live.[16]

At this time, perhaps more than ever, communication with the patient and family members is crucial. Involving clergy may be particularly important in order to provide support for what may be a spiritual crisis.

At the end of life, it is important to recognize that it is acceptable to offer a limited number of options that make sense in the process. Changing to no intubation but permitting cardiopulmonary resuscitation (CPR) probably makes no sense and should not be offered because intubation is part of CPR. However, limiting CPR to the initial shocks of the American Heart Association (AHA) algorithm may make sense. It is most important to maintain comfort for the patient and limit those things that cause discomfort. Treatment and care plans should be discussed with the patient, if appropriate, or with the family. One should avoid phrases that suggest discomfort, such as agonal breathing.

Initiating pain-reduction and anxiolytic therapy should generally be a first step in end-of-life care. Truog et al.'s article from the American College of Critical Care Medicine Guidelines provides an excellent discussion of the many approaches to this topic.[17] One approach is to start an intravenous solution of morphine and chlorpromazine in dextrose and water. Once comfort and sedation have been assured, the fractional inspired oxygen may be decreased to room air and the positive end-expiratory pressure (PEEP) to zero. If vasoactive medications or other cardiotonic drugs are being given, they should be discontinued. Then the ventilator may be withdrawn. How this is done should be carefully discussed with the family. Some physicians like to use a staged withdrawal and others like to switch to no ventilation and extubate the patient. One needs to be prepared for the fact that the patient may not have a patent airway and consider the use of a nasal trumpet or other means to provide an airway. Some physicians will leave the endotracheal tube in place; most will leave a tracheotomy if this is present. The physician must be very attentive to the situation to make sure that the process goes smoothly. As much as possible, everything should be discussed and planned in advance.

Ethics in Critical Care Research

Research in critical care is an important component in improving the quality of patient care. Many of the same issues are present here as in other areas of medicine. The primary difference is that many of the patients will not be able to provide informed consent to participate in the research as they lack the capacity because of their illness. In addition, sometimes the situation is emergent and time is at premium.

The ethics of research has had its share of problems over the years. This came to the forefront following the trials of the Nazi doctors who were convicted of murder. The trial verdicts also produced the Nuremberg Code.

The Nuremberg Code included ten points:

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random or unnecessary.
3. The experiment should be designed based on the results of animal experimentation and knowledge of the natural history of the disease or other problem under study so that the anticipated results will justify the performance of the experiment.
4. "Unnecessary physical and mental suffering and injury" should be avoided.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur, except, perhaps in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations must be made and facilities available to protect the subjects against even remote possibilities of injury.
8. The research must be conducted by scientifically qualified researchers.

9. The research must be terminated if it becomes clear that the subject will be harmed.
10. The subject must be allowed to withdraw voluntarily at any time.[18]

These principles are much the same as those that were already in effect prior to World War II and they were not necessarily original, but their placement in the judgment of the court gave them exposure. Ironically, one of the most complete set of standards for medical ethics, the Richtlinien of 1931, was written by the German Department of the Interior. Nevertheless, the doctors tried at Nuremberg had ignored the basic tenets that we now deem important as well as the guidelines that already existed in their own country.

The Japanese conducted equally brutal experiments that were largely ignored so that the occupying Western powers in Japan would have access to the scientists who had information on biological warfare. The silence was broken by Williams and Wallace in 1989.[19]

It was not only in Germany and Japan and during wartime that this occurred but also in the United States and other parts of the Western world. The Tuskegee Syphilis Study and the Willowbrook Hepatitis Experiments are two prominent egregious examples that occurred in the United States. Henry Beecher of Harvard University described the research that appeared in 22 articles published in the leading journals of the times that was considered unethical,[20,21] such as cervical cancer research in New Zealand, and the anesthesia study that prompted *Halushka v. University of Saskatchewan et al*. These issues and others resulted in the development of the US Code of Federal Regulations; the Declaration of Helsinki, written by the World Medical Association; and the Belmont Report.[22] The Belmont Report, in particular, was a reaction to the cases discussed above. It is important to note that the Tuskegee Study, which was conducted under the direction of the US Public Health Service, lasted much longer than it should have, with devastating consequences, despite the Belmont Report. Many researchers did not heed the lessons of the Belmont Report. The Belmont Report led to the written regulations of the US Department of Health and Human Services that we follow today.

The Belmont Report contains three principles: respect for persons, beneficence, and justice. Respect for persons led to a requirement for informed consent. Beneficence led to the determination of risk versus benefit in experimentation and its appropriateness. Justice led to the equitable selection of subjects.

Basic Requirements

The Nuremberg Code provides the basic requirements for all research, but it poses problems as mentioned previously. Perhaps there is no other place where research has such a potential for change, yet remains fraught with danger and difficulty in following the regulations and the ethical issues. Practicality and potential benefit to society must not allow us to trample on the rights of the research subject.

Conducting Critical Care Research

Patients with Decision-making Capacity

It is easier to have a subject who is capable of making his or her own decisions than one who is not, but the availability of those subjects may be limited in the critical care unit. Patients who seem to have capacity may not be free of the pressure of the situation when they are critically ill and may not understand either the process or the alternatives even when they are well presented. The physician must explain the situation clearly and carefully, preferably with family members or others in attendance who will be able to help ensure the patient's understanding. Nurses, social workers, clergy, and patient advocates are good examples of those who may have a positive role in ensuring that the patient can act autonomously.

Incapacitated Patients

Very often, patients in the ICU are so ill that they cannot make their own decisions. Some patients cannot speak because they are intubated, but they can communicate in other ways. One should not necessarily assume because a patient cannot talk that he or she is incapacitated; one should try to communicate with the patient. Having help from others will make this process easier. Consenting to participate in research, like consenting to accept treatment, is a process; in the case of research, however, there is no known direct benefit to the patient. The reason we do research is to find out whether something works. We need to remember that we really do not know if an experimental treatment works; if we did, there would be no equipoise and the process probably would not be ethical.

Proxy Consent

Recent controversies in the Acute Respiratory Distress Syndrome Network (ARDSnet) trial have brought to light the difficulties with the scientific design of studies.[23] Consent from critically ill patients is problematic for the reason of capacity both in thought process and in the stress of the situation when there is a tendency to want to try anything that has even a remote possibility of success. The Declaration of Helsinki clarifies the right of the family or surrogate to give consent for a patient to participate in research, but this is not uniformly recognized in the United States. Many states have legislation regulating who can consent for participation in research, and the federal government has a requirement for the "legally authorized representative" (LAR) to do so. Many states have not defined who that person can be and several of the original ARDSnet organizations have been cited for participating in this study without this definition of LAR in state regulations. The Office of Human Research Protections cited these institutions for not following their state's legislation or for lacking a definition and participating nonetheless.

Several states enacted legislation specifically to address the problem, but most have not.

Prospective Consent

One mechanism that would provide for prospective consent would be the addition of the proxy or surrogate's right to specifically consent to a patient's participation in research. In New York, this is the only way to do so.

Risk

Sometimes it is easy to determine the risk for the study in the intensive care unit; other times, the risk is not known. Reviewing the literature on humans and animals can form a reasonable basis for determining risk, understanding the disease process, and assessing the potential benefit. One can argue that treatment with known risks should only occur in the context of the research process when it is not known whether there is benefit.

Benefit

The issue of benefit is frequently difficult to determine and may be only applicable for future patients and not for the present subject. This is particularly true when comparing two types of treatment: one is an established treatment and the other experimental. Some people will choose only the known treatment, while others will want only the experimental one, about which little is known.

Informed Consent

We have spoken about the problem of obtaining consent. It can be difficult to obtain informed consent when little may be known about the potential results and problems of an experimental treatment. In addition, the person who obtains the consent is frequently the treating physician who is unknown to the subject or the family. The situation is also potentially conflicting because the patient is so ill and the family is depending on the person who is asking for consent. The confusion between an experimental and a known treatment exists not only for the patient and family but also for the person obtaining consent. The family may think, "If this is new, of course I want it for my loved one because it must be better," which may not necessarily be true.

Medical Emergency Consent

Obtaining consent may not be possible in emergency situations when the patient is not able and the family is not available. Research conducted in the field, in emergency rooms, and in the intensive care unit without consent prior to beginning treatment has special requirements. They are lengthy and require notification to the public. The research process is started without consent in these special circumstances and consent is obtained after the fact whenever possible. The concept has been used in the development of automatic defibrillators and the recent study on a blood substitute. The requirements, while cumbersome, are not impossible to implement.

Waiver of Consent

Federal regulations allow for waiver of consent in certain situations when there is minimal or no risk and privacy has been protected. These regulations are very clear, as are the conditions necessary to be allowed to waive consent.

Defining Death and Organ Transplantation

History

The history of determining death is thought by many to relate only to brain death, but the definition was debated years before. The invention of the mechanical ventilator made it possible to support patients who would have died a respiratory death in the past. The advent of organ transplantation made the clarification of the definition of death much more important and culminated in what is known as the Harvard Criteria[24] – a definition of brain death.

Brain Death

Whole Brain Theory

The concept of brain death was formalized by the development of the "uniform law" by the federal Uniform Law Commission. Two concepts are equated: death by cessation of functions of the heart and lungs, or by cessation of the functions of the whole brain. The concept was one of death of the whole brain, including the brain stem. This uniform law and those laws that are unique to individual states leave the actual process of determining death in most cases to medical judgment. In other cases, the process may be legislated by law or by requirements of each state's health department. It is important to know the actual requirements in the state in which one practices.

Adult

The current neurology and neurosurgical literature delineates recommendations for determination of death in adults.[25] The three criteria include: lack of cranial nerve functions, apnea testing, and lack of cerebral or cortical function. The cause of the coma must be determined and there should be no evidence of a drug or metabolic etiology that would interfere with the diagnosis.

The cranial nerve functions that are generally included in testing are pupil, corneal, "doll's eye" or oculovestibular, cold calorics or injection of ice water against the tympanum, and

absence of gag and cough reflexes. Sometimes vagal tone is tested with atropine injection. The trauma patient with an "uncleared cervical spine" may make the "doll's eye" maneuver difficult to test because of the inability to rotate the head safely. The brain-death evaluation should not be self-fulfilling.

Apnea testing is usually required only a single time and requires some skill to perform so that there are no adverse reactions. One must consider at all times that the patient is indeed alive until all the testing is completed and indicates otherwise. From the standpoint of the potential organ recovery, adverse effects on organs are important to avoid. In general, the patient needs a significant stimulus to breathe and that is usually a partial pressure of carbon dioxide of greater than 60 mmHg.[26] If the patient is unable to breathe unaided, a positive apnea test indicates brain death.

Lack of cerebral function can be inferred by the type of injury, or diagnosed following radiographic evaluation, CT scans, electroencephalogram, transcranial Doppler, MRI flow studies, or radionuclide cerebral blood flow studies. In patients with cardiac arrest, the testing is usually not performed until 24 h after the successful resuscitation.

Children

The determination of brain death in children may be a little different than in adults. Historical criteria for determining an immediate cause of death, as with adults, is the first step. The physical examination is similar in determining coma, apnea, and absence of brain-stem function. Perhaps what differs most is the observation period, which may vary from institution to institution and locale to locale. In general, in children under the age of 2 years, the use of confirmatory tests may be more frequent and there may be requirements for more than one apnea test.[27]

Philosophical and Religious Concepts

Some of the Jewish faith, particularly the Orthodox, may reject the concept of brain death as being consistent with their beliefs.[28] They recognize the concept of death in the cardiopulmonary tradition only. Although people have tried to reconcile this with the tradition of the beheaded individual, generally this has not been recognized. All states accept the determination of death to be by both cardiopulmonary and brain-death criteria. Two states make allowance for those with religious objections, but they are somewhat different: New Jersey law allows the family to object based on their religious beliefs and this must be honored; New York law says that the physician should consider the religious tradition of the individual – this ambiguity can be problematic.

Alternative Views to Whole Brain Death

A number of alternative definitions to brain death have been presented. The reasons to consider these concepts have their basis in the futility of treatments or organ donation. Probably the only two definitions to consider involve division of the whole brain concept. The cortical death theory suggests that what makes us "human" is our ability to think and reason, and if this ability no longer exists then we are effectively dead. The cerebral hemispheres no longer function, but the brain stem still functions and the individual may breathe, and the heart continues to beat. The anencephalic child is an example, such as happened in the case of Baby K and Fairfax Hospital. Baby K was born in Fairfax Hospital, Virginia, and the staff originally supported the mother's decision to treat the child. Later the child was placed in a chronic care facility and returned to the hospital for complications, requiring admission and mechanical ventilation. Eventually, the treating team refused to admit the patient to the hospital and ICU, which resulted in the case being taken to federal court and the team was charged with violating the Emergency Medical Treatment and Active Labor Act (EMTALA).[29]

In another definition, the brain stem does not function and the cortex is unable to process anything. This is similar to but different from the "locked in" syndrome. It differs in this case as there is no way to communicate with the outside nor is there reception into the cortex. All brain-stem function is lost and only the cerebral tissue remains. The patient does not spontaneously breathe and must be supported by a mechanical ventilator. The lesion is much higher in the brain stem. Brain-stem death has been proposed in some areas of Europe.

Organ Transplantation

Non-heart-beating Donor

If the patient's family decides to withdraw therapy or the patient's advanced directive includes instructions to do so, organ donation may be accomplished if an interest is expressed. The process came about secondary to the wishes of families, patients, and the organ-transplant community. The latter's interests were secondary to the extreme shortage of organs for transplantation.

In this case, either the patient does not meet the criteria for brain death or determination of death would be prolonged and the family does not want to wait. In order to have the possibility of donation, cessation of cardiac activity in a short time is necessary to avoid prolonged warm ischemic time and organ damage; that is, cardiac death must happen within a short period of time after withdrawal of the ventilator. Evaluation of the patient can usually determine whether this is likely in a reasonable amount of time. Obviously the patient must be a suitable donor, in particular for kidney donation.

