

Critical Care Medicine

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Critical care medicine encompasses multidisciplinary aspects of the management of severely ill patients. All areas of medicine may have relevance for critically ill patients, but this review focuses on aspects of cardiopulmonary monitoring and life support, technologic interventions, and disease states typically managed in the intensive care unit (ICU).

Cardiopulmonary Resuscitation and Rapid Response Teams

Sudden cardiac arrest is the leading cause of death in the United States. Most persons with sudden cardiac arrest have ventricular fibrillation at some point in their arrest. Resuscitation is most effective if defibrillation is provided within 5 minutes after collapse. Effective cardiopulmonary resuscitation (CPR) is important both before and after shock delivery and can triple a patient's chance of survival.

The *2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care* simplified the basic life support sequences, particularly for lay rescuers, and minimized the differences in the steps and techniques of CPR for infant, child, and adult victims. A universal compression-ventilation ratio (30:2) is recommended for all solo rescuers of infants (excluding newborns), children, and adults. Health care providers should deliver rescue breaths without chest compressions at a rate of 10 to 12 breaths per minute for adult patients with a pulse. They should also deliver cycles of compressions and ventilations when an advanced airway is not yet in place. After the airway is secured, there is no need to cycle between breathing and compressions: they should occur simultaneously at 12 breaths per minute and 100 compressions per minute without pauses for breaths. The guidelines should be consulted for more detail about the role of CPR, the coordination of CPR with defibrillation, the role of CPR in advanced life support, and basic and advanced life support for newborns, infants, and children.

Rapid response teams, also known as medical emergency teams, have emerged as a method to "expand the walls" of the ICU and attempt to identify critically ill patients before full cardiac arrest. These teams are generally made up of a physician, a critical care nurse, and a respiratory therapist. The key element for proper function

of this system is that specific calling criteria have been developed, general ward staff have been educated to recognize these criteria, and the team can be activated by anyone. After implementing these teams, institutions have demonstrated a trend toward reduced mortality and have reduced unplanned ICU admissions.

- Sudden cardiac death is a leading cause of death in the United States.
- Effective CPR is important both before and after shock delivery and can triple a patient's chance of survival.
- The *2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care* should be reviewed.
- Rapid response teams have demonstrated a trend toward reduced mortality and unplanned ICU admissions.

Airway Management

Expertise in management of the airway in critically ill patients, which pose unique challenges, is a required skill for anyone practicing in the ICU. Elective airway management in the operating room (OR) is associated with low rates of complication. However, emergent airway management in the ICU is associated with higher complication rates (about 25%) due to patient comorbidities, limited evaluation and planning time, and limited reserve of patients (respiratory failure and shock). With these limitations, many of the tools, equipment; and drugs that are available in the OR are not practical to use in the ICU. Components of successful management include assessment; preparation of the environment, patient, and equipment and drugs; and, most importantly, having a backup plan available to implement immediately if needed.

Endotracheal intubation allows maximal control of the airway, enables the delivery of specific inspired oxygen concentrations and positive pressure ventilation, and provides protection from aspiration. Indications for intubation include airway protection in cases of obstruction or loss of normal gag and cough reflexes, central nervous system injury or sedation with loss of normal control of ventilation,

and any cause of respiratory failure requiring positive pressure–assisted ventilation. Orotracheal intubation is usually achieved through direct visualization with a laryngoscope. In experienced hands, this procedure should be relatively quick and safe.

Complications of intubation include vomiting and aspiration, hypoxemia during the procedure, and inadvertent intubation of the esophagus.

An airway assessment of difficulty in performing mask ventilation or difficult intubation should be attempted on all patients (Table 4-1). Since a full airway evaluation is possible in only a minority of ICU patients, alternative schemes such as the LEMON (*look, Mallampati, obstruction, and neck mobility*) have been devised to help stratify risk. The Mallampati classification schema is widely used and consists of classes I (easy) to IV (difficult intubation).

1. Class I—entire tonsil is clearly visible
2. Class II—upper half of tonsil fossa is visible
3. Class III—soft and hard palate are clearly visible
4. Class IV—only hard palate is visible

Before intubation, the equipment, the environment, and the patient should be prepared. Being prepared for unforeseen problems is of utmost importance. Table 4-2 lists elements required for proper preparation.

Successful intubation is often dependent on adequate pharmacotherapy (Table 4-3). The typical sequence followed in the OR is premedication, induction, and paralysis. Owing to unique challenges in the ICU, this is not always practical or advisable. Many induction agents used in the OR cause vasodilation and hypotension, a condition to which ICU patients are already predisposed. The majority of ICU patients should be considered to have a full stomach and would be candidates for rapid-sequence intubation; however, the risks of obliterating spontaneous ventilation should be carefully weighed against the probability of “cannot intubate or ventilate.” It should also be noted that the most widely used short-acting paralytic, succinylcholine, often cannot be used owing to comorbidities (burns, upper motor neuron lesions, myopathy, crush injury, renal failure, and prolonged immobility) seen in the ICU population. In

Table 4-1 Predictors of Difficult Mask Ventilation and Intubation

Difficult Mask Ventilation	Difficult Intubation
Age >55 y	Short thick neck
Body mass index >26 kg/m ²	Limited neck flexion or extension
Edentulous	Thyromental distance <3 finger breadths
Male	Long upper incisors
Mallampati class IV	Presence of overbite
Beard	Inability to jut mandibular incisors anterior to upper incisors
History of snoring	Inability to open mouth >3 cm
	Mallampati class >II
	High arched palate

general, spontaneous breathing should be maintained in patients who are predicted to be difficult to intubate.

- Managing the airway in critically ill patients poses unique challenges.
- Successful management is predicated on proper preparation and planning.
- A backup method to direct laryngoscopy should be readily available.
- Use muscle relaxants with extreme caution.

Venous Access and Monitoring

Central Venous Catheterization

The first choices for access in patients requiring intravenous therapy are the peripheral veins. The most common locations for central access are the internal jugular, subclavian, and femoral veins. Indications for central venous access are lack of adequate peripheral veins, need for hypertonic or phlebotic medications or solutions, need for long-term access, measurement of central pressures, and access for procedures (hemodialysis, cardiac pacing).

Relative contraindications include inexperience of the practitioner, coagulopathy, inability to identify landmarks, infection or burn at the entry site, and thrombosis of the proposed central venous site. Central venous catheters are usually placed over a guidewire (modified Seldinger technique).

Complications of central venous catheterization include bloodstream infections, cardiac arrhythmias, pneumothorax, air embolism, catheter or guidewire embolism, catheter knotting, bleeding, and other potential complications of needle or catheter misplacement.

Table 4-2 Elements and Equipment Required for Successful Endotracheal Intubation

Adequate personnel
Proper patient positioning
100% oxygen
Well-fitting bag valve mask
Suctioning equipment
Nasal & oral airways
Working laryngoscope
Various types & sizes of laryngoscope blades
Endotracheal tubes with intact cuffs
Tube stylet
10-mL syringe
Head rest
Working intravenous line
Induction drugs
Vasoconstrictor drugs
End-tidal carbon dioxide detector
Method to secure tube

Table 4-3 Commonly Used Drugs for Airway Management in the Intensive Care Unit

Midazolam
Fentanyl
Etomidate
Propofol
Succinylcholine
Nondepolarizing agents

Pulmonary Artery Catheterization

Although common use (or overuse) of pulmonary artery catheterization has been criticized, data from pulmonary artery catheterization (Table 4-4) may aid in the diagnosis and treatment of many disorders encountered in ICUs. The usefulness of these measurements may be limited by the understanding of the physician interpreting the values. Table 4-5 shows hemodynamic patterns in the 4 shock states.

Indications for pulmonary artery catheterization include shock states, pulmonary edema, oliguric renal failure, indeterminate pulmonary hypertension, and myocardial and valvular disorders. Intravascular volume may be assessed more accurately, and the effects of therapeutic interventions (volume, vasodilator therapy, or inotropics) may be evaluated. Mixed venous oxygen saturation may also be measured (see detailed discussion later in this chapter). This may be particularly useful in assessing the effects of positive end-expiratory pressure (PEEP) on oxygen delivery (ie, improving arterial saturation but potentially decreasing cardiac output).

Complications of pulmonary artery catheterization include arrhythmias, right bundle branch block, complete heart block in patients with preexisting left bundle branch block, vascular or right ventricular perforation, thrombosis and embolism, catheter knotting, infection, and pulmonary infarction or rupture due to persistent wedging or overdilation of the balloon.

- Pulmonary artery catheterization provides useful clinical information.
- Misinterpretation or artifacts may limit usefulness of data and may cause harm.
- Unique patterns are seen in the various shock states.

Systemic Oxygen Transport

In addition to providing numerous measured and calculated values, pulmonary artery catheters can facilitate measurement of systemic oxygen transport (Table 4-6). Under normal circumstances, oxygen demand by the tissues is met by the supply. Oxygen delivery is defined by cardiac output (CO) multiplied by arterial oxygen content (CaO_2):

$$O_2 \text{ delivery} = CO \times CaO_2$$

Although cardiac output may decrease, oxygen consumption per unit time ($\dot{V}O_2$) of the tissues may be maintained by increased oxygen extraction. The content of oxygen in the blood is the total amount of oxygen bound to hemoglobin (Hgb) plus the amount dissolved.

$$O_2 \text{ content: } CxO_2 = (1.34 \times Hgb \times SxO_2) + (0.003 \times PxO_2)$$

(Bound) (Dissolved)

where x is arterial, venous, or capillary.

Under steady state conditions, the amount of oxygen used by the tissues equals the amount taken up by the lungs. The oxygen uptake ($\dot{V}O_2$) can be defined by the amount of oxygen leaving the lungs in pulmonary venous blood minus the amount of oxygen coming into the lungs in the pulmonary arteries. This should be familiar as the Fick equation:

$$\dot{V}O_2 = CO(CaO_2 - C\bar{v}O_2)$$

A shunt is defined by perfusion (Q) in the absence of ventilation (\dot{V}) (ie, $\dot{V}/Q=0$). With a pure shunt, PaO_2 does not increase even

Table 4-4 Hemodynamic Data Obtained With Pulmonary Artery Catheterization

Variable	Normal Values
Right atrial pressure (RAP)	2-8 mm Hg
Pulmonary arterial pressure (PAP)	16-24/5-12 mm Hg
Pulmonary capillary wedge pressure (PCWP)	5-12 mm Hg
Cardiac output (CO)	4-6 L/min
Cardiac index (CI = CO/body surface area)	2.5-3 L/min/m ²
Stroke volume (SV = CO/heart rate)	50-100 mL/beat
Stroke volume index (SVI = SV/body surface area)	35-50 mL/m ²
Systemic vascular resistance	10-15 mm Hg/L/min
[SVR = (blood pressure - RAP)/CO]	(×80 to convert to 800-1,200 dyne·s·cm ⁻⁵)
Pulmonary vascular resistance	1.5-2.5 mm Hg/L/min
[PVR = (PAP - PCWP)/CO]	(100-200 dyne·s·cm ⁻⁵)

Table 4-5 Hemodynamic Patterns in Various Shock States

Shock State	RAP	PCWP	SVR	CO
Hypovolemic	↓	↓	↑	↓
Distributive	↓→	↓→	↓	↑
Cardiogenic	↑	↑	↑	↓
Tamponade		Equalization of pressures		

Abbreviations: CO, cardiac output; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SVR, systemic vascular resistance.

though the fraction of inspired oxygen ($F_{I}O_2$) is increased to 100%. The normal shunt fraction is less than 3% to 5% of the total cardiac output. The shunt fraction is measured with the person breathing 100% oxygen and is expressed as follows:

$$\frac{Q_s}{Q_t} = \frac{CC'O_2 - CaO_2}{CC'O_2 - C\bar{V}O_2} = \frac{P(A-a)O_2 \times 0.003}{P(A-a)O_2 \times 0.003 + (Ca - C\bar{V})O_2}$$

where Q_s is the portion of cardiac output shunted, Q_t is the total cardiac output, $CC'O_2$ is capillary oxygen content, CaO_2 is arterial oxygen content, and $C\bar{V}O_2$ is venous oxygen content.

- Under normal conditions, oxygen demand is met by supply.
- When oxygen delivery is decreased, oxygen consumption can be maintained by increased extraction.
- The Fick equation can be used to calculate cardiac output.
- The normal shunt fraction is <5%; pure shunts do not improve with 100% oxygen.

Mixed Venous Oxygen Saturation

Many applications of the Fick equation are important in managing critically ill patients. One application involves continuous monitoring of mixed venous oxygen saturation ($S\bar{V}O_2$) by a specialized type of pulmonary artery catheter. Expressing oxygen content in terms of saturation and rearranging the Fick equation to solve for $S\bar{V}O_2$ yields the following:

$$S\bar{V}O_2 = SaO_2 - \frac{\dot{V}O_2}{CO \times Hgb \times 1.34}$$

where SaO_2 is arterial saturation, CO is cardiac output, and Hgb is hemoglobin concentration.

Note that decreased mixed venous oxygen saturation may be due to decreased arterial saturation, increased oxygen consumption, decreased cardiac output, or decreased hemoglobin. Certain disease states, particularly early sepsis, may be characterized by normal or increased mixed venous oxygen saturation because cardiac output initially increases along with impaired oxygen uptake by the tissues. Later in sepsis, due to decreased cardiac output, which causes decreased delivery of oxygen, the mixed venous oxygen saturation typically decreases.

Table 4-6 Oxygen Transport Variables

Variable	Reference Values
Mixed venous oxygen saturation ($S\bar{V}O_2$), %	70-75
Oxygen delivery (DO_2), mL/min	950-1150
Oxygen uptake ($\dot{V}O_2$), mL/min	250
Oxygen extraction ratio (O_2ER), %	20-30

- Decreased mixed venous oxygen saturation may result from decreased arterial saturation, increased oxygen consumption, decreased cardiac output, or decreased hemoglobin.
- In early sepsis, mixed venous oxygen saturation is normal or increased.

Pulmonary Artery Catheter Controversies

In case-control studies among patients who had a similar severity of illness, the use of a pulmonary artery catheter was associated with higher mortality than no use of a catheter. However, the validity of these findings is uncertain, and catheter use is still common clinical practice. Recent prospective trials of pulmonary artery catheterization in high-risk surgical patients and medical patients with acute respiratory distress syndrome (ARDS) randomly assigned to a conservative or liberal fluid management strategy showed no difference in outcome (ie, no clear evidence of benefit or harm) between catheterization and control groups.

Use of the pulmonary capillary wedge pressure (PCWP) as an indicator of left ventricular end-diastolic pressure assumes a continuous hydrostatic column extending from the pulmonary capillary to the left atrium. Although digital displays of PCWP are usually available, the pressure wave should be examined for potential artifacts and for the degree of respiratory variation. Because varying intrathoracic pressure may be sensed by the pulmonary artery catheter, the end-expiration PCWP should be recorded. Even with these measures, PCWP may be influenced by airway pressure and, thus, may not accurately reflect ventricular filling pressure, especially with high levels of PEEP.

- PCWP is an indicator of left ventricular end-diastolic pressure.
- PCWP may be influenced by airway pressure, especially with high levels of PEEP.

Catheter-Related Infections

Catheter-related infections are usually attributed to the migration of bacteria from the skin along the catheter tract. Catheter-related infection is usually defined by more than 15 colony-forming units per milliliter on semiquantitative culture of the catheter tip. Catheter-related bacteremia is defined by similar bacterial growth and blood cultures that are positive for the same organism as on the catheter tip. Risk factors include infected catheter site or cutaneous breakdown, multiple manipulations, the number of catheter lumens, and the duration of use of the same site (particularly after 3 or 4 days).

Treatment should include catheter removal and replacement at another site if necessary.

- Catheter-related infections usually are attributed to migration of bacteria from the skin along the catheter tract.
- Risk factors include infected catheter site or cutaneous breakdown, multiple manipulations, number of catheter lumens, and duration of use of same site.
- Catheters at an infected site should be removed.

Respiratory Failure

Effective functioning of the respiratory system requires normal central nervous system control, neuromuscular transmission and bellows function, and gas exchange at the alveolar-capillary level. Respiratory failure may result from disease at any of these levels. The 2 broad categories of respiratory failure are hypoxemic and hypercapnic.

Hypoxemic Respiratory Failure

Effective gas exchange requires adequate alveolar ventilation for the elimination of carbon dioxide, oxygen uptake across the alveolar-capillary membrane, and the delivery of oxygen to tissues. *Hypoxemia* may result from the following:

1. Decrease in the inspired partial pressure of oxygen (eg, at high altitude, including air travel or interruption of oxygen supply)
2. Hypoventilation
3. Ventilation-perfusion (\dot{V}/Q) mismatch
4. Shunt
5. Diffusion barrier

Estimation of the alveolar-arterial (A-a) gradient for oxygen is essential in analyzing the cause of hypoxemia (Table 4-7).

Alveolar Air Equation and the A-a Gradient

Alveolar gas consists of inspired gases saturated with water vapor. The alveolus also contains carbon dioxide delivered from the blood. The sum of the partial pressures of all gases present equals the ambient barometric pressure. The *alveolar air equation* defines this relationship as follows:

Table 4-7 Causes of Hypoxemia With Normal or Increased Alveolar-Arterial (A-a) Gradient

Normal A-a Gradient	Increased A-a Gradient
Low P_{iO_2} & low PB	\dot{V}/Q mismatch
Low F_{iO_2}	Diffusion
Hypoventilation	Shunt

Abbreviations: F_{iO_2} , fraction of inspired oxygen; PB, barometric pressure; P_{iO_2} , partial pressure of inspired oxygen; Q, perfusion; \dot{V} , ventilation.

$$PAO_2 = F_{iO_2}(PB - 47) - \frac{PaCO_2}{R}$$

where PAO_2 is alveolar partial pressure, PB is barometric pressure (about 760 mm Hg at sea level), P_{H_2O} is water vapor pressure (47 mm Hg), and R is the respiratory quotient ($\dot{V}_{CO_2}/\dot{V}_{O_2}$, which is normally about 0.8). The simplified equation is

$$PAO_2 = F_{iO_2}(PB - 47) - \frac{PaCO_2}{0.8}$$

Breathing room air ($F_{iO_2} = 0.21$) at sea level yields

$$PAO_2 = 150 - \frac{40}{0.8}$$

Normal PAO_2 is approximately 100 mm Hg.