Time of Death

The patient is taken to the operating room and prepared for donation; the team that manages the death cares for the patient until death from cardiac cessation occurs. This team determines

the time of death, which is usually a short time after cardiac activity stops. The time is short enough to avoid ischemia and long enough to ensure that auto-resuscitation will not occur. After the patient is pronounced dead, the organ recovery team may enter the room. The body is not placed back on the ventilator. The organ recovery team must be a separate team and not involved in the determination of death. The American College of Critical Care Medicine provides excellent guidelines for determining death in this group of patients.[30,31]

Conclusion

Understanding the concepts and issues presented in this chapter allows us to have a basis for everyday ethical problems encountered in the critical care unit. Basic knowledge of health care ethics and end-of-life care should be part of the armamentarium of every health care professional who works with the critically ill on a daily basis. There are many resources at our disposal that further explore these concepts including journals, books, meetings, and online courses. The ACCM book lists much of the literature now available.

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Scoring Systems and Outcome Prediction

Rui Moreno and Isabel Miranda

When you can measure a phenomenon about which you are talking and express it in numbers, you know something about it. But, when you cannot express it in numbers, your knowledge is vague and unsatisfactory. It may be the beginning of knowledge, but you progressed very little toward the state of science

–Lord Kelvin (1824–1907)

The rapid development and proliferation of intensive care units (ICUs) in the Western World during the last years created the systematic need for the evaluation of the effectiveness of their procedures and practices. Are those ICUs admitting the right patients at the right time? Are they discharging the right patients at the right time? Are the processes of care assuring, at the individual level, the best possible patient safety and, at a collective level, the best effectiveness of the clinical and nonclinical practices? In other words, are ICUs caring for the right patients at the right time and having the best possible results? So, in this young but dynamic specialty, there still exists little scientific evidence as to what treatments and practices are effective, and especially about the costs and the efficiency of the delivered care.

This evaluation is made more complex because intensive care is a complex process, which is carried out on a very heterogeneous population and is influenced by several non-clinical variables such as the differences in the background characteristics of the populations, in their lifestyles, in their cultural background, and in the different structures and organizations of the health care systems in different countries. It is, therefore, extremely difficult to reduce the quality of intensive care to a number, to something measurable, in order to quantify it and to compare it between different institutions.

The general severity-of-illness scoring systems were introduced in the field of critical care medicine in the early 1980s as a possible answer to these questions. Their rationale was close to perfection (better on the effectiveness side than in the economical side of the question) but their ease of use and interpretation, together with the appetence of intensivists for quantification, soon made them very popular.[1,2] At the end of the 1990s, the scientific community had several types of these instruments and their use was widespread, although not always correct.

Update on Terminology

At this moment, the intensivist can choose and use several different outcome assessment instruments. From these, the most common are *general severity of illness scoring systems* that aim at stratifying patients based on their severity of illness, assigning to each patient an increasing score as their severity of illness increases; and *general outcome prediction models* or *general prognostic models* that, apart from their ability to stratify patients according to their severity, aim at predicting a certain outcome (usually the vital status at hospital discharge) based on a given set of prognostic variables – assessed at a certain period in time – with one (or several) modeling equation(s).

They allow the clinician and the researcher dealing with severely ill patients to have the possibility to adjust for the underlying characteristics of the admitted patients (case-mix adjustment) and to standardize the outcome of different groups of patients. In this way, they allow the user to take into account all of the characteristics of patients known to affect

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their outcome, irrespective of the treatment received. Designed to be applied to heterogeneous groups of patients, they predict what would be the aggregated mortality at hospital discharge of a group of patients – with a certain number of comorbid diseases and a certain degree of physiologic dysfunction – if they were treated in a virtual Intensive Care Unit (ICU) used to develop the model.

During the mid-1990s, the attempt to develop instruments able to quantify not only mortality but also morbidity in specific groups of patients – especially in patients with sepsis – became evident and led to the development of the so-called *organ dysfunction/failure scores*, such as the Multiple Organ Dysfunction score (MODS),[3] the Logistic Organ Dysfunction (LOD) score,[4] and the Sequential Organ Failure Assessment (SOFA) score.[5] Organ failure scores are designed to describe organ dysfunction more than to predict survival, and their use at discharge to predict mortality after ICU discharge has been also described.[6]

Finally, some instruments have been designed to quantify the use of resources by each ICU patient, allowing not only an indirect prognostic estimation (since to some extent the severity of illness presents a positive correlation with the use of resources) but also to compute several efficacy indexes, such as the amount of nursing workload being expensed or the work utilization ratio.[7] All of them are quite similar in concept, assigning a certain number of points to each nursing activity and varying mainly in the number and type of tasks evaluated. For this reason, they are usually grouped under the name of *nursing* or *therapeutic activity scores.* The most common are the Therapeutic Intervention Scoring Systems or TISS (both the original[8,9] and its simplifications, including the TISS-28[10] and the Nine Equivalents of Nursing Manpower use score or NEMS,[11] or the Nursing Activity Score or NAS[12]).

Apart from these instruments, others have been introduced to be applied to unique types of patients (e.g., the Apgar score for newborns[13]) or to unique diseases (e.g., the Ranson score for acute pancreatitis,[14] the EuroSCORE for patients submitted to cardiac surgery[15]) or several specific systems for trauma, based either on the morphologic classifications of the underlying traumatic injury[16] or on physiology of the patient[17,18] or in a combination of both.[19]

They have all been criticized by their calibration based on pure Anglo-American databases, which hardly translate into different settings, and by their lack of prognostic accuracy in elderly patients presenting with various physiologic derangements and chronic diseases independent from the traumatic injury.[20] General severity of illness scores, such as the Simplified Acute Physiology Score (SAPS), on the other hand, work well in adjustment of physiologic derangement, but provide no means to describe the severity of trauma and, therefore, do also not perform well in trauma patients.[21] The issue is still a matter of debate, as recently stated by Glance et al. "it is currently impossible to use one of these systems to determine 'best of practice' for trauma care and recommended to update the existing systems."[22]

Given the general nature of this book chapter, we will just review the uses and potentialities of general outcome prediction scores and models in general surgical patients.

General Severity of Illness Scoring Systems and General Outcome Prediction Models

Introduced in most ICUs in the early 1990s (at least 50% of the general ICUs worldwide according to data not published from the SAPS 3 study), the Acute Physiology and Chronic Health Evaluation (APACHE II and III) models,[23,24] the New Simplified Acute Physiology Score (SAPS II),[25] and the Mortality Probability Models (MPM II)[26] had their golden era during the 1990s. These instruments have been used in almost all the clinical studies done during this period and constituted the basis for ICU evaluation in a series of national and international audit centers.

By the end of the decade, their prognostic performance began to slowly deteriorate as time passed. Differences in the baseline characteristics of the admitted patients, on the circumstances of the ICU admissions, and on the availability of general and specific therapeutic measures introduced an increasing gap between actual mortality and predicted mortality.[27] Overall, in the late 1990s, we witnessed in almost all countries of the world an increase in the mean age of the admitted patients, with a larger number of chronically sick patients and immunosuppressed patients, and an increase in the number of admissions due to severe infection and sepsis.[28–30] Also, an inappropriate use of these instruments outside their sampling space was responsible for some misapplication of the instruments, especially for risk adjustment in clinical trials.[31,32]

Temporarily, customization was used to face these problems. Since all the existing general outcome prediction models nowadays use logistic regression equations to estimate the probabilities of a given outcome in a patient with a certain set of predictive variables, the first possible approach to improve the calibration (the ability of the model to correctly predict outcome over the entire range of risk) of a model, when the original model is not able to adequately describe the population, is customization.[33] Several methods and suggestions have been proposed for this exercise,[34] based in the choice of one of two strategies:

- The customization of the logit (first level customization), introducing slight modifications in the logistic equation (without changing the weights of the constituent variables) such as proposed by Le Gall or Apolone[35,36]
- The customization of the coefficients of all the variables in the model (second level customization) as we described for the MPM II_0 model[33]

Both of these methods have been used in the past with a partial success in increasing the prognostic ability of the models.[33,37] However, both fail when the problem of the score

is based on discrimination (ability of the model to separate the patients into two groups; e.g., those who survive and those who die) or in poor performance in subgroups of patients (poor uniformity-of-fit).[38] This fact can be justified by the lack of new variables, more predictive in this specific context.

Examples of this approach have been the development in France by Jean-Roger Le Gall et al. of a customized SAPS II model and an expanded SAPS II model,[39] and the publication – also in France – by Philippe Aegerter et al. of another variant of the SAPS II model.[40] The publication in the UK, by David A. Harrison et al. of the Intensive Care National Audit and Research Centre (ICNARC) model,[41] is really at the border between an extreme adaptation of the APACHE II model – already customized at country level in the early 1990s by Kathy Rowan et al.[42–44] – and the development of a new system, although very country-specific.

During the last few years, three new general outcome prediction models have been developed and published: the SAPS 3 admission model in 2005, the APACHE IV in 2006, and the MPM III_0 in 2007.[45] They represent the current standards of practice in the use of these models in general populations, and for this reason will be reviewed here.

The SAPS 3 Admission Model

At almost the same time as the attempts to customize the existing models, our group decided to address the problem by starting from scratch. This effort resulted in the publication of the SAPS 3 admission model,[46,47] developed by Rui Moreno, Philipp Metnitz, Eduardo Almeida, and Jean-Roger Le Gall on behalf of the SAPS 3 Outcomes Research Group. The project was endorsed by the European Society for Intensive Care Medicine (ESICM), and supported by the Austrian Centre for Documentation and Quality Assurance in Intensive Care Medicine (ASDI), the Portuguese Society of Intensive Care (SPCI), and the Medical Economics and Research Centre (MERCS) in Sheffield, UK. The study used a total of 19,577 patients consecutively admitted to 307 ICUs all over the world from 14 October to 15 December 2002. This high-quality multinational database reflected the heterogeneity of current ICU case-mix and typology. The project was first intended to focus on Europe because it was believed that such a strategy would produce a more homogeneous cohort of patients, which would in turn provide a more stable reference line for further comparisons. This idea was discussed during several investigator meetings and finally abandoned, allowing the SAPS 3 database to better reflect important differences in patients' and health care systems' baseline characteristics that are known to affect outcome. These include, for example, different genetic make-ups, different styles of living, or a heterogeneous distribution of major diseases within different regions, as well as issues such as access to the health care system in general and to intensive care in particular, or differences in availability and use of major diagnostic and therapeutic measures within the ICUs. Although the integration of ICUs outside Europe and the USA surely increased its representativeness, it must be acknowledged that the extent to which the SAPS 3 database reflects case-mix on ICUs worldwide cannot yet be determined.

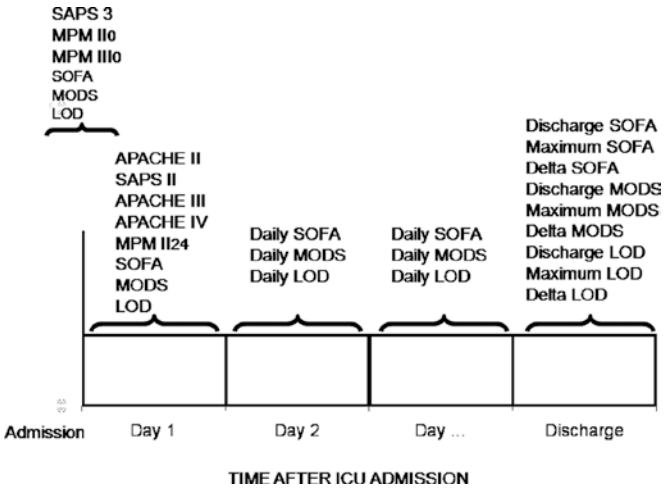

FIG. 58.1. Time window after ICU admission for the application of each severity score.

Based on data collected at ICU admission (±1 h), the authors developed regression coefficients by using multilevel logistic regression to estimate the probability of hospital death. The final model, which comprises 20 variables, exhibited good discrimination, without major differences across patient typologies; calibration was also satisfactory. Customized equations for major areas of the world were computed and demonstrate an overall goodness-of-fit. Interestingly, determinant of hospital mortality changed remarkably from the early 1990s,[24] with chronic health status and circumstances of ICU admission being now responsible for almost ¾ of the prognostic power of the model.

The model is completely free of charge for use in the scientific community and all the data and software needed for its computation are available at the project Web site (www.saps3.org). Several validation studies in Europe and South America seem to show positive results but they have not been published in full.

The APACHE IV Model

Half a year after the publication of the SAPS 3 model, Jack E. Zimmerman, one of the original authors of the original APACHE models, published in collaboration with colleagues from Cerner Corporation (Vienna, Virginia, USA) the APACHE IV model.[48] The study was based on a database of 110,558 consecutive admissions during 2002 and 2003 to 104 intensive care units in 45 hospitals in the USA participating in the APACHE III database.

APACHE IV uses the worst values during the first 24 h in the ICU and a multivariate logistic regression procedure to estimate the probability of hospital death. Predictor

variables were similar to those in APACHE III, but new variables were added and different statistical modeling has been used. The accuracy of APACHE IV predictions was analyzed in the overall database and in major patient subgroups. APACHE IV had good discrimination and calibration. For 90% of 116 ICU admission diagnoses, the ratio of observed to predicted mortality was not significantly different from 1.0. Predictions were compared with the APACHE III versions developed 7 and 14 years previously: there was little change in discrimination, but aggregate mortality was systematically overestimated as model age increased. When examined across disease, predictive accuracy was maintained for some diagnoses but for others seemed to reflect changes in practice or therapy.

More information about the model and the possibility to compute the probability of death for individual patients is available at the Web site of Cerner Corporation (www.criticaloutcomes.cerner.com).