The A-a oxygen difference is defined by PAO_2 minus PaO_2 , which is normally less than 10 to 20 mm Hg when breathing room air. The A-a gradient normally increases to approximately 50 to 100 mm Hg as the F_{iO_2} increases from 0.21 to 1.0, and it also increases slightly with age. Hypoxemia due to hypoventilation is characterized by increased $PaCO_2$ and decreased PaO_2 but a relatively normal A-a gradient. In hypoxemia due to ventilation-perfusion mismatch, an increased A-a gradient is present.

- Hypoxemia due to hypoventilation is characterized by an increased $PaCO_2$, decreased PaO_2 , and a normal A-a gradient.
- Normal PAO_2 is approximately 100 mm Hg.

Hypercapnic Respiratory Failure

Hypercarbic or hypercapnic respiratory failure is caused by inadequate alveolar ventilation that is generally the result of airway obstruction, increased dead space or failure of respiratory bellows (chest wall, diaphragm, or neural control) (Table 4-8).

The partial pressure of carbon dioxide ($PaCO_2$) in the blood is directly proportional to the amount of carbon dioxide produced (\dot{V}_{CO_2}) and inversely proportional to alveolar ventilation (\dot{V}_A):

$$PaCO_2 = k \frac{\dot{V}_{CO_2}}{\dot{V}_A}$$

Alveolar ventilation is equal to total ventilation (\dot{V}_E) minus dead space ventilation (\dot{V}_D). Thus, physiologic dead space is defined by the portion of a breath that does not participate in gas exchange. Dead space volume (V_D) may be anatomical (conducting airways) or alveolar (areas of ventilation that receive no perfusion):

$$\dot{V}_A = \dot{V}_E - (V_D \times f)$$

where f = breaths per minute.

Table 4-8 Causes of Hypoventilation and Hypercapnic Respiratory Failure

Central nervous system	Muscular dysfunction
Drugs	Muscular dystrophies
Hyperthyroidism	Guillain-Barré syndrome
Ondine curse	Myasthenia gravis
Brainstem injury	Amyotrophic lateral sclerosis
Metabolic alkalosis	Malnutrition
Chest wall disorders	Acidosis
Kyphoscoliosis	Hypoxemia
Rib fractures	Anemia
Pain	Low cardiac output
Flail chest	Steroids
Diaphragm disorders	Aminoglycosides
Rupture, myopathy	Calcium channel blockers
Spinal cord & peripheral nervous system	Post-paralytic condition
Lesion at C3 to C5	Detraining, atrophy, overuse fatigue
Neuropathy	Increased workload
Trauma	

Dead space ventilation can be calculated using the following formula (Bohr equation):

$$\frac{V_D}{V_T} + \frac{P_{aCO_2} - P_{ECO_2}}{P_{aCO_2}}$$

where P_{CO_2} is the partial pressure of expired carbon dioxide, and V_T is tidal volume. Normally V_D/V_T is less than 0.25 to 0.30.

The dead space-to-tidal volume ratio is calculated by measuring the partial pressure of carbon dioxide in an arterial blood gas sample (P_{aCO_2}) and an expired gas sample (P_{ECO_2}).

- Physiologic dead space is defined by the portion of breath not participating in gas exchange.
- Increased dead space leads to decreased elimination of carbon dioxide at any given level of total minute ventilation.

Mechanical Ventilation

Mechanical ventilation may be valuable in various conditions of respiratory failure, including loss of respiratory control, neuromuscular or respiratory pump failure, and disorders of gas exchange. Many specific variables that have been suggested as criteria (or general guidelines) for ventilator support are listed in Table 4-9.

Physiologic Definitions and Relationships

To understand mechanical ventilation, including its targets, patient-ventilator interactions, and ventilator alarms, one must have a basic understanding of lung mechanics.

Lung Volumes

Total lung capacity (TLC) is the total volume of gas in the chest at the

Table 4-9 Criteria for Ventilator Support

Respiratory rate >30/min
Minute ventilation >10 L/min
Maximal inspiratory pressure <-20 cm H ₂ O
Vital capacity <10 mL/kg
PaO ₂ <60 mm Hg with FIO ₂ >0.60
PaO ₂ /FIO ₂ <100-150
P(A-a)O ₂ >300 mm Hg with FIO ₂ =1.0
V _D /V _T >0.60
PaCO ₂ >50 mm Hg

Abbreviations: A-a, alveolar-arterial; FIO₂, fraction of inspired oxygen; V_D, dead space volume; V_T, tidal volume.

end of a maximal inspiration. *Vital capacity* (VC) is the volume of a maximal breath (expired or inspired). *Tidal volume* (V_T) is the volume of a normal breath. *Functional residual capacity* (FRC) is the lung volume at the end of a normal expiration. It reflects the relaxation point of the respiratory system or the point at which outward recoil of the chest wall is balanced by inward recoil of the lungs.

Compliance

Compliance (C) of the lungs or respiratory system is defined by the change in volume (ΔV) for a given change in pressure (ΔP):

$$C_{\text{STATIC}} = \frac{\Delta V}{\Delta P}$$

where ΔV is measured in milliliters and ΔP in centimeters of water. Normal compliance is approximately 200 mL/cm H₂O. Emphysema causes the loss of recoil and, thus, increased compliance. Most other disease states, particularly interstitial diseases, fibrosis, pulmonary edema, and ARDS, cause decreased compliance (ie, "stiff" lungs, or increased transpulmonary pressure for a given volume change).

- Normal compliance is approximately 200 mL/cm H₂O.
- Emphysema causes the loss of recoil and increased compliance.
- Interstitial diseases, fibrosis, pulmonary edema, and ARDS cause decreased compliance.

Resistance

Resistance (R) to airflow is defined by the change in pressure (ΔP) for a given change in flow ($\Delta \dot{V}$):

$$R = \frac{\Delta P}{\Delta \dot{V}}$$

where ΔP is measured in centimeters of water and $\Delta \dot{V}$ in liters per second. Common causes of increased airway resistance include biting of endotracheal tube, bronchospasm, and airway secretions.

- Common causes of increased airway resistance are biting of endotracheal tube, bronchospasm, and airway secretions.

The total pressure required to inflate the respiratory system (spontaneously or with a mechanical ventilator) is the pressure required to overcome elastic recoil (due primarily to lungs and chest wall) plus the pressure to overcome flow resistance (due primarily to airways and endotracheal tube):

$$P_{\text{inflation}} = \frac{\Delta V}{C_{\text{STATIC}}} + R \times \Delta \dot{V}$$

(Elastic Load) (Resistive Load)

Modes of Mechanical Ventilation

Modes of mechanical ventilation refers to the pattern of cycling of the machine breath and its relation to the spontaneous breaths of the patient (eg, assist/control mode, intermittent mandatory ventilation, and pressure support ventilation). Table 4-10 shows the basic settings of a ventilator.

Volume Preset Assist/Control Mode

The *volume preset assist/control mode* is defined by a machine-assisted breath for every inspiratory effort by the patient. If no spontaneous breaths occur during a preset time interval, a controlled breath of predetermined tidal volume is delivered by the ventilator. The backup rate determines the minimum minute ventilation the patient will receive. The advantage of assist/control mode ventilation is that it allows maximal rest for the patient and maximal control of ventilation. The disadvantage is that hyperventilation or air trapping (or both) can occur in patients making rapid inspiratory efforts.

Pressure Support Ventilation

Pressure support ventilation may be used to assist spontaneously breath-

ing patients, with or without intermittent mandatory ventilation (IMV) breaths. In this technique, for each inspiratory effort by the patient, the ventilator delivers a high rate of flow of inspired gas, up to a preset pressure limit. This pressure support occurs only during the spontaneous inspiratory effort, so that the rate and pattern of respiration are determined by the patient.

Volume Preset Intermittent Mandatory Ventilation

Volume preset intermittent mandatory ventilation allows a preset number of machine-assisted breaths of a given tidal volume. Between machine breaths, patients may breathe spontaneously. The IMV mode was developed as a mode for weaning patients from the ventilator so that the number of mechanical breaths could be decreased gradually, allowing for increasing spontaneous ventilation. However, recent trials have shown that this mode of weaning is inferior to weaning with T-piece trials or pressure support ventilation.

- Assist/control mode ventilation allows maximal rest for the patient and maximal control of ventilation, but it may result in hyperventilation in patients with high intrinsic breathing rates.
- IMV is inferior to other weaning techniques (T-piece trials or pressure support ventilation).
- Pressure support ventilation may improve patient ventilator synchrony.

Table 4-11 summarizes basic modes of ventilation.

PEEP

PEEP is intended to increase functional residual capacity, recruit partially collapsed alveoli, improve lung compliance, and improve ventilation-perfusion matching. An adverse effect of PEEP is an excessive increase in intrathoracic pressure with decreased cardiac output. Overdistention of lung units may also worsen gas exchange because of ventilator-induced lung injury. At levels of PEEP greater than 10 to 15 cm H₂O, barotrauma is of particular concern. The optimal, or best, PEEP may be defined as the lowest level of PEEP needed to achieve satisfactory oxygen delivery at a nontoxic FiO₂ (<60%).

- PEEP recruits partially collapsed alveoli, improves lung compliance, and decreases atelectotrauma (recruitment and derecruitment of alveoli).
- PEEP may decrease cardiac output due to an increase in intrathoracic pressure.
- The optimal, or best, PEEP is the lowest level of PEEP needed to achieve satisfactory oxygenation at a nontoxic FiO₂ (<60%).

Table 4-10 Basic Ventilator Settings

Mode	Volume targeted
	Complete mechanical ventilation
	Assist/control
	Pressure targeted
	Pressure support
	Pressure control
	Pressure control inverse ratio
	Mixed
	Synchronized intermittent mandatory ventilation
Tidal volume	Standard: 10mL/kg ideal body weight
	In adult respiratory distress syndrome: 6 mL/kg ideal body weight
Rate—titrated to desired minute ventilation for PCO ₂	
Positive end-expiratory pressure & fraction of inspired oxygen (FiO ₂)—titrated to FiO ₂ <60%	
Inspiratory flow rate	Set to meet patient demand
	Allow adequate time for exhalation

Approach to the Alarming Ventilator

The approach to an alarming ventilator begins with disconnecting the patient from the ventilator and hand bagging the patient to relieve pressure in breath stacking or tension pneumothorax. Increasing sedation may be appropriate if evaluation shows no change in peak or plateau pressures and there was evidence of dyssynchrony with the ventilator. Mucous plugging, biting the tube, or bronchospasm causes an increase in airway resistance, resulting in an increase in peak pressure without a change in plateau pressure.

Table 4-11 Summary of Modes of Ventilation^a

Ventilation	Rate	Volume	Trigger	Effect of Spontaneous Breath
CMV	Physician	Physician	Time	Nothing
PS	Patient	Compliance	Patient	Pressure supported
AC	Both	Physician	Time & patient	Volume supported
SIMV	Both	Physician	Time & patient	Pressure or volume supported

Abbreviations: AC, assist/control; CMV, complete mechanical ventilation; PS, pressure support; SIMV, synchronized intermittent mandatory ventilation.

^a Table indicates whether patient or physician determines rate, time, and volume delivered and what happens when spontaneous breath occurs.

Both peak and plateau pressures increase when there is a change in compliance such as worsening edema, mainstem intubation, breath stacking (intrinsic PEEP), or tension pneumothorax.

Complications and Prophylaxis

Complications of mechanical ventilation may be related to airway access, physiologic responses to positive pressure, and complications related to other organ systems. Examples are given in Table 4-12. Other complications, such as pulmonary embolism or malnutrition, may also reflect the underlying disease state. Management of these complications requires ongoing surveillance and recognition. In patients receiving mechanical ventilation, pneumonia may be difficult to diagnose because pulmonary infiltrates are frequently present, tracheal secretions may be colonized by bacteria, and signs such as fever and leukocytosis are frequently blunted. In this setting, quantitative cultures of secretions obtained from bronchoalveolar lavage or protected-specimen brush may aid in the diagnosis of ventilator-associated pneumonia. Prophylaxis is commonly given to reduce stress-related gastritis and ulceration. H₂-blockers may increase colonization of the respiratory tract by gram-negative bacteria. Sucralfate or frequent use of antacids is an alternative. The hemodynamic complications of increased intrathoracic pressure may be overcome with the administration of fluid; however, there is often a coexisting condition of capillary leak and pulmonary edema that may worsen.

- Pneumonia may be difficult to diagnose in patients receiving mechanical ventilation.

Table 4-12 Complications of Mechanical Ventilation

Airway injury, bleeding, infection
Ventilator malfunction—leaks, power loss, incorrect settings, or alarm failures
Barotrauma; pneumothorax; interstitial, subcutaneous, or mediastinal air
Decreased right ventricular filling, increased right ventricular afterload, decreased cardiac output, hypotension
Gastrointestinal tract bleeding, stress gastritis, ulceration
Decreased urine output
Alteration in intracranial pressure

- Prophylaxis is commonly given to reduce stress-related gastritis and ulceration.
- H₂-blockers may increase colonization of the respiratory tract by gram-negative bacteria; sucralfate or frequent use of antacids is an alternative.

Intrinsic Positive End-Expiratory Pressure

An important and occasionally subtle complication of positive pressure ventilation is called *intrinsic PEEP*, *auto PEEP*, *breath stacking*, or *dynamic hyperinflation*. In this phenomenon, inadequate time during the expiratory phase of the respiratory cycle results in a mechanically assisted breath being delivered before passive expiration of the lungs is complete. Thus, a new machine breath is delivered before the previous breath is completely exhaled. This may worsen hyperinflation, increase intrathoracic pressure, reduce venous return, and worsen the associated complications (eg, barotrauma), especially in patients with airway obstruction. Intrinsic PEEP may occur in spontaneously breathing patients with obstructive airway disease, but the effect is most important in mechanically ventilated patients. Treatment typically involves optimizing bronchodilator therapy and altering the ventilator cycle to allow maximal expiratory time.

Oxygen Toxicity

Pulmonary oxygen toxicity appears to be the result of direct exposure to high tensions of inspired oxygen or alveolar oxygen. For adults, oxygen toxicity is not believed to be a major clinical concern if the FIO₂ is less than 0.40 to 0.50. Higher levels of inspired oxygen may be associated with acute tracheobronchitis (most likely an irritant effect). After several days of exposure, a syndrome of diffuse alveolar damage and lung injury may develop. The pathologic features may resemble those of ARDS.

- Pulmonary oxygen toxicity is the result of direct exposure to high tensions of inspired oxygen or alveolar oxygen.
- The syndrome of diffuse alveolar damage and lung injury may develop.

Tracheostomy

For patients who require prolonged mechanical ventilation or airway support, the timing of tracheostomy is controversial. The use of high-volume, low-pressure endotracheal tube cuffs has decreased the

frequency of tracheal injury and stenosis caused by prolonged intubation. Tracheostomy has the advantages of decreased laryngeal injury, increased patient comfort, ease of suctioning, and, in certain patients, allowance for oral ingestion and speech. Complications may include tracheal injury and stenosis, bleeding, tracheoesophageal fistula, and possibly increased bronchial or pulmonary infections. Tracheostomy is commonly considered for patients who have needed or are expected to need intubation and mechanical ventilation for more than 2 to 4 weeks.

- High-volume, low-pressure endotracheal tube cuffs have decreased the frequency of tracheal injury and stenosis.
- Tracheostomy is considered for patients who have needed or are expected to need intubation and mechanical ventilation for more than 2 to 4 weeks.

Weaning

Patients are candidates for weaning from mechanical ventilation when they are hemodynamically stable and have adequately recovered from respiratory failure. It is important to identify these patients in order to decrease costs, ICU lengths of stay, and infectious and other complications of mechanical ventilation. The most effective way to wean patients is with a nursing or respiratory therapist protocol. General criteria are listed in Table 4-13. The rapid shallow breathing index (RSBI) is a sensitive and specific marker of weaning failure:

$$\text{RSBI} = \text{Respiratory frequency} / \text{Tidal volume} = f/V_T$$

If $f/V_T > 105$, there is a 95% chance of spontaneous breathing trial failure; if $f/V_T \leq 105$, there is an 80% chance of success.

If the patient seems ready for weaning, a spontaneous breathing trial should be instituted. This is typically done with a T-tube system. A daily interruption of sedation and institution of a 2-hour T-piece trial leads to extubation 1.5 days earlier and decreases by half the rate of mechanical ventilation for more than 21 days. A weaning protocol is presented in Figure 4-1.

Acute Respiratory Distress Syndrome

Diffuse lung injury with acute hypoxic respiratory failure may result from various injuries. Acute lung injury is a frequent primary cause

Table 4-13 General Weaning Criteria

Inspiratory pressure > -20 cm
Tidal volume > 5 mL/kg
Vital capacity > 10 mL/kg
Resting minute ventilation < 10 L/min
Able to double resting minute ventilation
Satisfactory gas exchange ($\text{PaO}_2 > 60$ mm Hg on $\text{FiO}_2 < 40\%$)
Not unstable, no ischemia
Adequate mental status

Abbreviation: FiO_2 , fraction of inspired oxygen.

of critical illness and may occur as a complication or a coexisting feature of multisystem disease. ARDS is commonly defined as diffuse acute lung injury with the following major features: diffuse pulmonary infiltrates, severe hypoxemia due to shunting and ventilation-perfusion mismatch, and normal or low pulmonary capillary wedge pressure (ie, noncardiogenic pulmonary edema) (Table 4-14). Mortality from all causes averages about 50%. For nearly 30 years after this syndrome was described, no single therapy was shown to alter outcome, although gradual improvement in overall mortality was attributed to multidisciplinary ICU management. Recently in prospective, controlled trials, a strategy of mechanical ventilation with reduced tidal volumes was associated with improved survival (discussed below).

- Diffuse lung injury with hypoxic respiratory failure may result from various injuries.
- Among patients with ARDS, mortality from all causes averages approximately 50%.

Etiology, Pathophysiology, and Prognosis

ARDS was described initially as a posttraumatic or shock-induced injury, but it occurs with various states (Table 4-15). The relative risks of developing ARDS have been estimated from studies of predisposed groups. The greatest frequency is among patients with sepsis (approximately 40%), gastric aspiration (30%), multiple transfusions (25%), pulmonary contusion (20%), disseminated intravascular coagulation (20%), pneumonia requiring ICU management (12%), and trauma with long-bone or pelvic fractures (5%).