The MPM III_0 Model

The MPM III_0 was described by Tom Higgins et al. and published in 2007.[45] It was based on the retrospective analysis of data from 124,855 patients admitted to 135 ICUs at 98 hospitals participating in Project IMPACT between 2001 and 2004 (North American ICUs). The authors found that all MPM-II_0 variables remained associated with mortality (with sometimes a change in their relative weights), and added two new factors to the new model. In the developing population, MPM-III_0 calibrated well by graphic comparison of actual versus expected mortality, overall standardized mortality ratio, and a low Hosmer–Lemeshow goodness-of-fit statistic (11.62; $p = 0.31$). The area under the receiver operating characteristic curve was 0.823. To the best of our knowledge, no single independent validation study has been published even as an abstract about the application of this new method to an independent population.

Organ Dysfunction/Failure Scores

Similar in their basic concepts, these different multiple organ dysfunction scores (MODS) differ in the organ systems included in the score, the definitions used for organ dysfunction, and the grading scale used.[49,50] The majority of these scores include six key organ systems: cardiovascular, respiratory, hematologic, central nervous, renal, and hepatic, with other systems, such as the gastrointestinal system, less commonly included. Early scoring systems assessed organ failure as either present or absent, but this approach is very dependent on where the limits for organ function are set, and newer scores consider organ failure as a spectrum of dysfunction. Most scores have been developed in the general ICU population, but some were aimed specifically at the septic patient.[5,51–54] Three of the more recently developed systems will be further discussed, the main difference between them being in their definition of cardiovascular system dysfunction. They are the MODS,[3] the SOFA (Sequential Organ Failure Assessment) score,[5] and the LODS (Logistic Organ Dysfunction System) score.[4]

Very similar among them (especially the MODS and the SOFA scores), the main difference between the three described models relies on the method chosen for the evaluation of the cardiovascular dysfunction: SOFA uses blood pressure and the level of adrenergic support, MODS uses a composed variable (heart rate x ratio of central venous pressure divided by the mean arterial pressure [heart rate x central venous pressure/mean arterial pressure]) and LOD score (the heart rate and the systolic blood pressure). A comparison among them, published only as abstract, was presented at the tenth Annual Congress of the European Society of Intensive Care Medicine in 1997, and the results seemed to indicate a greater discriminative capability of MODS score and SOFA score over LOD score.[55] However, the small size of the sample requires further validation.

These models also allow an estimation of the risk of death after ICU discharge.[6] Derived measures, such as the maximum score and the delta score (maximum minus admission scores), have been also described as interesting prognostic markers, allowing the individualization of the amount of organ failure present at admission from organ failure that occurs while the patient is in the ICU.[56]

Mixed models, integrating organ failure assessment scores and general severity scores, have been published[57,58] but they never gained widespread acceptance.

Making a Decision

In the last 3 years, we assisted with the development and implementation of the new generation of general outcome prediction models. More complex than their old counterparts, relying heavily upon computerized data registry and analysis (although the SAPS 3 model can be still computed easily by hand) and incorporating more extensively the reasons and circumstances responsible for ICU admission – namely infection – these instruments have now to be properly evaluated outside their development populations.

The choice between them remains present at the present time largely subjective and dependent upon the reference database that the user wants to use: the US centers participating in the APACHE III database (APACHE IV) or North American ICUs participating in the IMPACT project (MPM III_0), or a more heterogeneous sample of ICUs across all major regions of the globe (SAPS 3). The absence of any fee regarding the SAPS 3 model and the existence of equations specific for each region of the world should be weighted with the paid participation in a continuous database program, providing a more professional support and analysis of the data. As more data accumulates about specific countries, it is probable that more country-specific equations will be developed.

It is probable, as science evolves, that we should expect further information about our genotypes and phenotypes to be incorporated into the process of clinical decision making. This information will certainly be used to stratify patients for the risk of certain diseases such as acute lung injury or sepsis[59,60] and used to help the clinician to choose the best therapy for an individual patient. Consequently, we will be challenged in the future to incorporate this information in our models, evolving from group predictions to individual predictions. When we will do that, we will be able to better control for the variations in individual patient characteristics and to evaluate more precisely the performance and the cost-effectiveness of the ICU practices.

For the time being, and no matter the model chosen, the users should keep in mind that the accuracy of these models is dynamic and should be periodically retested, and that when accuracy deteriorates they must be revised and/or updated. Also, their use should be complementary and not alternative to the use of clinical evaluation, since predictive methods are prone to error,[61] especially in the individual patient.[62] Finally, in order to maximize their predictive accuracy, they must be used in the most strict respect for the time-windows of data collection and definitions of the variables (Fig. 58.1).[63]

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59
Improving the Intensive Care Unit

Allan Garland

Intensive Care Units (ICUs) are a major component of modern healthcare systems. This, coupled with evidence demonstrating numerous problems with ICUs, mandate serious and sustained efforts to improve their performance.

The importance of ICUs is evidenced by a number of observations. One-third to one-half of Americans spend time in an ICU during their final year of life,[1,2] and one-fifth die there.[3,4] Beyond death rates, pain and other suffering is common among ICU patients.[5] Substantial dissatisfaction among relatives and friends of ICU patients[6,7] indicate that suffering is not limited to the patients. In addition, the economic costs of ICU care are large. One day in an ICU costs 2–3 thousand dollars; this is sixfold higher than for non-ICU care.[8,9] Comprising 13% of acute hospital beds, ICU care accounts for 0.6–0.9% of all economic activities in the United States,[10,11] equivalent to $76–112 billion in 2005. And ICU utilization is increasing.[2,11] ICUs are a smaller portion of the healthcare systems in other industrialized countries, but still represent an important and disproportionate segment of medical care and costs.[12–15]

A necessary starting point for efforts to improve healthcare is to recognize that problems of quality are common and serious throughout our healthcare system. The U.S. healthcare system is by far the most expensive in the world,[16] while ranking 37th in overall performance and 72nd in population health.[17] This poor performance is not explained by society's violence, health habits, or cholesterol levels.[18] Canadian healthcare is the tenth most expensive, ranking 30th and 35th on these measures, respectively.

There are many contributors to this poor performance. Failure to adhere to established standards of care is related to poor outcomes,[19,20] yet 30–50% of Americans do *not* get recommended care,[21] and 20–30% receive unnecessary interventions.[18,21] Medical errors and hospital-acquired complications are prevalent, often leading to disability and resulting in large costs, and 27,000–98,000 deaths per year.[22,23] ICUs share these problems. Iatrogenic complications, adverse events (AEs), and medical errors occur frequently in ICUs.[24] Amplifying the concern about these observations, one-third of ICU physicians and nurses denied having ever made an error, while at the same time they admitted that errors are often *not* acknowledged or discussed.[25]

ICU staff, especially nurses, perceive that ICU communication and teamwork are often poor.[25,26] Such deficiencies lead to poor understanding of shared goals, and worse patient outcomes.[27,28]

Another problem is widespread variation in practice and outcomes not explained by patient or illness characteristics. There are no data demonstrating, or any other reason to believe, that doing the same thing in a multitude of ways results in better outcomes than doing them in a uniform manner consistent with the best available evidence. Thus, variation in practice suggests that suboptimal care is common. Variation has been found for many outcomes in a broad range of settings, with important differences by geographic region,[1] hospital,[29] physician,[30,31] and insurance status or payer system.[30,32] Widespread variation occurs in ICUs as well.[33–37] Lest one think otherwise, large variation is not just an American phenomenon.[33,38]

Given the frequency of death in ICUs, it is particularly troubling that they suffer from major deficiencies regarding palliative and end-of-life care. ICU patients frequently receive care whose philosophy and intent are inconsistent with their wishes.[5,39] Patients' surrogates are often dissatisfied with the amount, nature, and clarity of communications with caregivers.[7,40] These contacts, which are often delayed[39] and

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too brief,[40] often engender confusion, uncertainty, and even conflict.[7,39,40] In addition, end-of-life and palliative care are also plagued by remarkable practice variation.[33,35,41,42]

These data demonstrate that ICU care is important, expensive, and problematic. Therefore, vigorous efforts are needed to critically examine and improve ICUs. Because *quality* is a vague term used to subtend a variety of other vague concepts, this chapter will instead refer to the more operational concept of ICU *performance*, and use the term Performance Improvement (PI) in place of the various alternatives.

Since it would require us to believe that ICU care is different from every other area of human endeavor, it is not plausible that all ICUs perform equally well, or that any given ICU is performing optimally. Since not even individual physicians can accurately assess their performance,[43] identifying how well a given ICU performs requires quantitation of relevant, objective indices of performance. However, ICUs are complex organizations and it is challenging to clearly define or measure such indices. In fact, the meaning, scope, and measurement of performance in healthcare have evolved and broadened over the past two decades. Some of the most widely used approaches to improving performance in healthcare have proven ineffective. This chapter will discuss both the conceptual basis and practical aspects of a superior method of evaluating and improving ICU performance.

Defining ICU Performance

Defining ICU performance is a complex task involving medical knowledge, economics, ethics, sociology, and systems engineering. Appropriate and meaningful assessment of ICU performance depends on two essential principles: (1) evaluate multiple parameters spanning the domains of ICU performance, and (2) use performance measures that are primarily relevant, or that have a proven relationship to primary measures.

There are a several domains within which an ICU should be judged (Table 59.1). While ICUs exist to serve the medical needs of patients, they also are important to the families and friends of patients, healthcare workers, the hospital, and society. Judging ICUs based only on patients' health outcomes fails to recognize the larger social value associated with expert care of these patients. In addition, no single metric is adequate to address any of the categories of outcomes listed in Table 59.1.

Assessing performance requires assessing parameters that are relevant to patients, society, and the hospital. Table 59.1 lists measures of ICU performance. Most efforts assessing ICU performance have used measures such as ICU or hospital mortality rates and lengths of stay (LOS). Though easy to acquire, such short-term outcomes are problematic because what matter most to people are long-term survival and quality of life (QOL).[44,45] Short-term measures can even be misleading; by virtue of being more concordant with patients' end-of-life wishes, higher short-term mortality could reflect superior care. Reduction in short-term LOS and mortality rates may merely reflect shifting the place of death from one location to another.[46] Although ICU costs and LOS are reduced by transferring patients out of the ICU,[9] premature transfer can lead to higher mortality.[47,48]

Table 59.1. Domains (▶) and measures (•) of ICU performance.

- ▶ Medical outcomes:
  - • Survival or mortality rates – ICU, hospital, 30-day, 1 year, longer-term
  - • Complication rates related to care
  - • Medical errors
  - • Adequacy of symptom control
- ▶ Economic outcomes:
  - • Resource consumption – ICU, hospital, post-hospital
  - • Cost-effectiveness of care
- ▶ Psychosocial and ethical outcomes:
  - • Long-term functioning and quality of life among survivors
  - • Patient satisfaction
  - • Family satisfaction
  - • Concordance of desired and actual end-of-life decisions
  - • Appropriateness of medical interventions provided
- ▶ Institutional outcomes:
  - • Staff satisfaction and turnover rate
  - • Effectiveness of ICU bed utilization
  - • Satisfaction of others in the hospital with the care and services supplied by the ICU
  - • Efficiency of processes/procedures/functions involved in ICU care

Thus, to meaningfully judge critical care, we should assess longer-term, patient-centered outcomes.[49] LOS or other measures of resource utilization should account for hospital utilization after ICU discharge. The benchmark for mortality outcomes should be vital status assessed at 30 days, or even longer, after admission. Since survival with poor QOL is common,[50–52] but not highly valued,[44,45] we should ideally measure QOL in tandem with survival at 30 days after admission. A variety of questionnaire-based tools exist for quantifying different aspects of QOL,[53] including some devised for ICU patients.[54] However, the effort required to measure post-hospital survival and QOL contributes to only low use of these measures.[55] It is even more difficult, but more valuable, to combine them into a measure of long-term survival that is adjusted for the QOL, e.g., quality-adjusted life years.[56] Although such practical difficulties force many ICUs to only include short-term outcomes in their PI efforts, they should strive to acquire sources of data providing measures such as 30-day survival.

Complication and error rates are commonly used measures of ICU performance. These are relevant because of potential causal relationships of such adverse events with increased mortality, morbidity, or costs.[23] However, adverse events do not necessarily lead to clinically relevant consequences; some studies have found little effect[57,58] and even seemingly obvious causal relationships can be false.[59] Therefore, great care must be taken to ensure a true relationship to relevant outcomes exists for any medical error or complication whose rate is used as a surrogate of ICU performance. Since only a fraction of medical practices have been rigorously proven to

be efficacious,[60] deviations from recommended practice may have no such relationship.

Symptom control and end-of-life decision-making are important aspects of ICU care. As indicated above, there is much room for improvement in this area. These parameters are measured using survey tools.[61] However, use of these outcomes as measures of ICU performance has been limited by the effort needed to have patients or surrogates complete the surveys, the lack of training and orientation on these topics among physicians,[62] and other factors.[41]

Because ICU care is expensive, resource consumption should be part of every institution's assessment of ICU performance. A measure balancing simplicity and information content is ICU LOS, though as discussed previously, this has substantial limitations. Others that require much effort to acquire include monetary charges or costs,[63] usage of various diagnostic and/or therapeutic procedures, and summations of resources used, as exemplified by the Therapeutic Intervention Scoring System (TISS) score.[64] However, spending a lot of money is justifiable if the benefits are commensurately large, while even small expenditures that generate no benefits are wasted; thus resource use is most relevant in combination with the non-economic outcomes in Table 59.1. Indeed, recent data demonstrating large variation in costs without differences in mortality or LOS indicate opportunities to improve the cost-effectiveness of ICU care.[36] While measuring cost-effectiveness[65] requires resources beyond those of most local PI efforts, it would be a powerful tool to assist society in clarifying the value of ICUs, as well as to assess the performance of individual ICUs. A simpler approach to assessing cost-effectiveness that could be adapted within a single ICU depends on case-mix adjustment of short-term mortality and LOS (see below).[66]

Effective use of ICU beds is important because they are a limited and expensive societal resource. Although arguments have been advanced about what constitutes appropriate ICU triage,[67,68] data allowing for evidence-based approach to assessing the appropriateness of ICU triage decisions exists for few conditions.[69,70] That the dynamic between need and availability is complex and important is indicated by evidence that transferring patients out of ICU early due to "bed pressure" has serious negative consequences.[47,48] Nonetheless, ICU triage decisions are often inefficient, and can be improved without adverse medical consequences.[71] It is reasonable to assign a low priority for ICU beds to those unlikely to benefit either because they are not very ill, or because they are hopelessly ill. Possible measures of triage performance include: (1) the percentage of ICU patients who are admitted to ICU for "monitoring only," i.e., not requiring use of the special active interventions that are used there[72]; (2) the fraction of patients who die within 6 h of entry, or otherwise represent an exercise in medical futility; and (3) patients who remain in an ICU longer than their need for its special capabilities.