The pathophysiologic mechanism of ARDS depends on damage to the alveolar-capillary unit. The earliest histologic changes are endothelial swelling, followed by edema and inflammation. Mononuclear inflammation, loss of alveolar type I cells, and protein deposition in the form of hyaline membranes may occur within 2 or 3 days. Fibrosis may develop after days or weeks of the process. Damage to type II alveolar cells leads to loss of surfactant. The surfactant that is produced may be inactivated by proteins present in the airways. Alveolar filling and collapse cause intrapulmonary shunting and ventilation-perfusion mismatch with hypoxemia.

Death from ARDS is not usually caused by isolated hypoxemic respiratory failure. The most frequent causes of death are complications of infection, sepsis syndrome, and failure of other organ systems. In addition to the clinical risk factors listed above, specific factors associated with death include less than 10% band forms on a peripheral blood smear, persistent acidemia, bicarbonate less than 20 mEq/L, or blood urea nitrogen greater than 65 mg/dL. Therefore, the systemic effects associated with ARDS may be important to the outcome.

- Death from ARDS is not usually caused by isolated hypoxemic respiratory failure.
- Infection, sepsis syndrome, and failure of other organ systems are the usual causes of death.
- Factors associated with death: $< 10\%$ band forms on a peripheral blood smear, persistent acidemia, bicarbonate < 20 mEq/L, or blood urea nitrogen > 65 mg/dL.

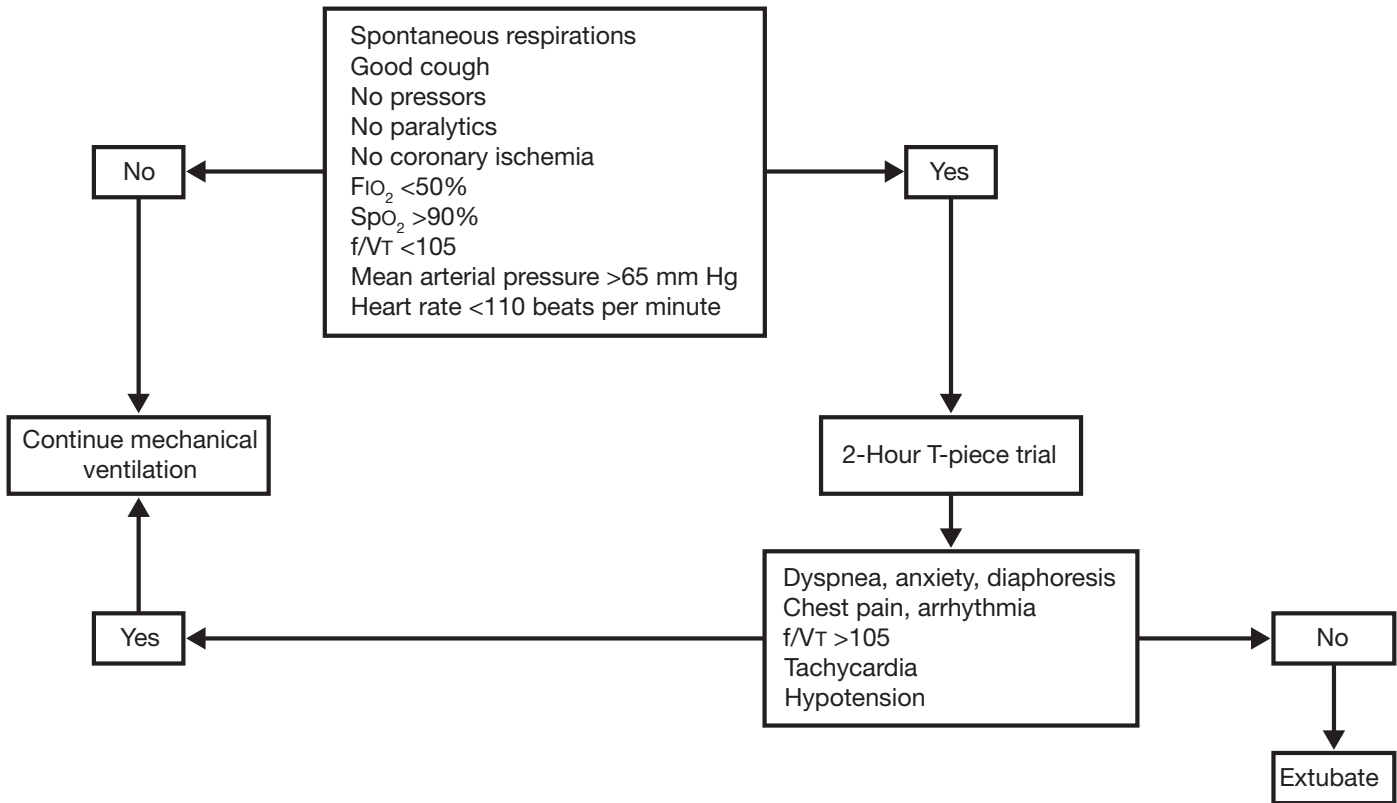


Figure 4-1. Ventilatory Weaning Protocol. FIO₂ indicates fraction of inspired oxygen; f/VT, respiratory frequency divided by tidal volume (rapid shallow breathing index); SpO₂, arterial oxygen saturation.

Therapy for ARDS

The traditional therapy for ARDS involves optimization of physiologic variables and supportive management of associated complications. Measures include optimization of gas exchange and hemodynamics, nutrition, ambulation, and control of infections. Hypoxemia typically is corrected with positive pressure ventilation with supplemental oxygen and PEEP. PEEP provides potential benefits of increased lung volume and lung compliance and improvement in ventilation-perfusion relationships. Maintaining PEEP at a level adequate to prevent repetitive opening and closing (atelectrauma) of gravitationally dependent lung units (ie, at a level greater than the *closing volume*) may be helpful in limiting tissue shear forces that can potentiate capillary injury and worsen the degree of diffuse alveolar damage. Beyond the optimal level of PEEP, an increase in intrathoracic pressure may be associated with decreased venous return, increased pulmonary vascular resistance, decreased left ventricular filling, and a corresponding decrease in cardiac output.

Limiting the degree of alveolar distention during peak inflation may limit the potential for alveolar disruption and subsequent barotrauma, often referred to as *ventilator-associated lung injury*. This is achieved by delivering tidal volumes of limited size, either by a volume preset or a pressure-targeted mode of ventilation. In the management of ARDS, *protective ventilatory strategy* refers to the use of

PEEP levels chosen to prevent alveolar closure and tidal volumes chosen to prevent alveolar overdistention. A landmark randomized study found improved survival among ARDS patients receiving a tidal volume of 6 mL/kg ideal body weight compared with a control group receiving a tidal volume of 12 mL/kg ideal body weight. This is the only specific therapy for ARDS that has been shown to improve survival. In many patients supported according to these ventilator guidelines, the achieved level of alveolar ventilation results in an increase in arterial PCO₂. This phenomenon, *permissive hypercapnia*, does not appear to be harmful. Indeed, recent evidence indicates that mild hypercapnia and respiratory acidosis may decrease the degree of ventilator-induced lung injury.

- Hypoxemia typically is corrected with positive pressure ventilation with supplemental oxygen and PEEP.
- A protective ventilatory strategy in ARDS is designed to limit ventilator-induced lung injury.
- A tidal volume of 6 mL/kg ideal body weight is the only intervention shown to improve survival among ARDS patients.

Because increased capillary permeability allows greater intravascular fluid leak at any given hydrostatic pressure, intravascular volume is usually limited to that necessary for systemic perfusion.

Table 4-14 Criteria for Diagnosis of Acute Respiratory Distress Syndrome

Appropriate setting
Pulmonary injury, shock, trauma
Acute event
Clinical respiratory distress, tachypnea
Diffuse pulmonary infiltrates on chest radiography
Interstitial or alveolar pattern (or both)
Hypoxemia
PaO ₂ /FIO ₂ ratio <150
Exclude
Chronic pulmonary disease accounting for the clinical features
Left ventricular failure (most series require pulmonary artery wedge pressure <18 mm Hg)

Abbreviation: FIO₂, fraction of inspired oxygen.

However, associated shock states may demand volume expansion or increased inotropic support. Crystalloids can provide adequate filling pressures in patients with shock states, but large volumes may be required. Specific applications for colloids in ARDS include blood products (eg, for coagulopathies or anemia). Supplemental nutrition typically is provided throughout the course of critical illness. Many patients with ARDS have associated multiorgan injury and may have ileus or gastrointestinal tract dysfunction that precludes enteral feeding. Enteral feeding is recommended if tolerated. The consequences of malnutrition may include impairment of respiratory muscle function, depressed ventilatory drive, and limitation of host defenses. Mobilization, ambulation, and ventilator weaning are carried out as early as practical.

- Crystalloids can provide adequate filling pressures in patients with shock states.
- Many patients with ARDS have associated multiorgan injury.

Potential therapeutic and prophylactic agents have been directed against steps in the arachidonate pathways. Corticosteroids decrease cell membrane disruption and have other anti-inflammatory properties. Specifically, no differences in mortality have been observed in prospective, randomized studies of ARDS patients receiving methylprednisolone or placebo and a recent randomized controlled trial conducted by the ARDS Clinical Network found that mortality was increased if corticosteroid therapy was started after 2 weeks.

- Corticosteroids decrease cell membrane disruption and have other anti-inflammatory properties.
- Corticosteroids may decrease the time to resolution of fibroproliferative (late-phase) ARDS but should not be started after 2 weeks.

Pulmonary vasodilators, of which nitric oxide has been studied most widely, have been used as adjuncts to traditional therapy. Inhaled nitric oxide, delivered by a mechanical ventilator, naturally distributes to relatively well-ventilated regions of each lung. Nitric oxide acts as

Table 4-15 Disorders Associated With Acute Respiratory Distress Syndrome

Disorder	Cause
Shock	Any cause
Sepsis	Lung infections, other bacteremic or endotoxic states
Trauma	Head injury, lung contusion, fat embolism
Aspiration	Gastric, near-drowning, tube feedings
Hematologic	Transfusions, leukoagglutinin, intravascular coagulation, thrombotic thrombocytopenic purpura
Metabolic	Pancreatitis, uremia
Drugs	Narcotics, barbiturates, aspirin
Toxic	Inhaled—O ₂ , smoke Chemicals—paraquat Irritant gases—NO ₂ , Cl ₂ , SO ₂ , NH ₃
Miscellaneous	Radiation, air embolism, altitude

a dilator of the alveolar capillary and is rapidly inactivated in the bloodstream, thereby potentially improving perfusion to ventilated areas without systemic vasodilation.

Several studies of inhaled nitric oxide have shown dramatic short-term improvement in oxygenation and pulmonary artery pressures in patients with ARDS. However, outcome studies have not shown improved survival. Other vasodilating agents, including prostacyclin and prostaglandin E₁ have also been tried.

- Pulmonary vasodilators improve oxygenation with no documented effect on survival.

Prone positioning has been tried in an attempt to open flooded dependent alveoli and to improve ventilation-perfusion matching and oxygenation. Three randomized controlled trials of prone positioning in ARDS have been conducted: all showed improvements in oxygenation, none showed an improvement in mortality, and there was a high rate of complications, such as dislodgment of the endotracheal tube and central venous catheters, and obstruction of the endotracheal tube. Numerous other systemic and inhaled drugs and alternative ventilatory strategies have been tried; they have failed to improve survival among ARDS patients (Table 4-16).

- Prone positioning improves oxygenation with no effect on survival.

Prognosis

The prognosis for recovery of lung function in patients who survive ARDS is good. Studies of survivors have shown nearly normal lung volumes and airflow 12 months after the illness, with mild impairment in gas exchange—decreased diffusing capacity, desaturation with exercise, or widened A-a gradient. However, these patients are still severely impaired owing to neurologic complications such as

Table 4-16 Therapies That Have Not Improved Survival in Acute Respiratory Distress Syndrome**Drugs**

Corticosteroids
N-acetylcysteine
 Dietary supplements
 Immunonutrition
 Prostaglandin E₁
 Lisofylline
 Ketoconazole

Other adjuncts

Prone position
 Partial liquid ventilation
 High-frequency oscillation
 High positive end-expiratory pressure
 Ventilator modes other than volume control

Aerosol therapies

Surfactant C & B
 Prostacyclin
 Nitric oxide

critical illness polyneuropathy and posttraumatic stress disorder. Therefore, the incentive is strong to continue aggressive measures in patients with otherwise reversible organ dysfunction who have a clear understanding of long-term outcomes.

- The prognosis for the recovery of lung function in patients surviving ARDS is good.
- Mild decreases in lung volumes, oxygenation, and diffusing capacity are typically observed after 6 to 12 months.
- Survivors are severely impaired owing to neurologic complications.

Shock

Shock is defined by evidence of end-organ hypoperfusion usually (but not necessarily) associated with hypotension. The most common classification is the Weil-Shubin classification: cardiogenic (decreased cardiac output), hypovolemic (decreased blood volume), obstructive, and distributive (variable cardiac output, decreased systemic vascular resistance). All forms of shock are usually characterized by end-organ hypoperfusion manifested as altered mental status, tachycardia, tachypnea, decreased urine output, and lactic acidosis. Hypotension is usually (but not always) present. The clinical history often helps determine the diagnosis (eg, blood loss, trauma, myocardial infarction, or systemic infection). Unlike other forms of shock, distributive shock is often characterized by relatively warm extremities and normal or increased cardiac output.

- Shock is defined by evidence of end-organ hypoperfusion, usually associated with hypotension.
- Common classification: cardiogenic, hypovolemic, obstructive, and distributive.

- Shock is usually characterized by hypotension, tachycardia, tachypnea, altered mental status, decreased urine output, and lactic acidosis.
- Distributive shock is often characterized by relatively warm extremities and normal or increased cardiac output.

After a rapid initial assessment, treatment of shock is directed at the presumed source, for example, volume (blood loss, hypovolemia), vasodilator or inotropic therapy (cardiogenic), or fluids, antibiotics, and drainage of any infected space (sepsis). Treatment of all forms of shock is usually aimed at stabilizing physiologic abnormalities and treating the underlying cause. Many times vasopressor agents are used; different agents are chosen for different states (Table 4-17).

Cardiogenic Shock

Cardiogenic shock typically manifests as low cardiac output, high systemic vascular resistance, and high filling pressures. This topic is covered in detail in Chapter 3 (“Cardiology”).

Hypovolemic Shock

Causes of hypovolemic shock are listed in Table 4-18. Findings on physical examination and basic laboratory testing are diminished skin turgor, dry skin and mucosa, hypotension, low urine sodium levels and high urine osmolarity, oliguria, and a high serum urea nitrogen–creatinine ratio (>20:1). The hemodynamic pattern is one of decreased cardiac output and filling pressures and increased systemic vascular resistance. As in other forms of shock, physiologic abnormalities need to be corrected immediately and underlying processes (bleeding, dehydration, etc.) need to be treated. The American College of Surgeons defines blood loss in classes I through IV. Class III is defined as loss of more than 30% of the body’s blood, with normal compensatory increases in heart rate and systemic vascular resistance unable to maintain normal perfusion. This marks the onset of hemodynamic collapse, end-organ hypoperfusion, and shock. Some clarification is needed for the traditional evaluation of the bleeding patient. Tachycardia is absent in most patients with moderate to severe blood loss. Orthostatic vital signs are of limited value in the ICU; to be effective they should be measured with the patient lying down and then standing. Even if measured correctly, for patients older than 65, the sensitivity is only 14% to 40%. Frequent checks (every 2–4 hours) of hemoglobin and the hematocrit are unnecessary. Changes in the hematocrit show poor correlation with blood volume in acute bleeding and are usually the result of infusion of crystalloid. Therefore, changes in the hematocrit most likely represent ongoing resuscitation and may not reflect active bleeding. Finally, the traditional practice of placing patients in the Trendelenburg position to increase blood pressure may increase blood pressure, but it does not increase cardiac output, which is the ultimate goal.

Obstructive Shock

Obstructive shock is associated with a physical impairment to adequate forward circulatory flow, involving mechanisms different from those of primary myocardial or valvular dysfunction. Several hemodynamic patterns may be observed, depending on the cause: a frank

Table 4-17 Vasoactive Agents, Common Dosages, and Hemodynamic Effects^a

Agent	Dose	Cardiac		Vascular		DA
		HR	C	VC	VD	
Dopamine	1-4 mcg/kg/min	↑	↑	—	↑	↑↑↑↑
	4-20 mcg/kg/min	↑↑	↑↑↑	↑↑↑	—	↑↑
Norepinephrine	2-20 mcg/min	↑	↑↑	↑↑↑↑	—	—
Epinephrine	1-20 mcg/min	↑↑↑↑	↑↑↑↑	↑↑↑↑	↑↑↑	—
Vasopressin	0.03-0.04 U/h	—	—	↑↑↑	—	—
Phenylephrine	20-200 mcg/min	—	—	↑↑↑	—	—
Isoproterenol	1-5 mcg/min	↑↑↑↑	↑↑↑↑	—	↑↑↑↑	—
Dobutamine	2.5-15 mcg/kg/min	↑↑	↑↑↑↑	—	↑↑	—
Amrinone	0.75 mg/kg bolus; 5-15 mcg/kg/min	↑	↑↑↑	—	↑↑	—

Abbreviations: C, contractility; DA, dopaminergic; HR, heart rate; U, units; VC, vasoconstriction; VD, vasodilation.

^a Number of arrows indicates relative strength of effect; dash indicates no clinically apparent effect.

decrease in filling pressures (as in mediastinal compressions of great veins); trends toward equalization of pressures (as in cardiac tamponade); or markedly increased right ventricular filling pressures with low pulmonary capillary wedge pressure (as in pulmonary embolism). Cardiac output is usually decreased with increased systemic vascular resistance. Common causes are tension pneumothorax, cardiac tamponade, and massive pulmonary embolus.

- Obstructive shock is associated with physical impairment of cardiac output not associated with primary myocardial or valvular dysfunction.

Distributive Shock

Of the many forms of distributive shock (Table 4-19), sepsis is probably the best known. Distributive shock manifests typically as a warm, vasodilated shock. The hemodynamic pattern is low filling pressures, high cardiac output, and low systemic vascular resistance. As in other forms of shock, treatment is supportive and is aimed at the underlying cause.