The importance of satisfaction among patients and their families as measures of ICU performance is highlighted by data documenting that poor communication and dissatisfaction are common.[7,40] Usually, little is done in this area because measuring satisfaction requires questionnaires or interviews that are unfamiliar, and time-consuming to administer and analyze. Potential dimensions to such surveys in ICU care include satisfaction with: (1) care from physicians, nurses, and other ancillary healthcare personnel; (2) involvement in decisions regarding care; (3) amount and quality of communications with healthcare and administrative personnel; (4) outcomes of care; (5) administrative hospital functions such as admissions, discharge, and billing; (6) food; and (7) housekeeping. Various tools do exist to measure satisfaction, including several created specially for ICU use.[73,74]

The satisfaction of those who work in the ICU is another component of ICU performance. It is important because low job satisfaction and burnout cause job turnover,[75] which: (1) is costly;[76] (2) further degrades staff morale while increasing stress on remaining staff; and (3) diminishes the ability of the ICU to perform as an experienced, highly functioning team,[77] possibly leading to worse patient outcomes.[78] And, retaining ICU staff is more difficult and more important than ever before; already ICU nurses, respiratory therapists, and physicians experience low job satisfaction and high burnout,[79–81] and are in short supply.[82–84] These problems will worsen as aging of the population affects both the demand for ICU care, and the ICU workforce.[84,85] Measuring staff retention rates is done in a straightforward way from personnel records. Job satisfaction data are obtained from questionnaires or interviews. Many survey tools exist to assess job satisfaction, burnout, and related constructs.[86–89] In these efforts, it is necessary to separately address the job satisfaction of each worker group.

ICU readmission rate is not included in Table 59.1 because it is, at best, a questionable measure of ICU performance. Although readmitted patients have higher mortality rates and longer LOS,[90] for the readmission rate to be a meaningful factor requires that: (1) premature ICU discharge caused a subsequent detrimental outcome due to a problem that was present during the time in the ICU, and (2) the outcome would not have occurred if the patient had remained longer in the ICU. There are no data that have demonstrated this.[90,91] The optimal readmission rate is unknown, and a low one might actually indicate that, on an average, patients are remaining in the ICU longer than necessary, increasing costs of care and exposing them to increased risk of dying.[92]

Finally, since they are generally easier to acquire, surrogate measures, such as processes of care or intermediary outcomes, are often used in PI efforts. While assessing surrogate endpoints is usually a component of PI, this must not substitute for assessing the true outcome parameters, unless the surrogate measure has a proven relationship to the relevant outcome.[93] For example, since elevating the head of the bed of mechanically ventilated patients has been shown to reduce ventilator-associated pneumonia (VAP) rates,[94] this process of care is a reasonable surrogate as part of efforts to reduce such rates. On the other hand, since the degree of hypoxemia in acute

respiratory distress syndrome (ARDS) is not clearly related to clinically relevant outcomes,[95] this physiologic parameter cannot be used to gauge the benefits of interventions to improve outcomes in ARDS. While changing structures and processes are the necessary means to the ends, changing the means may not result in improvement in the ends, and does not obviate the need to measure them.

Measuring and Interpreting ICU Performance

PI is an activity that requires collection of high quality data about the performance measures in Table 59.1, and statistical analysis of that data. Inaccurate, incomplete, inadequate, or otherwise misleading data negate efforts to improve performance.

Many performance measures relate to adverse events (AEs) suffered by individuals. However, it is fundamental that detection and analysis of individual AEs cannot be used to measure performance. Instead, we must calculate the rate of AEs, obtained by dividing the number of individual events by the number of at-risk patients, patient-days, or other appropriate denominator. Even an AE apparently caused by human error that led to harm is not proof that overall performance is poor. For example, a surgeon who once amputated the wrong leg could have a superior overall complication rate. Only accurate, cumulative, quantitative information – rates of death, errors, complications, staff turnover, family dissatisfaction, etc. – truly represents ICU performance. The goal is always to improve these rates.

Systematically identifying AEs is difficult. The usual methods – chart review and incident reports filed by clinical staff – are unreliable as they consistently and considerably underestimate AEs.[96–98] Therefore, PI requires establishing reliable methods of systematically collecting data on the performance parameters being surveyed. Both the denominator and numerator must be accurate. This topic is beyond our scope, but a few guidelines are: (1) prospectively collected data are superior to retrospective data; (2) information collected by computerized information systems is superior to that collected by humans, especially if they are specifically programmed to acquire the desired information; (3) data collected by personnel dedicated to that job are superior to that collected by healthcare workers tasked with collecting data in addition to their usual clinical responsibilities; (4) direct observation in real time is superior to retrospective assessment for AEs; and (5) identification of AEs should use objective, predefined criteria rather than human judgment.

To quantitate ICU performance we calculate the rate for binary variables such as death or AEs, and the mean, median or interquartile range for continuous variables such as a 0–100 patient satisfaction scale. Such values are then compared to benchmarking standards, such as the value in other ICUs, or in that same ICU during a prior time interval. But drawing correct conclusions requires sufficiently large samples to ensure that differences or changes are not due to random statistical fluctuation[99,100]; standard statistical methods are used to assess this issue. For example, many ICUs track monthly VAP rates, but because the monthly number of cases and at-risk patient-days are low, they overinterpret impressive-looking changes seen over 1 or 2 months on their graph.

It is obvious that performance measures can be influenced by patient demographics, comorbidities, and type and severity of acute illness. These factors are cumulatively referred to as case-mix. This may be true even for institutional outcomes such as staff satisfaction.[101] While raw data are not incorrect, it is problematic for comparing ICU performance between samples having different case-mix. For example, increasing ICU mortality over time in a single ICU may *not* represent worse care if sicklier patients were admitted in succeeding epochs. Even seasonal differences that occur in some critical illnesses[102] can create this problem. Important case-mix differences are even more likely in comparing performance between different ICUs.[103,104]

Thus, PI efforts should try to collect at least some case-mix variables. Which ones depend on the purpose of the PI project? In general, they should include patient age, gender, race, the presence or absence of important comorbid states, the organ system most responsible for ICU admission, and ICU admission source.[105–108] With more data collection resources one should consider collecting: (1) a measure of the severity of acute illness,[109] such as the Acute Physiology and Chronic Health Evaluation (APACHE) score, or Multiple Organ Dysfunction Score; (2) finer differentiation of the ICU admission diagnosis; and (3) socioeconomic variables such as insurance category.[110,111] Special case-mix variables should be chosen for special purposes; e.g., measuring outcomes in hypoxemic respiratory failure leads one to record each patient's initial PaO2/FIO2 ratio as a measure of the severity of this state.

The simplest way to use case-mix variables is to evaluate whether they are statistically similar between the time periods (or ICUs, or patient populations) being compared; if so, then it is reasonable to compare raw values of the performance parameters. When case-mix is dissimilar, it is best to adjust for the observed differences.

A common adjustment method uses a "prefabricated" ICU risk prediction system, such as APACHE, Simplified Acute Physiology Score (SAPS), Mortality Probability Model (MPM) and Project IMPACT for general adult patients[109,112,113]; Pediatric Risk of Mortality (PRISM) for pediatric patients[114]; and others for specialized patient subsets.[115,116] These systems are equations that take demographic and clinical information and predict outcomes for each patient, such as the chance of dying. Most of these systems explicitly generate scores that should not be confused with the predictions, but can themselves be used to assess elements of case-mix; e.g., the APACHE acute physiology score is a reasonable summary measure of the severity of acute illness in general, adult ICU patients.

Unfortunately, most prefabricated systems only predict hospital mortality. For PI purposes, the individual predictions are conglomerated to calculate the standardized mortality ratio (SMR), defined as the observed hospital death rate of a cohort divided by the average of the individuals' predicted chances of dying. The SMR is thus a case-mix adjusted measure of a short-term death rate in the cohort, equivalent to comparing outcomes in your ICU to those of the inception cohort upon which the system was derived. Though the individual predictions are inadequate for evaluating care of individual patients,[117] the SMR performs reasonably well for cohorts.[118] Unfortunately, the only ICU performance measures for which there are published, validated, ready-made systems that can be used in case-mix adjustment are hospital mortality and ICU LOS.[105,119]

Even for the parameters predicted by prefabricated systems, there are problems of calibration,[120] accuracy within some diagnostic subsets,[121] generalizability to other countries,[122] and other factors.[123] In addition, none of them include non-medical variables that may be important determinants of outcomes, such as socioeconomic factors. While some of the latest prefabricated systems are proprietary and expensive, these produce only modest increases in predictive power over earlier, free versions.[124–126]

All of the prefabricated prognostic systems discussed are prospective in that predictions are generated from data available at the start of the ICU admission, representing the clinical situation before ICU care was provided. However, use of commercially available, retrospective prognostic systems based upon administrative or claims data is growing – in some cases mandated by regulatory agencies. In generating the predictions, many of these systems incorporate events that occurred during care; this represents a fundamentally flawed approach to evaluating performance and should not be used in PI efforts. Not only is the accuracy of administrative databases problematic,[127] but such an approach cannot distinguish whether poor outcomes are due to bad care or the severity of illness. For example, an ICU where many patients die due to avoidable complications could fail to be identified as a poor performer by a system that incorporated those complications into its prediction of the risk of death.

A superior, but more difficult, approach to case-mix adjustment uses multivariable regression analyses to create adjustments customized to the local data.[128,129] Instead of comparing local outcomes with that of the development cohort of a prefabricated system, the customized approach makes internal comparisons, either in the same ICU over different intervals, or between ICUs. It allows adjustment of any type of performance parameter for all potentially confounding variables available in the data set. The method involves entering the data in a spreadsheet program with each patient as a separate row. Columns contain the outcome and case-mix variables, and indicator variables representing the comparison of interest, such as time intervals (e.g., this year versus last year), or the different ICUs being compared. Using standard statistical programs, a regression equation is generated for each performance measure; logistic regression for binary outcomes, and linear regression for continuous ones. The magnitude and statistical significance of the coefficient for the indicator variable tells whether there is a difference in performance after adjusting for the case-mix variables. In this approach, it is convenient to use elements of prefabricated systems as case-mix covariates. For example, a custom regression using the APACHE III acute physiology score, source of ICU admission, and ICU admission diagnosis provided superior predictive power to the APACHE III predictions themselves.[130] A reassuring finding is that there is much redundancy within clinical ICU data, as shown by a study in which customized regression excluding the vital signs, but including many other variables, resulted in predictive power similar to that of APACHE III.[106] However, custom case-mix adjustment requires non-trivial expertise in computer applications and statistical modeling.

Special comments must be made discouraging the use of Diagnosis Related Groups (DRGs) in PI. DRGs are rarely chosen by clinicians, and contain significant inaccuracies.[131] In addition, the hospital discharge DRG is generally chosen to maximize reimbursement, not to reflect the reason for ICU admission; it may even reflect an avoidable complication of care.[132] Likewise, the hospital admission DRG may not represent the reason for transfer to ICU.

Additional mention must be made of external benchmarking in ICU PI efforts. This is the process of comparing performance of one ICU against that of others. This can be affected by membership in a consortium, such as the University HealthSystems Consortium or the Institute for Healthcare Improvement. While consortium membership is often valuable, there is usually a fee. Retrospective benchmarking is easier; as mentioned, calculating the SMR in one ICU using a prefabricated system such as SAPS is equivalent to retrospective benchmarking against the patient cohort upon which those equations were created. An even simpler method of retrospective benchmarking is to compare the performance variable of interest in one ICU to values reported in the literature from other ICUs. Of course, due care must be taken to ensure that the comparisons are valid.[129]

Framework for Improving ICU Performance

Improving ICU performance involves sequential steps of: (1) measuring indices of ICU performance relevant to the topic or area of interest; (2) making interventions aimed at improving those measures; and then (3) re-measuring the indices to document the effect of the intervention.[135] This section will develop a framework for understanding the interventions required to improve ICU performance.

There are two domains of change for improving ICU performance: (1) the technical components of ICU care, and (2) the organizational features of the ICU. Medical training and

literature almost exclusively emphasize the technical. Thus, the attention of clinicians is dominated by diagnostic and therapeutic choices such as imaging modalities, intensive insulin therapy, and the angle of the bed during tube feeding. These are important, but changes to ICU structures and processes are given little attention and are at least as significant.[132] Specifically, organizational changes are required to ensure that the appropriate technical choices are applied uniformly.

A simple but powerful framework for addressing interventions to improve medical care is adapted from Berwick.[136] He tells us that we must: (1) know what works, (2) use what works, and (3) do well what works.

Knowing what works requires reading and appropriately interpreting the medical literature. Besides the time commitment needed, we face three important barriers in this effort. First is the limit of current knowledge. On many or most topics, we simply do not have high quality evidence demonstrating the best way to do things.[60] Furthermore, the nature of statistical inference used to draw conclusions in medicine [137]inevitably leads to some results that are subsequently brought into doubt, or contradicted.[138] Here, we must accept that the "best evidence" is a moving target, and be aware of the potential pitfalls of making major changes in practice based on single studies.[137] Second, many studies utilize surrogate or secondary endpoints instead of clinically relevant ones. Practice based on such data is worrisome,[93] as evidenced by studies showing improvement in surrogate outcomes while patients derived no discernable benefits,[95] or were harmed.[139] Third, many physicians lack the statistical and logical skills needed to understand and correctly interpret the literature.[140,141]

As problematic is our state of knowledge, *the single biggest problem in healthcare is the frequent failure to adhere to evidence-based best practices* (EBBP).[142,143] Even simple, universally accepted practices such as aspirin and beta-adrenergic blockers after acute myocardial infarction are often forgotten, leading to many unnecessary deaths.[144] Seminal studies in the most widely read journals often do not change practice.[145] To address this problem, and to ensure that all patients uniformly receive every applicable EBBP, a paradigm shift is required.