Table 4-18 Etiology of Hypovolemic Shock

Source	Cause
Trauma, postoperative	Bleeding
Gastrointestinal tract loss	Bleeding, vomiting, diarrhea
Renal loss	Diuretics, diabetes mellitus, diabetes insipidus
Skin	Burns, exudative skin lesions
Respiratory	Bronchorrhea
Third spacing	Pancreatitis, crush injuries
Disabled, bed-bound patients	Lack of access to water

Sepsis

Sepsis is an exaggerated inflammatory response to a noxious stimulus and is characterized by a severe catabolic reaction (up to 1% lean body mass per day), widespread endothelial dysfunction, and release of inflammatory agents. To achieve a common terminology, *systemic inflammatory response syndrome* (SIRS) was introduced for findings of fever or hypothermia, tachycardia, hyperventilation, and leukocytosis or leukopenia regardless of cause. *Sepsis* is defined as SIRS with a known or presumed source of infection, and *severe sepsis* is defined as sepsis associated with organ system dysfunction and systemic effects, including hypotension, decreased urine output, or metabolic acidosis. *Septic shock* refers to persistent signs of organ hypoperfusion despite adequate fluid resuscitation.

The mortality of patients with sepsis and multiorgan failure may be greater than 70% to 90%. Adverse risk factors include age older than 65 years, continued systemic signs of sepsis, persistent deficit in oxygen delivery, and preexisting renal or liver failure. Physiologic scoring systems (eg, Acute Physiology and Chronic Health Evaluation [APACHE]) may predict outcome more accurately for subgroups of patients.

- Mortality of patients with sepsis and multiorgan failure may be >70%-90%.

Table 4-19 Causes of Distributive Shock

Sepsis
Adrenal crisis/hemorrhage
Neurogenic
Anaphylactic
Hepatic failure
Pancreatitis
Thiamine deficiency

Multisystem organ failure, or *multiple organ dysfunction syndrome* (MODS), is usually defined as acute dysfunction of 2 or more organ systems lasting more than 2 days. Sepsis is the most common cause. The pathogenesis is attributed to the hemodynamic and immunologic effects of endotoxin, cytokines (tumor necrosis factor α), interleukins (ILs) (IL-1, IL-2, IL-6, IL-8), platelet-activating factor, arachidonic acid metabolites, polymorphonuclear leukocyte–derived toxic products, and myocardial depressant factors. Corticosteroids have no known benefit and may cause adverse effects in patients with sepsis syndrome, with or without ARDS. An exception is the use of relatively low doses of hydrocortisone or methylprednisolone in patients with documented adrenal insufficiency and severe sepsis, for which benefit has been reported.

Treatment

The Surviving Sepsis Campaign is a group of organizations and professional societies that have created guidelines for the treatment of sepsis (Table 4-20).

Antibiotics

The main recommendations are to collect samples for blood cultures before antibiotics are given; start other cultures and perform imaging studies as indicated; give appropriate antibiotics within 1 hour; and select specific antibiotics after 72 hours as appropriate and continue their use for 10 days. The source of the infection must be sought and drained if needed.

Early Goal-Directed Resuscitation

Early goal-directed resuscitation (EGDR) is an attempt to stabilize filling pressures, normalize physiologic abnormalities, and maintain cardiac output and systemic oxygen delivery to prevent the cascade of events leading to septic shock and multisystem organ failure. Previous ICU-based studies of goal-directed therapy did not show improved outcomes, presumably because the inflammatory cascade was well advanced and not reversible. A key component of the sepsis guidelines is the concept of EGDR, started immediately on recognition of sepsis. In these guidelines, resuscitation should begin as soon as severe sepsis or sepsis-induced tissue hypoperfusion is recognized. In a single-center study, this strategy decreased hospital mortality from 46% to 30% (absolute risk reduction, 16%). Goals of therapy within the first 6 hours (Figure 4-2) are as follows:

1. Mean arterial pressure ≥ 65 and ≤ 90 mm Hg
2. Urine output >0.5 mL/kg/h
3. Central venous oxygen saturation ($ScvO_2$) $\geq 70\%$ or mixed venous oxygen saturation (SvO_2) $\geq 65\%$

If the goals are not achieved with fluid resuscitation during the first 6 hours, do 1 or both of the following:

1. Administer transfusion of packed red blood cells to increase the hematocrit to at least 30%
2. Administer dobutamine (maximal rate, 20 mcg/kg/min) to reach the goal

Typically a fluid challenge is performed in patients with suspected hypovolemia by giving 500 to 1,000 mL of crystalloid solution over 30 minutes, with additional doses based on response and tolerance. The input is typically greater than output owing to venodilation

Table 4-20 Summary of Surviving Sepsis Campaign Guidelines and Grade of Recommendation

Guideline	Grade
Deep vein thrombosis prophylaxis	A
Stress ulcer prophylaxis	A
Weaning protocol with spontaneous breathing trials	A
Early goal-directed resuscitation for severe sepsis	B
Do not use dopamine for renal protection	B
Activated protein C in patients with high risk of death	B
Avoid high tidal volumes & plateau pressures	B
Sedation protocols with daily awakening	B
Corticosteroids for 7 days in septic shock patients receiving vasopressors	C
Do not use bicarbonate if pH ≥ 7.15 in lactic acidemia	C
Cultures before beginning antibiotic therapy	D
Measure serum lactate to assess organ perfusion	D
Vasopressin if refractory to other pressors	D
Early empirical broad-spectrum antibiotic therapy	D, E
Vasopressors to keep mean arterial pressure 60-80 mm Hg (central & arterial access)	E
Provide rapid source control as appropriate	E
Maintain blood glucose <150 mg/dL	E
Reassessment of antimicrobials in 48-72 hours	E
Nutrition protocol, preferably enteral	E
Consider limitation of support when appropriate	E

and capillary leak. Most patients require continuing aggressive fluid resuscitation during the first 24 hours of management. Vasopressor therapy should be initiated if an appropriate fluid challenge fails to restore adequate blood pressure and organ perfusion or it should be used transiently in the face of life-threatening hypotension, even when fluid challenge is in progress. Norepinephrine and dopamine are first-line agents for correcting hypotension in septic shock. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in septic shock patients. Dopamine may be particularly useful in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic. Another agent, vasopressin, is being used more frequently in resistant shock and to help in weaning from catecholamines.

Activated Protein C

In a controlled prospective trial of recombinant human activated protein C (drotrecogin alfa) administered intravenously over 96 hours, the mortality among patients with severe sepsis had a 19% relative reduction (6% absolute decrease). Most of the benefit was in the sickest groups of patients. It is now recommended only for those with 2 or more dysfunctional organ systems (especially disseminated intravascular coagulation) or an APACHE II score of 25 or more. Activated protein C has anti-inflammatory and profibrinolytic properties that may contribute to this benefit. The main adverse effect of recombinant human activated protein C is bleeding.

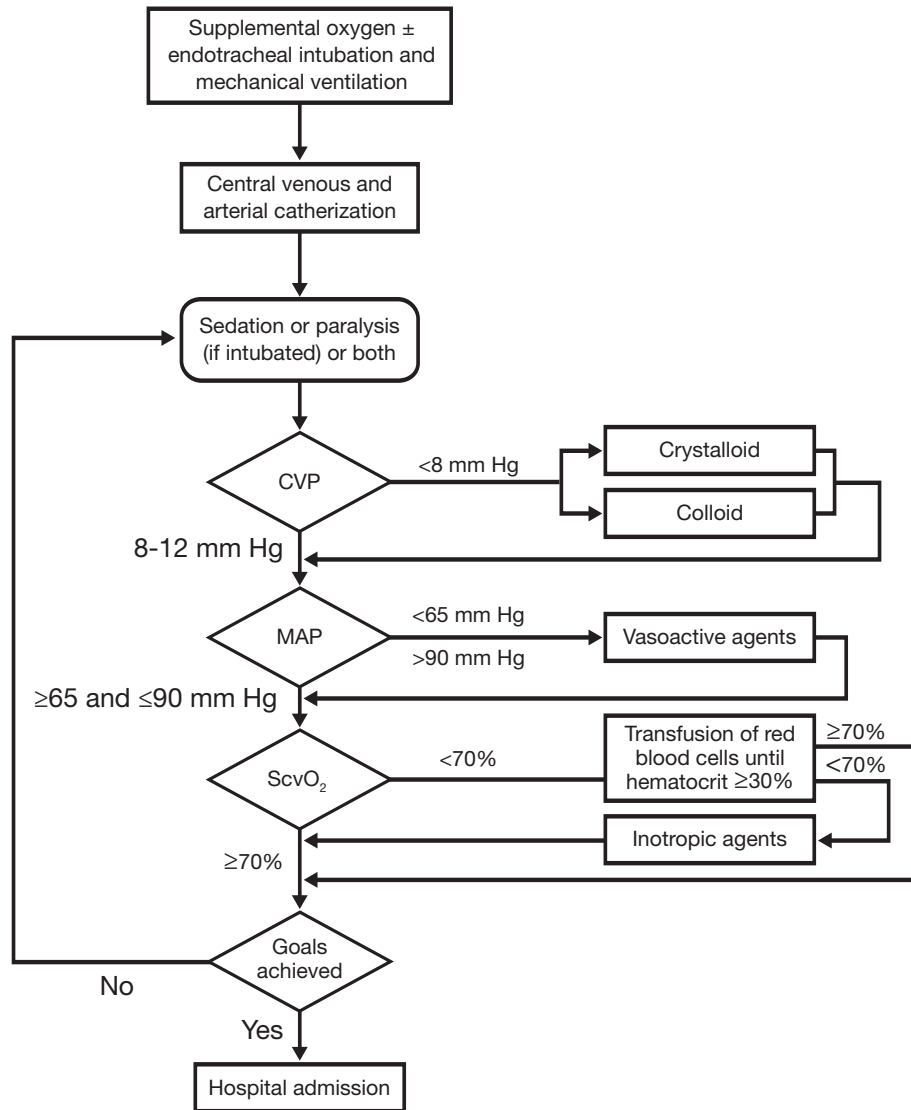


Figure 4-2. Protocol for Early Goal-Directed Therapy. CVP indicates central venous pressure; MAP, mean arterial pressure; ScvO₂, central venous oxygen saturation. (From Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al, for the Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345:1368-77. Used with permission.)