The prevalent physician-centered paradigm of medical care holds individual physicians entirely responsible and free to guide care as they will, regardless of whether their choices concur with the best practices, and independent of effective accountability.[146] Such a system, where patients are entirely dependent on the knowledge, memory, and best intentions of their physicians, is not rational, and is not in the best interests of patients or physicians. This is not an indictment of physicians – there are too many important things to learn and remember to expect that any physician will always do all the right things. Instead, it is necessary to create structures and implement processes in the ICU that ensure that every patient, every time, receives every applicable EBBP.

But ensuring the uniform application of EBBPs is not the only reason we must re-engineer ICUs. The performance of complex organizations, such as ICUs, is determined by their structure.[147] This concept originated with the seminal recognition that only 15% of errors and problems are a result of inadequate performance by individuals. Rather, 85% of the opportunities for performance improvement relate to flaws in institutional systems and processes that hinder the ability of individuals to perform their jobs well.[148–150] Emphasizing that most opportunity for PI derives from altering the system itself, Deming, Juran, and others created the most effective method known of improving performance in complex organizations.[148,149] This concept of PI, often called Total Quality Management (TQM), applies equally well to service industries such as healthcare,[147,150–152] and indicates that making changes in ICU organization offer equal or greater opportunities to improve performance than the gains from purely technical improvements.[153] Though this systems engineering approach is largely alien to healthcare, it is the recommended method of PI.

Within this paradigm, *every* structure, process, activity, function, and relationship – clinical and non-clinical – that influences the ICU in any way is open to scrutiny and change (Table 59.2). Examples of altering the role of personnel include transferring lower level patient care activities from highly trained nurses to less highly trained nurse extenders,[155] and shifting some of the responsibilities of ventilator weaning from physicians to respiratory therapists,[156] or computers.[157]

Because ICUs comprise numerous, interrelated components, it can be difficult to comprehend the mechanisms by which changing organization improves performance; but they go beyond simply increasing the use of EBBPs. Examples will make this more concrete. Making a computer program

TABLE 59.2. Total quality management in the ICU – some potential areas for change.

• The need for a function
• How a function is performed
• Which personnel perform a function
• The functional relationship between personnel
• How personnel communicate with each other
• The existence, frequency, and nature of ICU rounds
• The role of equipment (including computers)
• The interactions between personnel and equipment (including computers)
• The administrative, medical, and functional structures of the ICU
• The administrative, medical, and functional structures of ICU personnel
• The rules governing responsibilities, practice privileges, etc.
• The training, skills, competence, knowledge, and experience of personnel
• The scheduling of personnel – including shift coverage, night coverage, weekend coverage
• Workload per worker
• The availability of supportive technology in the hospital (e.g., advanced imaging)
• The choice of products and services used in the ICU
• Number of ICU beds
• Physical layout of the ICU
• Availability of intermediate care and ward beds
• Making outcomes data available to the ICU and hospital community
• Making outcomes data available to the public

for "expert" antibiotic consultation available at every hospital workstation raised the adequacy rate of initial antibiotics from 77 to 94%, while reducing ordering delays.[158] Altering the structure of morning ICU work rounds to include a pharmacist reduced avoidable drug errors by 65%.[159] What appeared to be the ultimate in physician error – surgery on the wrong side of the body – actually represented inadequate processes in place in the operating room and setting this right to avoid such errors.[160]

Within TQM it is understood that *performance is a moving target that can be improving all the time, even in the absence of identified problems*. Benchmarking – most simply against performance in the same ICU during earlier intervals – allows for realizing this goal. The purpose is to reduce waste, rework, and complexity, while improving relevant outcomes, reducing costs, and improving teamwork.[150] But TQM represents a major paradigm shift, and is often actively opposed by physicians.[161] TQM does not respect existing professional standards, instead it continually demands development of new ones that are more effective.[152] To increase use of EBBPs and decrease errors, it emphasizes teamwork and standardization over individual autonomy.[161,162] Thus, it asks physicians and other professionals to alter their mindset regarding their place in the healthcare system; away from viewing themselves as singular individuals with skills that set them apart from their similarly trained colleagues to that of an "equivalent actor."[162]

Shifting the focus from identifying and remediating defective workers, to identifying and re-engineering defective structures and processes is necessary, according to Berwick, to correct "the defects that we have built into our complex medical systems…the waste we encounter in outmoded habits, the rework we pay for when things fail to work correctly the first time, the complexity we build into our processes for no good reasons at all."[136] In most ICUs, the existing systems and processes make it easy for well-meaning people to make mistakes, and hard to do things efficiently and correctly, the first time; the goal of TQM is to *reverse* this situation.

Systems engineers understand that performance deteriorates unless the structures and processes of the organization evolve with the needs they serve. The usual way hospitals cope with growing demand is to increase the existing system to scale. However, such growth by accretion inevitably leads to a cumbersome, inefficient system. In the face of the continued projected rise in demand for ICU services,[84] what is needed, instead, is evolution of new systems and processes that match the growing needs.

Systems-oriented PI is very different from the Quality Assurance/Quality Improvement (QA/QI) method that is still used in many ICUs. QA/QI strives to address individual errors, AEs, or other problems that are noted. Since problems are addressed only if they are noted and after they occur, QA/QI is *reactive*, instead of proactive. Leadership then convenes a group, usually composed of supervisory-level personnel, to identify and remediate the source of the problem, via "root cause analysis." The Morbidity and Mortality Conference held regularly in most institutions is an example of this flawed approach to improving performance.[163]

In fact, both components of QA/QI, identification of individual problems, and root cause analysis, are seriously deficient. Methods to identify problems include medical record reviews, incident reporting, and use of prospective indicators; an example of an indicator is a document that bedside nurses complete when a mechanically ventilated patient is inadvertently extubated . As usually applied, all of these methods are severely limited.[58,96–98,127,164–167] More importantly, as discussed previously, the evaluation of individual problems is a misguided method of measuring performance. Root cause analysis is a process where a group is convened to perform a detailed review of an adverse event to identify its cause. Yet, there is very poor inter-rater agreement about the causes of AEs, and even the occurrence.[58,97,98] In fact, it is almost never true that a single root cause exists, instead, according to Berwick, "most system failures result from complex interactions between latent failures…and specific actions; conclusions about root causes are often illusions created by hindsight bias."[168] Pooled data from thousands of root cause analyses show that many do seek to identify single causes, and then recommend ineffective responses.[169] To make matters worse, instead of simplifying the overly complex and mistake-prone processes that are the true explanations, many hospitals respond to severe AEs by adding additional layers aimed at eliminating the possibility of that particular problem; this frequently creates an even more complex and maladaptive system that becomes more prone to a variety of other mishaps.[161] Despite decades of use, the published, peer-reviewed literature does not support the notion that QA/QI or root cause analysis are effective in improving the performance of healthcare systems.[169,170]

On the other hand, the ICU is an *opportune* place to establish a systems-oriented PI environment. Although the details of implementing such a program are beyond the scope of this review, some key concepts should be mentioned. First, leaders must lead. TQM requires substantial commitments of leadership, resources, training, and time. Investments must often be made in data gathering and analysing capabilities. Second, personnel must be convinced that discovery of problems, even of human error, will not lead to any retaliatory punishment. Only such non-punitive environments successfully encourage reporting of AEs and "near misses," and can effectively respond to such events using the principles of TQM.[171] The commercial aviation industry is an example of a culture that has achieved ultrasafety by using TQM principles,[172,173] and has observed that the most effective flight crews spend more time discussing errors and threats.[25] Medicine, however, is an industry containing substantial pressures to cover up mistakes, thereby losing the opportunity to address their true causes.[25] Third, the process must be inclusive of the full range of personnel who actually do the work. TQM includes, but is not controlled by, management-level personnel. Its functional unit is the multidisciplinary Quality Circle that replaces managerial authority with a participatory approach that emphasizes

collective rather than individual responsibility.[152] Quality Circles should primarily comprise workers, *not* managers. Their participation must be explicitly valued, as evidenced by paying them for the time needed to participate. Fourth, the entire process is driven by collection of data about relevant outcome parameters, and scrutiny of the underlying structures and processes that generate those outcomes. With institutional support, data are collected, case-mix adjusted if necessary, statistically analyzed, and displayed to illuminate important relationships. Though analyzing individual AEs and near-misses must not serve as the primary method of PI, discussing individual events focuses the attention of a Quality Circle, and assists in identifying the structures and processes that require alteration. The Quality Circle then designs interventions, with explicit focus on simplifying problematic processes. Following implementation, the performance parameters are re-measured to document improvement.

Among the impediments to systems-based PI in medicine, the largest is *resistance* from physicians. Physicians receive little or no education in these concepts,[174] usually resist proposals perceived as abridging their professional autonomy,[143] and frequently respond to objective results about performance by insisting that the data are inaccurate. Resistance often stems from the belief that medicine is fundamentally different from the wide range of human endeavors in which TQM has succeeded in improving performance. Rejoinders include observing that: (1) TQM is effective because it targets the limitations common to all human endeavors; (2) by incorporating systems-based approaches, anesthesia succeeded in dramatically improving its safety, and indeed is the least error-prone part of modern medicine[23,175]; and (3) there are increasing examples of the success of TQM across medical practice.[176,177] But, in fact, gaining physician acceptance and participation is a necessary ingredient for a successful TQM program. Strategies to achieve this include incorporating large numbers of physicians in the process from the start, especially those considered opinion-leaders,[178] sending some of those opinion leaders off to workshops that teach TQM principles, and displaying sensitivity to their concerns about presentation of data in ways that could be perceived as threatening.[179]

Dramatic examples exist demonstrating the power of TQM to improve relevant outcomes.[176,177] Indeed, not only does measuring performance promote improvement,[180] but the benefits of implementing a TQM program extend beyond the targeted performance projects.[181]

Specific Strategies to Improve Performance

A modest but growing body of literature assesses strategies to improve healthcare system performance via organizational change. These strategies range from simple to complex, and address widely differing aspects of change. They fall loosely into two categories: (1) strategies to increase or improve the use of specific EBBPs, and (2) changes in structures and processes not directly related to the technical aspects of medical care. The latter are a diverse group of interventions. The former include education, audit with feedback, clinical practice guidelines, reminders, order sets, computerization, and combinations of these interventions.

Strategies shown to be effective by existing, published evidence are convenient, ready-made tools that individual ICUs can adopt. Though these are likely to be generally effective, concerns about extrapolating organizational research findings to other centers is even greater than for research about the technical aspects of care. While it is best if the efficacy of each organizational strategy is demonstrated by local data comparing outcomes *before* versus *after* implementation, there should be no hesitation in making changes that have credible literature support even if one ICU does not have the resources needed to carefully validate their local efficacy.

Changes to ICU Structures and Processes Not Directly Related to Specific Technical Aspects of Care

Numerous structures and processes comprise every ICU, with many differences even between ICUs that appear superficially similar. Some organizational elements are concrete and easy to comprehend, such as whether pharmacists participate in daily ICU rounds. Others, such as those relating to the underlying social-professional structure, have important implications but are less obvious.[78,182] Since the number of studies is too large to comprehensively cover, salient examples will be discussed.

The best studied of these topics compares “closed” versus “open” ICUs, referring to whether or not all the patients are under the care of a single attending physician. While numerous investigations have shown that patient outcomes are superior in closed ICUs, the organizational differences between ICUs and differences in study design make it difficult to identify the essential explanation(s) for this finding. A recent systematic review avoided restrictive definitions by analysis according to the intensity of intensivists’ involvement in ICU care[183]; high intensity involvement results in significantly lower mortality rates and shorter LOS. After case-mix adjustment, none of the individual studies observed worse outcomes with more intensivist involvement. Estimates indicate that high intensity involvement by intensivists for all ICU patients in the U.S. would save 54,000 lives per year.[184] It is notable that nurses’ job satisfaction, an outcome unrelated to patients, improved after transition from open to closed ICU structure.[185]

A variety of other ICU organizational issues have been studied, though, for many, a consensus does not yet exist. A few of these include 24-h intensivist presence,[186,187] telemedicine,[188,189] use of a daily goals sheet,[27] pharmacist participation in ICU rounds,[159] nurse-physician collaboration,[190] different nurse staffing ratios,[191,192] implementation of a rapid response team,[193,194] and availability of an intermediate care unit.[195,196]

Some interventions represent radical departures from current practice and are really challenging to implement. As discussed, improving ICU performance requires a *genuine openness* to new ideas and ways of doing things, and a *commitment* to beneficial change. Human factors should not keep us from doing what has been shown to work best. The Quality Circles of every ICU should evaluate this literature now and as it evolves, and implement beneficial structural changes that are feasible with available resources.

Strategies to Increase Use of EBBP

EBBPs are technical components of care that have been demonstrated to improve clinically relevant outcomes. As discussed, these are frequently not applied when indicated. The opportunity to improve ICU care by uniform implementation of EBBPs is enormous; estimates indicate that 168,000 lives would be saved yearly in American ICUs if specific EBBPs were uniformly utilized[197] (e.g., elevation of the head of the bed, daily sedation interruption, assessment of readiness to extubate, peptic ulcer disease prophylaxis, and deep venous thrombosis prophylaxis for ventilator-associated pneumonia prevention). While there are some data-assessing strategies to increase use of EBBPs, much more of this form of translational research is urgently needed.[198,199]

Didactic education – such as conferences, rounds, meetings, and symposia – is the traditional method of teaching practitioners how to care for patients. Continuing medical education (CME) is a requirement for health professionals in most industrialized countries. A systematic analysis of CME[200] found that the quality of this data is poor; any benefit present was small and limited to CME interventions having interactive elements. Another analysis also concluded that passive educational methods did not improve physician performance or patient outcomes.[201] Consonant with this, *interactive* and *participatory* educational strategies are more effective at increasing physicians' knowledge than is passive education.[202] We must be careful in interpreting this literature, because studies showing larger benefits from CME have almost always mixed didactic education together with other modalities such as reminders, or audit with feedback.[203]

Audit with feedback refers to a summary of recent clinical performance that is communicated back to practitioners. The feedback may be written, oral, or electronic, and can include recommendations for improvement or action. For example, the hospital could send each physician a quarterly report identifying the number of patients cared for with acute myocardial infarction, detailing the fraction who were promptly placed on beta-blocking and anti-platelet drugs. The report could also show these data from all the other physicians, coded to be anonymous (or not). The idea behind audit with feedback is that professional performance will improve if well-meaning professionals know how they are doing. But the influence of audit and feedback may depend not only on the quality and timeliness of the data, but also on the organizational context in which it is delivered.[204] The body of literature assessing this intervention is of poor quality, generally showing only small benefits,[205,206] though a few studies have indeed observed larger benefits.[207] A likely reason for the weak effects of audit with feedback is that it does *not* provide real-time information that is specific to the patient at hand. Indeed, audit with feedback is less effective than real-time reminders.[201]

Practice guidelines represent attempts to increase use of EBBPs by making the recommendations for care available to clinicians who practice them. The concept behind guidelines is that EBBPs are omitted because clinicians are not aware of them, or forget about them. Characteristics of high quality guidelines have been described.[208] Guidelines range from simple, to complex and comprehensive. An increasing concern is how multiple guidelines interact, when applied simultaneously to a given patient.[209] Unfortunately, many physicians harbor negative attitudes about practice guidelines,[210] and various factors influence their acceptance, utilization, and benefits. These factors include knowledge about their existence, their complexity, manner of dissemination, local input into their construction, characteristics of the targeted practitioners, ease of accessibility, and ease of use.[201,211,212] Most importantly, guidelines are not effective without concomitant use of other strategies to ensure that they are actually used.[201,211]

Because the number of EBBPs that clinicians are expected to implement is prohibitively large and constantly growing, no person can possibly know about, remember, and use each applicable one, each time, for each patient. This is why education, audit with feedback, and clinical practice guidelines are weak approaches to improving use of EBBPs. The most consistent theme emerging from implementation research is that combining multiple strategies is more effective than individual ones.[201,213] However, combinations of weak strategies do not assure success.[214] More effective strategies to improve use of EBBPs, in combination with practice guidelines, include real-time reminders, order sets, and computerization.

Reminders about a specific patient, provided at the point of care, and at the time of care, are a powerful way to improve use of EBBPs. They relieve clinicians from the need of a perfect memory to provide optimal care. Reminders are one of the most effective ways of improving adherence to recommended practices, especially if they are generated by computers.[201,215] The main limitation is effecting reliable and timely delivery of reminders to clinicians. While reminders provided by specially designated personnel increased compliance with recommended care and improved outcomes,[216] hiring an army of outcome managers to perform this function is not practical. *Computer-generated reminders*, discussed below, are a much more workable solution to this problem.

Another approach to increasing use of EBBPs is prefabricated order sets that have those practices built into them. For example, an order set could be created incorporating all

the EBBPs currently recommended to reduce the incidence of ventilator-associated pneumonia,[94] and applied, by default, to all newly intubated patients; the Institute for Healthcare Improvement's "ventilator bundle" embodies this concept.[217] A standing set of routine ICU admission orders could increase use of EBBPs of wide applicability; for example, they could give nurses authority to begin prophylaxis against venous thromboembolism. Examples from the small published literature about prefabricated order sets do show improvements.[218–220] It is quite important to note that some assessments have been unsuccessful because order sets were written such that the EBBPs were not implemented unless they were actively chosen, i.e., "off by default." In most cases the reverse of this strategy is much better – i.e., "on by default" – so that EBBPs are implemented unless explicitly switched off. This principle was impressively illustrated in a study of vaccine administration to inpatients.[221] This study found that a well-designed, computerized, real-time reminder system resulted in lower rates of appropriate care compared to a system that bypassed the physicians by having the nurses implement a computer-generated order for eligible patients. Although appropriate caution must be exercised in choosing EBBPs that should be on by default, concern that it would cause more harm than good is misplaced, in light of evidence that errors of omission are much more prevalent than errors of commission.[21,222] Just as for reminders, computerization offers a superior way to create and use prefabricated order sets to improve use of EBBPs.

One conclusion emerging from this material is that major responsibility for ensuring use of EBBPs has passed from the individual clinicians to the institution, more specifically, to the systems and processes put in place within the institution. In addition to fully implementing a TQM program, this necessitates: (1) Quality Circles regularly reviewing recent literature for new practices with sufficiently strong evidence to merit installing them as standard practice, (2) creation of clinical practice guidelines that are unequivocally understood to be the expected standard of care for all practitioners, (3) installation of practicable strategies, such as those discussed above and in the next section, to ensure effective implementation. The websites of the National Quality Forum[223] and Institute for Healthcare Improvement contain many recommended EBBPs applicable to ICUs that provide an excellent starting point for ICUs beginning this process. Ideally, all these steps for change would be sandwiched between collection of outcomes data, and each clinician would get regular statistical feedback about her/his performance. The latter may be of minimal value in improving outcomes, but all the same, it is important for professionals to be involved, and be aware of their performance.

Lastly, efforts to improve use of EBBPs must attend to the *human* component. Poor communication and lack of clear discussion about goals between ICU physicians and nurses can thwart implementation of the simplest EBBPs.[224] However, even such problems are amenable to systems-based solutions.[27]

Information Technologies in ICU Performance Improvement

Computers and other information technologies are powerful tools for improving ICU performance. Unlike people, computers can keep track of almost limitless amounts of information, never forget, and are essentially flawless in performing their assigned tasks. Table 59.3 lists ways in which the information system can contribute to PI efforts.

Keeping track of patient-related information is an ever-increasing challenge. ICU patient data originates from many sources, including observations and manual measurements made by numerous healthcare workers, bedside monitors, the laboratories, radiology, pharmacy, the blood bank, devices such as infusion pumps and ventilators, progress notes, clinical flow sheets, and various hospital information systems. In most ICUs, collecting this mass of diverse information requires physicians to read paper records, use several different computer systems, and leave the ICU to obtain information residing elsewhere. This situation makes it difficult and inefficient for clinicians to acquire and integrate all the necessary data, and is prone to errors and oversights. For several decades in most hospitals, simple information systems have facilitated access to laboratory results. Many hospitals now possess Picture Archiving Communications Systems (PACS), making it possible to view radiologic images without leaving the ICU. Although there is conflicting evidence as to whether PACS leads to more timely viewing of images by clinicians,[225,226] it *does* make viewing more convenient and save time.[227] Barcode labeling of medications and blood products has been shown

TABLE 59.3. Uses of information technology in ICU performance improvement.

• Acquire, integrate, store, analyze, and display information
• More efficient and less error-prone entry of orders
• More efficient, available, and legible entry of progress notes and other patient information
• Make clinical data more readily available
• Make knowledge more readily accessible
• Facilitate availability and use of EBBPs, including clinical practice guidelines
• Provide clinical reminders
• Facilitate use of order sets
• Facilitate communication
• Assist with calculations
• Assist with clinical monitoring
• Continuous, real-time monitoring for complications, adverse events, etc.
• Provide real-time decision support
• Examine large amounts of data for meaningful patterns
• Automated assistance with technical aspects of care
• Automated regulation of mechanical ventilators, and other complex devices
• Verify correct administration of medications, blood products, etc. (e.g., via bar coding with bedside scanning)
• Facilitate data collection and case-mix adjustment for TQM purposes

to reduce errors.[228,229] However, much more capable information systems are needed to address in entirety the serious challenge of ICU data acquisition and presentation.[230] Commercial systems now exist that automatically acquire data from bedside devices and other computer systems in the hospital, and from information manually entered at bedside terminals. They can display the data as customizable tables and graphs that people can understand and use at any enabled workstation, including those at remote locations connected via the Internet. Because of these advantages, "paperless" medical records should become increasingly common. The future includes increasing use of handheld devices for wireless remote access to clinical data, and more rapid communication to clinicians of problems.[231]

Computer technologies have vastly improved access to sources of medical knowledge. Textbooks, databases such as MEDLINE, full text journals, and other authoritative sources are widely available around-the-clock from Internet-ready terminals in ICUs. It no longer requires a trip to the hospital library to research answers to clinical questions pertaining to the patient who just arrived. An increasing amount of medical knowledge is even more conveniently accessible via handheld devices.[232]

Errors in order writing are the most common type of medical error.[23] Handwritten orders suffer from illegibility, mistakes in transcription, drug dosing errors, and other such ills. Computer order entry dramatically reduces such errors and their consequences,[233,234] and can reduce costs.[235] It should be noted that a recent study raised concerns about the detrimental effects of computer order entry.[236] However, that report related to a poorly designed order entry program (which the author has used), and illustrates that information systems may not be beneficial unless their design and human interfaces are attentive to real-life work habits and address other practical concerns.[237,238]

As discussed previously, reminders and prefabricated order sets are potent strategies to increase use of EBBPs. However, both are limited by practical difficulties in making the information available to clinicians in a reliable, convenient, and timely way. Information systems can solve these problems. Computer-based order entry systems can be programmed to offer order sets relevant to a given patient. Each time a caregiver logs into the system it is an opportunity to deliver a reminder, or offer up a relevant practice guideline; making it convenient for the clinician to act on them. Additionally, as the clinician writes an order, the system could automatically generate a reminder to write an appropriate related order.[239] For example, we could be prompted to order elevation of the head of the bed every time we order tube feeding.[94]

Computer systems with access to all the patient data residing in an electronic medical record are required to allow this concept to achieve its full potential. An integrated ICU information system linked to both the ventilator and the medication administration record could identify that a patient is a mechanically ventilated patient and not receiving prophylaxis for stress gastritis, and automatically generate a reminder, or the order itself. If the patient was receiving sedatives, the computer could suggest use of the ICU's sedation protocol[217] and automatically present the necessary orders for the clinician to implement the same. As discussed, even better compliance with an EBBP would result if the indicated order were, by default, generated in the appropriate setting by the computer, with the clinician having the option to cancel it if he so desired.

Extending these uses of information systems is computer-aided decision support (CADS). CADS systems having electronic access to patient data provide clinicians with "expert" medical advice. For example, when the physician enters an order for gentamicin into the computer-ordering system, it automatically accesses and gleans the patient's current weight from the paperless daily nursing notes, latest creatinine value from the laboratory, and age from the admitting department's computer. Its expert system estimates pharmacokinetic parameters and *recommends* a dosing regimen.[240] When peak and trough levels become available to it from the laboratory computer, it could include those in the calculations, so the next time the clinician accesses that patient's electronic medical record it would *suggest* revised dosing. These smart systems can help avoid incorrect dosing, and proactively identify drug interactions.[241] A recent publication found that a CADS system decreased the rate of venous thromboembolism among inpatients by automatically: (1) using various data available in the paperless medical record to identify high-risk patients, (2) using the computerized order system to identify high-risk patients not currently on prophylaxis, and then (3) alerting those patients' physicians to the need for prophylaxis.[242] Most studies have shown benefits from using such highly competent systems, especially if they are designed with certain usability characteristics.[243]

The potential of computers to assist in management of ICU patients extends beyond providing technical advice. A computer linked to real-time monitoring can be programmed to automatically adjust devices such as ventilators and infusion pumps to maintain optimal parameters in a way impossible for humans. In a recent comparison versus usual ventilator management in pressure support mode, complete computer control of the ventilator maintained respiratory rate, tidal volume, and end-tidal PCO2 within desired limits a higher percent of the time, and reduced ventilator-days and LOS.[157] The ability of computers to continuously monitor and analyze the entire ICU data stream in real-time makes them superior to people for tasks such as early detection of physiologic instability, adverse events,[244] and surveillance for care practices outside of established practice guidelines.[245] The observed benefits of a commercially available "virtual ICU" system[246,247] may be partly due to the ability of its powerful data surveillance and analysis programming to identify physiologic deterioration before it becomes obvious to bedside nurses and doctors.

The future promises even more: an *automated* ICU environment in which some EBBPs are effected without the need

for humans to remember to order or even remember them. For example, a computer could automatically elevate the head of the computer-controlled bed for a patient, it senses, is on a computer-regulated mechanical ventilator, receiving enteral feedings being delivered by a computer-controlled infusion pump.

In addition to assisting in care of individual patients, computer applications greatly facilitate implementation of a systems-based PI program. Acquisition, analysis, and presentation of the information necessary for such efforts is labor intensive and costeffective .[132] Creating a comprehensive ICU patient database is an important step that will somewhat ease the personnel demand in a PI program. With a completely electronic medical record it is possible to automate collections of case-mix variables, and even adjustment for case-mix.[106] Manual calculation of scores and predictions from systems like APACHE is cumbersome and time consuming; computers linked to hospital information systems can compile, organize, calculate, and store these parameters automatically. Such databases are themselves potent tools for systems-based PI. They can be queried to identify subtle relationships between variables that suggest opportunities for improving performance that are not obvious even to those intimately involved in day-to-day care. For example, an evaluation of database information identified laboratory ordering patterns in an ICU that led to policy changes and subsequent cost savings.[248]

Except for viewing of diagnostic results, only a small fraction of US and Canadian hospitals currently possess any of the information technologies that have already proven beneficial.[249,250] The barriers to more widespread adaptation of information technologies include a paucity of commercially available systems, high cost, poor human interfaces, and opposition from clinicians.[231] Currently available, highly capable systems that include paperless records, computer order entry, programmable alerting, and decision support, costs up to 10 million dollars each.[249] Governmental support will almost certainly be required to fund this large, but ultimately necessary, upgrade in our national medical infrastructure.

Summary and Conclusions

The pivotal role of ICU care in our healthcare systems, along with its numerous deficiencies, requires us to vigorously work to improve our ICUs. Defining and measuring ICU performance are complex tasks. Every ICU should collect data on a variety of relevant measures of ICU performance. Efforts to detect individual adverse events and errors must not be substituted for systematically collecting data and calculating cumulative measures of performance. If there are reasons to suspect substantial differences in case-mix variables between the cohorts being compared, then some adjustment should be made for these differences. However, the resources needed to collect and adjust for case-mix often exceed those available, requiring dependence on unadjusted data. Such limitations must not lead to nihilism and inaction. Though unadjusted data could be misleading, they cannot possibly be more misleading than having no performance data at all. Similarly, adjustments made with the currently available, "prefabricated" methodologies are better than raw data. Although benchmarking the performance of one ICU against others is desirable, the simplest performance comparison is between successive time intervals.

Improving ICU performance requires a paradigm shift away from the discredited notion that most omissions, adverse events, errors, and other problems are the fault of individuals, and can be fixed by interventions aimed at individuals. Instead, it requires a *systems-oriented approach* of meaningful and sustained improvement; this is achieved by a relentless process of studying and changing the ICU structures and processes that make it easy for people to make mistakes and hard for people to do their jobs well, in order to transform them into the opposite.

Even the smallest ICU should have an appropriately constituted, multidisciplinary, systems-oriented Quality Circle that meets at least once in a month . The Quality Circle should quantitatively assess ICU performance: improving it by implementing changes to ICU structures and processes designed to standardize care and ensure uniform use of EBBP.

While PI is much easier in an ICU having the resources to hire personnel and purchase information systems, even an ICU with few resources *can* improve its performance. The most difficult, labor-intensive, and cost-effective component of PI is data collection. Though suboptimal, ways to make this process less burdensome include assessing outcomes for which data are already being collected as part of regulatory requirements, or new outcomes that can be gathered relatively easily on paper reporting sheets by clinical personnel in the ICU. If resources are insufficient to perform case-mix adjustment of outcomes data, then unadjusted data should be used without apology. Although it is not preferred, in place of the large effort needed to identify and collect data on an outcome of primary relevance (Table 59.1), one could substitute the lesser effort to collect information about an associated process-related variable. For example, it takes a large amount of work to identify the rate of ventilator-associated pneumonia, but much less to measure the utilization rate of a bedside intervention such as semi-recumbent positioning, that has been demonstrated to reduce the rate of that complication.[94] An ongoing program of such small-scale efforts, Plan-Do-Study-Act cycles, can produce large improvements in performance.[135] Even an ICU with literally no data collection resources can use systems principles by implementing interventions shown effective in the medical literature, without actually assessing the local benefits of those practices. Of course, such humble versions of PI should be accompanied by ongoing efforts to *convince* the hospital's administration that providing resources to improve ICU performance is money well spent.

Therefore, every ICU should have a systems-oriented PI program that is multidisciplinary and inclusive, has the vigorous support of hospital and ICU leadership, and has sufficient

personnel and support to succeed. These ideas must become an integral part of the ICU's routine activities; its concepts and methods must be incorporated into the culture of the ICU. Movement toward these goals should begin *now*.

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60
Continuing Education in Critical Care Medicine

Elizabeth H. Sinz

Historical Overview and New Approaches

Historically, basic medical, nursing, and other healthcare training started with the mastery of a specified body of didactic material demonstrated by successful completion of written, often multiple choice, tests in each subject area. Next, basic patient evaluation and treatment in a clinical setting with expert guidance and feedback provided by experienced clinicians was coupled with directed reading and/or lectures. Evaluation consisted of more written exams, and perhaps a clinical grade that encompassed the faculty's overall impression of the student's clinical performance. If successful, the student would progress to specialty training with a focused apprenticeship in the area of interest. Board exams were viewed as an end-point designating competency for future practice. Ongoing education was largely left up to the initiative of the individual, or perhaps to the local requirements of the workplace, and measured in hours of continuing education.

The current and evolving educational model, however, has incorporated a new technology and a different philosophy. Early clinical exposure and correlation with the didactic material is intended to motivate students to adopt an "adult-learning" mode. Rather than studying to pass a test, students are shown that what they learn *applies* directly to their current and future roles as caregivers. The importance of lifelong learning is emphasized early and reinforced frequently during training, to establish habits that will continue after formal training is completed.

The new educational model includes aspects of patient care that had previously been given scant attention, such as professionalism and teamwork. These topics are now taught and assessed on an even par with other topics such as diagnosis and treatment options. Procedural skills are objectively assessed rather than just "logged" as case numbers, and credentialing is being tied to competent demonstration of skills. Some procedures can be practiced until a minimal level of competence is achieved in a simulated setting, protecting patients from the discomfort and potential danger of beginner learning.

Technology has facilitated this transition by providing systems that allow students to master didactic materials in a more learner-centered manner. Information can be easily presented as audio, video, or written media, and all can be made widely available through the Internet,[1] podcasts, or loaned materials. Students can work at their own pace with self-assessment tests that foster self-guided study. Much of the material that was previously delivered as lectures can now be accessed in multiple formats at a time and place convenient for the learner. This fundamentally shifts the role of the teacher; instead of counting the number of lecture hours or quantity of facts delivered, teachers must coordinate, update, and assess the education provided based on learner outcomes and performance. Nurse educators have been leaders in this arena due to their longer tradition of having both nursing and education expertise; teaching physicians have, traditionally, not had specific training in education theory,[2] but this is changing now.

Underlying this new approach to healthcare education is the recognition that the pace of new discoveries and procedures creates a continual challenge to stay current and updated. Teaching and research have been the mainstays of continuing education for academic practitioners; textbooks, journals, lectures, and meetings have provided ongoing education and updating for those in non-academic practice. These traditional methods do remain valid;however, technology has provided a host of new media options that can improve access to current information for busy professionals. Immersive techniques can provide practice in a safe environment with directed feedback that focuses on the performance of the learner creating

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an opportunity to efficiently improve individual skills. This chapter will explore the new education paradigm in critical care medicine.

Improving Traditional Methods of Continuing Medical Education

There are few methods of learning that remain as important as written materials. Journals are convenient sources of current, high-quality information for the practitioner, particularly for new research findings. Numerous journals are dedicated specifically to the practice of critical care and targeted to key audiences such as doctors, nurses, or respiratory therapists. Access to particular journals or areas of interest has been enhanced by on-line availability of articles and efficient search engines that quickly locate material related to key words. Services exist that can notify providers about the latest publications across multiple journals in particular areas of interest via e-mail alert. Despite the potential value of reading journals as a means of continuing education[3] there are also limitations to this approach.[4] It may be difficult or impossible to keep up with much of the published work. The number of articles published on medical issues each year is already in the millions and still growing, making it impossible for anyone to read even a small fraction of what is available.[5,6] It may also be difficult for providers to know how or when to integrate new ideas or evidence into their specific practice. And the time needed to review, consolidate, and apply the vast numbers of articles available on a topic may be prohibitive for busy clinicians.

New techniques and management strategies have emerged as research and development have moved the field of critical care medicine forward. For example, something as seemingly straightforward as the placement of a central venous catheter has undergone remarkable advances in the past decade. When data indicated that pulmonary artery catheters were *not* improving patient outcomes, many experts believed that this might be due to improper education and understanding of how and when to use these devices and the data obtained from them. A combined effort of multiple organizations led to PACEP, or the Pulmonary Artery Catheter Education Project. This teaching program was widely distributed through the Internet with both educational modules and self-assessment test questions. This use of the Internet was a model for widespread dissemination of information intended to improve practice across a broad field. Most importantly, this educational module was created through the collaboration of experts who had developed consensus on how to use a device through review of the evidence available and development of consensus across specialties. This information remains readily available to anyone interested in learning the material (PACEP.org). The PACEP project is a good example of a collaborative project that provides Web-accessible materials with self-assessment activities that can be used in a manner as best serves the learner. Many other resources are also available on the Internet, with varying levels of usefulness and quality.

Textbooks can help provide efficient summary and review of the body of knowledge in a field, and although texts become outdated rather quickly, they provide a source of reference and a mechanism to "get up to speed" on a topic relatively quickly. Many textbooks are also becoming available in a computer format, allowing easier and timelier updates. UpToDate (http://www.uptodate.com) is an example of a computer-based textbook available on the Internet with continually updated material. Each topic is extensively cross-referenced with other topics as well covered in the resource, and the date the work was completed is prominently displayed so that the reader knows when the material was last updated. Compilations and guidelines can capitalize on the benefits of the Internet related to ease of access and wide dissemination of information, while overcoming some of the challenge of determining the quality of so much readily available information. Online materials often contain hypertext, allowing the reader to quickly access additional information on a topic as they read, or other features not available in written works such as video clips, and this may improve learning.[7] Many of the Web-based resources provide enhanced searchability, easier access to current materials, and greater portability as Internet access becomes ubiquitous, although text remains the underlying method to convey information and ideas (Table 60.1).

Lectures and Presentations

Another prevalent method of teaching has historically been lectures, both for basic education and for continuing medical education (CME). Lectures are efficient for teachers, allowing them to summarize and convey large amounts of information to large groups of learners with limited effort. Technology has improved on this teaching format by making it possible for lectures to be distributed in real time, and later repeated to an ever-widening audience. Time is a precious commodity and in the continuously active environment of the modern hospital, "lunchtime" presentations may not be convenient venues for a large proportion of interested providers to participate in educational opportunities. Recorded didactics in the form of video, audio, or Internet-accessible materials make it possible for individuals to hear lecture material at different times, or from remote locations. Commercial entities such as Audio-Digest (http://www.audio-digest.org) provide current recorded lectures in a variety of topic areas either by CD, pod-cast, or MP3 format.

Despite the improvements in accessibility to lectures brought about by technology, many criticisms have been leveled against this teaching method due to its relatively *inefficient* transfer of knowledge and skills to the audience. Some studies have indicated that lectures are not particularly effective at changing performance,[8] possibly due to the passive stance of the learner. Many people, and especially adults, seem to retain more when they are engaged in an active way as learners, particularly if behavioral change is the marker.[9,10] New approaches involving *lecture-discussion*, more formally categorized as problem-based learning or case-based learning courses, are commonly replacing lecture alone. Although such sessions often require

TABLE 60.1. Selected Internet resources for critical care medicine.

PACEP Pulmonary Artery Catheter Education Project	A collaborative educational effort designed to provide a state-of-the-art educational program on how to use the pulmonary artery catheter in the clinical environment and measure learning outcomes for the end-user	http://www.pacep.org/
Agency for Healthcare Quality and Review Morbidity and Mortality Rounds on the Web (AHRQ Web M & M)	An online journal and forum on patient safety and health care quality with expert analysis of medical errors reported anonymously by readers	http://webmm.ahrq.gov/index.aspx
Critical Care UK		http://www.anaesthesiauk.com/SectionContents.aspx?sectionid=203
The LearnICU Web page from the Society for Critical Care Medicine	Organizes learning opportunities systematically into categories that are accessible to members on the SCCM Web site. Information for critical care healthcare providers (members and non-members) and for the general public (families and patients) is provided	http://sccmcms.sccm.org/SCCM/LearnICU/
Pulmonary and Critical Care Update by the American College of Chest Physicians	Offers CME for two lessons per month plus a variety of on-line educational offerings	http://www.chestnet.org/education/online/pccu/
Online critical care journals		
American Journal of Critical Care		http://ajcc.aacnjournals.org/
American Journal of Respiratory and Critical Care Medicine		http://ajrccm.atsjournals.org/
Journal of Intensive Care Medicine		http://jic.sagepub.com/
Indian Journal of Critical Care Medicine	Offers a list of related journals	http://www.ijccm.org/

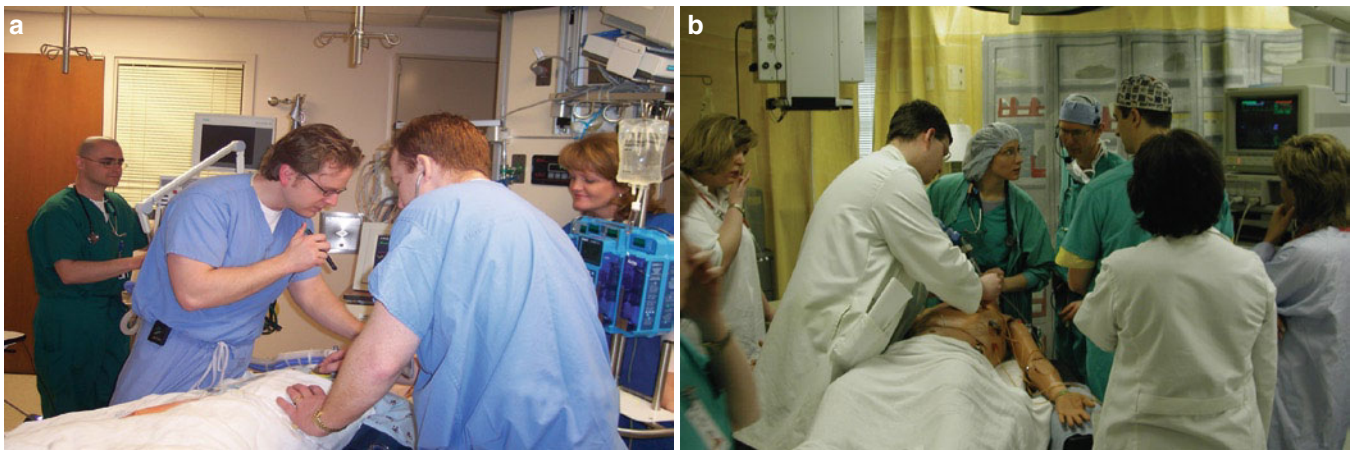

FIG. 60.1. Use of a full human patient simulator for teamwork skills, (**a**) in a real ICU setting with a portable manikin (in situ simulation), and (**b**) in a simulation lab with a high-fidelity non-portable manikin.

more teaching resources compared to simple didactics, the learners may experience increased efficiency in acquisition and retention of useful information that can be translated into their practice. CME is increasingly being offered in *interactive* formats in the hope that physician performance will be affected in a way that improves patient outcomes more readily.

Immersive Education: Simulation and Virtual Reality

Bedside teaching and practice was the primary interactive teaching technique for most medical training for decades, with real patients receiving treatment and simultaneously serving as teaching cases. Now, a reasonable substitute for some components of bedside training can be found in full patient *simulation* (Fig. 60.1). Human simulators can mimic a host of illnesses, particularly those involving cardiovascular and respiratory system abnormalities such as dysrhythmias, respiratory failure, and hemodynamic derangements. This allows healthcare providers to practice common and uncommon patient events by experiencing them in a safe simulated environment where no patient is at risk from mistakes, in contrast to actual clinical practice. Depending on what is being learned, various manikins or a specially trained actor known as a standardized patient can

be used to represent a patient or family member. The event can be handled either in a teaching lab or in a real clinical setting with individuals or teams of varying compositions depending on what is being emphasized. For example, individuals or groups can observe or manage every type of life-threatening cardiac dysrhythmia to practice and review diagnosis and treatment options. "Routine" emergencies can be drilled and time to treatment shortened, which are likely to result in better patient outcomes.[11] In addition, rare events that cannot be practiced with adequate frequency in a clinical setting can be staged and practiced in a simulated environment with key practitioners or entire healthcare teams. Most simulation modalities have been utilized for teaching critical care skills including computer screen-based simulation, actors, animals, human cadavers, partial-task trainers, videotape, and full-scale human patient simulators. Simulators have been effective for teaching multiple aspects of critical care medicine to all types of trainees without risk to patients.

Teamwork has been identified as a necessary element for delivering good patient care, and high acuity patient environments such as the intensive care unit, operating room, and emergency department require the highest level of teamwork skills. Rather than hoping that good team skills will evolve with time, intense training and study are now dedicated to this skill set.[12–16] Several methods of team training often adapted from business, military, or flight-tem models emphasize key factors such as communication, leadership, and decision-making. There is ample evidence that individuals are not adept at self-assessment, particularly when the basis for their assessment is their confidence that they have mastered a task.[17,18] Since teamwork skills can be difficult to quantifiably assess, participants are encouraged to evaluate their own performance using video of their actions in the simulation laboratory. Using video this way encourages reflective practice and can be combined with available metrics that define successful performance. These aspects of simulation-based education give students the tools they need to continually improve their skills in real clinical patient care. Disaster Training requires a special variety of teamwork and relies on a well-functioning system. Disasters are rare and by their very nature cannot be planned with great certainty, but planning and practice can reduce the impact of many of the common features of disasters; and large-scale simulation exercises have been conducted in many locations, often revealing systems' limitations that can be addressed before an actual crisis occurs.

New Procedural Skills and Credentialing

Technological advances have introduced new procedures at a rapid pace. Every healthcare provider will need to acquire new skills or work with new equipment many times during their careers. Traditionally, physicians have learned these skills while actively engaged in patient care, or perhaps a colleague might demonstrate and even coach them through a new procedure. Workshops given by experts or sales representatives have fulfilled some of the educational needs related to new developments. Simulation is evolving as a useful and increasingly proven technique for learning procedural skills, and in some cases, assessment of these skills prior to using new techniques in clinical practice.

The key to mastery of new psychomotor skills across many domains is intentional practice with feedback. Many of the newer virtual reality devices are designed with feedback mechanisms that can provide performance evaluation to the learner so that they can improve their skills even without a live coach or teacher present. For example, virtual reality bronchoscopy simulators have been shown in several, different learner groups to provide excellent training for novices[19–22] (Fig. 60.2). These studies have confirmed that the simulation-based learning can *impact* the care of the initial patients who undergo this procedure, presumably because the initial learning has already occurred.

When new techniques such as ultrasound-guided vascular access become available, new simulators are rapidly introduced to teach the new skills required. A precedent has been set where FDA approval of a new device was coupled with the requirement that practitioners demonstrate they can perform the procedure on a simulator before they are allowed to use the device in patients. Simulation may become a common testing and accreditation mechanism in the near future, particularly for procedural skills.

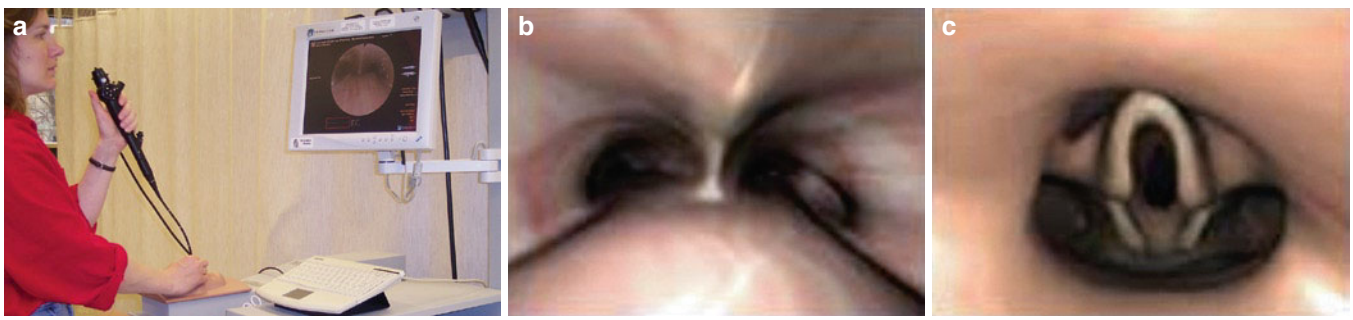

FIG. 60.2. (**a**) A haptic-based virtual reality bronchoscopy simulator using a case-based teaching format with intrinsic performance feedback; (**b**, **c**) details of the simulator images.

Serious Games

Serious games, or the use of games and game theory for education, has been used heavily by the military and is now spreading into healthcare education. The military first used a war-game video game as a recruiting tool, and this evolved into the use of similar technology as a training tool, as described in the April 1997 edition of *Wired* magazine. Conceptually, this is the use of conceptual games to convey and practice key skills and ideas to the participants, and particularly applies to the use of computer games or virtual reality. Some educators are developing this type of virtual environment for the purpose of learning and practicing crisis management and medical management concepts. Team training or rare events management can be undertaken with avatars, and participants can participate from close or remote locations via Internet connections. The financial investment in healthcare teaching is a tiny amount compared to commercial gaming, but the relevant technology is now starting to "trickle down" into the education domain.

Future Directions

Why require a fellow from anesthesiology to learn how to manage an airway? Why require a surgery fellow to repeat their lesson on chest tubes? Why waste the time of a fellow from internal medicine who already knows how to work-up a patient with pneumonia? There is too much to be learned to spend precious time and resources on topics that already have been mastered. In some ways, the field of critical care is in an ideal position to test the new paradigm of outcomes-based education, which moves the focus from "What is the teacher teaching?" to "What has been mastered by the learner?" As practitioners have increasingly varied backgrounds upon entering critical care, it becomes more challenging to teach in a manner that is efficient for the learner. Many of the emerging tools and techniques allow learners to demonstrate their competence in one area, and focus their efforts in the areas they need to, often without a live teacher required.

The ultimate goal is a system that provides individuals the skills needed to perform alone and as part of a team, with the focus always on the patient. Practice and training should be part of a continuous feedback loop that provides ever better outcomes for providers and healthcare systems. Technology, education, systems engineering, safety, and human empathy are all driving forces in these changes, as are economics, fear, and politics. Many of the changes made in today's educational system will not be fully appreciated for years to come and the effect will be long-lasting. Let us hope that the decisions made will continually improve healthcare.

Summary

Despite the recent challenges to the CME system and changes that have been suggested or made to address its shortcomings, the idea that clinicians must continually learn new facts and new techniques throughout their career is *not* in question.[23] What is evolving is the concept about how best to improve the knowledge, skills, and judgment, as well as the practice of our clinicians, with the ultimate goal of measurably improving patient care. In time, it is likely that a variety of educational methods will be acceptable as long as the outcomes are good. For now, one is offered a host of new and exciting options for CME that were not readily available in the past, but there is more to come in the future.

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Erratum to:

Surgical Intensive Care Medicine, Second Edition

John M. O'Donnell and Flávio E. Nácul

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2
Airway Management in the Intensive Care Unit

Denis H. Jablonka and William Rosenblatt

page 16

Right column

Section: Opioid Agents
Fourth line of the first paragraph: 1–2 mg/Kg is incorrect.
The correct unit is: 1–2 mcg/Kg.

Right column

Section: Opioid Agents
Fourth line of the second paragraph: 1.5–2.5 mg/Kg is incorrect.
The correct unit is: 1.5–2.5 mcg/Kg.

Right column

Section: Opioid Agents
Seventh line of the second paragraph: 30–40 mg/Kg is incorrect.
The correct unit is: 30–40 mcg/Kg.

3
Vascular Cannulation

Shawn E. Banks and Albert J. Varon

The legends for Figures 3.3 and 3.4 are reversed:

Figure 3.3. The legend is incorrect. It should refer to Figure 3.4.

The correct legend is: Three approaches for access to the internal jugular vein. (**A**) Anterior to the sternocleidomastoid. **(B)** Central between the clavicular and sternal heads of the sternocleidomastoid. **(C)** Posterior to the sternocleidomastoid.

Figure 3.4. The legend is incorrect. It should refer to Figure 3.3.

The correct legend is: Pressure tracing recordings with corresponding locations as the pulmonary artery catheter is passed into the "wedge" position.

11
Optimization of the High-Risk Surgical Patient

Nawaf Al-Subaie and Andrew Rhodes

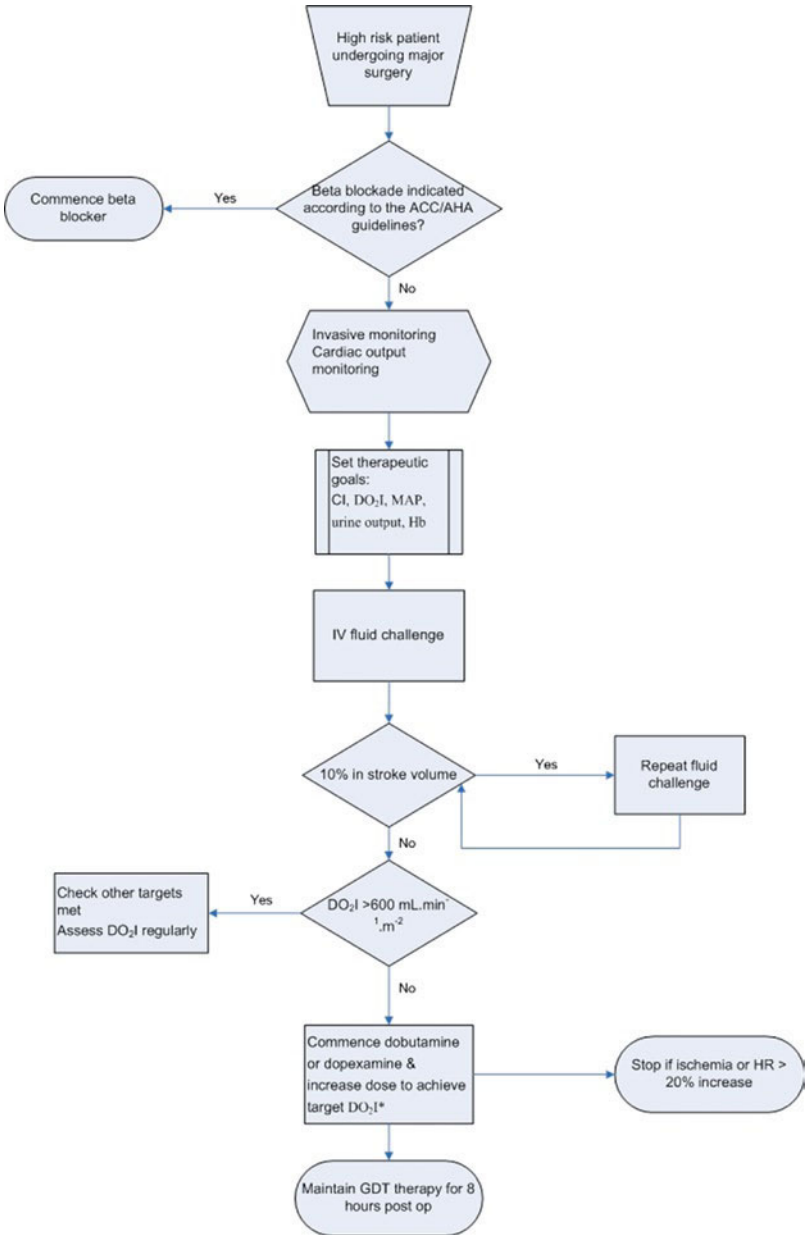
Page 110

There are three errors within Figure 11.3

- The “100% in stroke volume” field should read “10% in stroke volume”.
- The arrow that connects “10% in stroke volume” with “Repeat fluid challenge” should point in the opposite direction.
- The “Check other targets met/Asses Do_2I regularly” field should read “Check other targets met/Assess DO_2I regularly”.

Please see the corrected figure on the following page:

The online version of the original chapters can be found under
DOI 10.1007/978-0-387-77893-8


High risk patient undergoing major surgery
Beta blockade indicated according to the ACC/AHA guidelines?
Yes
Commence beta blocker
No
Invasive monitoring Cardiac output monitoring
Set therapeutic goals: CI, DO_2I, MAP, urine output, Hb
IV fluid challenge
10% in stroke volume
Yes
Repeat fluid challenge
No
DO_2I >600 mL.min^{-1}.m^{-2}
Yes
Check other targets met
Assess DO_2I regularly
No
Commence dobutamine or dopexamine & increase dose to achieve target DO_2I*
Stop if ischemia or HR > 20% increase
Maintain GDT therapy for 8 hours post op

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