Corticosteroids

High-dose corticosteroids are of no benefit in sepsis and have shown harm in the past. Recent randomized controlled trials have shown a mortality benefit from administration of low-dose hydrocortisone, 100 mg intravenously every 6 hours, and fludrocortisone, 50 mcg by mouth daily for 7 days, in patients who have sepsis and relative adrenal insufficiency. *Relative adrenal insufficiency* is defined as an increase in the serum cortisol level of less than 9 mg/dL in relation to baseline after intravenous administration of cosyntropin, 250 mcg, measured at 0, 30, and 60 minutes. The number needed to treat (NNT) to save 1 life is 7. This test should not be used in patients who have received etomidate for intubation since it is a selective inhibitor of β -hydroxylase and could therefore blunt the cortisol response to corticotropin.

- Sepsis syndrome typically is defined by a known or presumed source of infection associated with SIRS.
- Treatment is directed at the presumed source.
- Septic shock commonly is associated with multiorgan injury.
- Multisystem organ failure: acute dysfunction of ≥ 2 organ systems for > 2 days.
- High-dose corticosteroid treatment is of no known benefit.

Miscellaneous

Glucose Control

There has been much interest in intensive insulin therapy for strict control of blood glucose. In 2 large randomized studies conducted in Belgium in surgical ICUs and medical ICUs, morbidity was

prevented and, in the surgical population, mortality was improved. These studies have been widely criticized on internal and external validity. However, it is generally agreed that allowing blood glucose levels to increase to 200 mg/dL is unacceptable. The American Association of Clinical Endocrinologists recommends maintaining strict normoglycemia (<110 mg/dL) to see the benefits of tight control. This strict control, though, is associated with frequent episodes of hypoglycemia.

- Tight glucose control may be beneficial, but it is associated with hypoglycemia.
- Numerous subsequent validation studies are underway.

Stress Ulcer Prophylaxis

Definite risk factors for stress ulcer formation are mechanical ventilation for more than 48 hours and coagulopathy. H₂ blockers and sucralfate have both been shown to be effective prophylactic agents in this patient population. Owing to issues with medication binding and difficulty of administration, sucralfate is not the preferred agent. Proton pump inhibitors have not been studied as extensively and have not proved to be superior. Studies of head injury and burn patients have had conflicting results; however, it is reasonable to use prophylaxis in this population as well.

Management of Anemia and Transfusion

A restrictive transfusion strategy has been shown to be superior to a liberal strategy in ICU patients: Do not transfuse unless hemoglobin is less than 7 mg/dL for ICU patients in stable condition; if there is active ischemia, the threshold is less than 10 mg/dL. With use of this strategy, hospital mortality rates were significantly lower (22.3% vs 28.1%, $P=.05$).

Nutrition

Nutritional support improves body weight and mid arm muscle mass, but the effect of nutritional support on other outcomes such as survival and ICU length of stay is unclear. In general it is accepted that nutritional support should be given to patients who have preexisting malnutrition and to those who are expected to have inadequate intake for more than 5 days. The enteral route is preferred since there is no difference in outcomes between enteral and parenteral routes and enteral feeding is associated with fewer complications. Patients receiving enteral nutritional support should be maintained in a semirecumbent position, be given feedings slowly, and have gastric residual volumes checked. Reasonable goals for most

ICU patients are 25 kcal/kg per day and 2 g of protein per day. There is no evidence that immunonutrition works. Previously it was believed that small-bowel feedings were superior to gastric feedings and were associated with fewer adverse events such as aspiration, but it is now known that there is no difference. Practically, it is much easier to feed into the stomach.

Disease-Severity Scoring Systems

The use of a severity-of-illness scoring system is increasingly prevalent in the ICU. These systems may define quantitative overall risks for populations of patients. An accurate quantifiable description of the pretreatment status of critically ill patients can allow improved precision in the evaluation and implementation of new therapies (ie, clinical research). Furthermore, these systems can be of great use in quality improvement efforts. In most systems, however, the role in individual case management is unclear. The types of clinical scoring systems have ranged from simple counts of failing organs to highly sophisticated methods that incorporate clinical and physiologic parameters (acute and chronic) into proprietary logistic regression prediction equations derived from large databases.

The Glasgow Coma Scale (GCS) was developed in the early 1970s as a triage tool for evaluation of patients with head injury. This scoring system assigns a weighted point score for 3 behavioral responses: eye opening (1-4 points), best verbal response (1-5 points), and best motor response (1-6 points). Thus, GCS scores range from 3 to 15 points and are categorized into 3 levels of dysfunction: severe dysfunction (3-8 points), moderate dysfunction (9-12 points), and mild dysfunction (≥ 13 points). The GCS system has been shown to correlate with mortality and the level of ultimate brain function in patients with traumatic brain injury. Because of its efficacy and simplicity, the GCS has been used within other scoring systems.

Several multisystem scoring systems have been developed for use in critically ill patients. Although a detailed review of these systems is beyond the scope of this text, they include the APACHE system, Simplified Acute Physiology Score (SAPS), Mortality Probability Model (MPM), Project IMPACT, and Therapeutic Intervention Scoring System (TISS).

- Severity scoring systems attempt to quantify overall risk for populations of patients.
- Severity scoring systems can be of great use in clinical research and quality assurance functions.
- The best role for most scoring systems in the care of individual patients is undefined.

Critical Care Medicine Pharmacy Review

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Review of Drugs Commonly Used in the ICU That Potentially Can Cause Delirium

Analgesics	Antihypertensives	Miscellaneous cardiac drugs
Opiates	Captopril	Antiarrhythmics
NSAIDs	Clonidine	Atropine
	Diltiazem	β -Blockers
Anesthetics & sedatives	Enalapril	Digoxin
Benzodiazepines	Hydralazine	
Bupivacaine	Methyldopa	Miscellaneous
Ketamine	Nifedipine	Antihistamines
Lidocaine	Nitroprusside	Corticosteroids
Propofol	Verapamil	Theophylline
		Tricyclic antidepressants
Anticonvulsants	Antimicrobials	H ₂ -blockers
Barbiturates	Aminoglycosides	
Carbamazepine	Cephalosporins	
Phenytoin	Carbapenems	
	Macrolides	
Antifungals & antivirals	Metronidazole	
Acyclovir	Monobactams	
Amphotericin	Penicillins	
Ketoconazole	Quinolones	
	Tetracyclines	
	Trimethoprim-sulfamethoxazole (Cotrimoxazole)	

Abbreviations: ICU, intensive care unit; NSAIDs, nonsteroidal anti-inflammatory drugs.

Data from McGuire BE, Basten CJ, Ryan CJ, Gallagher J. Intensive care unit syndrome: a dangerous misnomer. *Arch Intern Med.* 2000;160:906-9, and Fish DN. Treatment of delirium in the critically ill patient. *Clin Pharm.* 1991;10:456-66.

Critical Care Medicine Pharmacy Review (continued)**Review of Drugs Commonly Used in the ICU for Agitation With Ventilation**

Drug	Comments	
	Pros	Cons
Benzodiazepines Midazolam Lorazepam Diazepam	Useful for anxiety-related agitation, inexpensive, minimal hemodynamic effects	Risk of oversedation & accumulation, especially prolonged use; depress respiratory drive; potential withdrawal reaction with long-term use
Anesthetic Propofol	Predictable, short-term sedative/hypnotic effects, no accumulation	Hypotension risk, depresses respiratory drive, high expense, deaths associated with acidosis
Neuroleptic Haloperidol	Specific for delirium, no effect on respiratory drive	Cardiac toxicity & hypotension risks, lowers seizure threshold
Sedative Dexmedetomidine	Pain and anxiolytic properties, does not depress ventilation	Short-term use only (until further research completed), potential withdrawal reaction
Opiates/analgesics Fentanyl Hydromorphone Methadone Morphine	Useful for pain-induced agitation (accurate history for pain important)	May contribute to delirium & confusion, may contribute to hypotension due to histamine release

Abbreviation: ICU, intensive care unit.

Critical Care Medicine Pharmacy Review (continued)

Clinically Important Toxic Overdoses and Management

Drug Overdose	Clinical Syndrome	Basic Treatment
Acetaminophen (paracetamol)	0.5-24 h: Nausea, vomiting 24-72 h: Nausea, vomiting, RUQ pain, increased LFTs & PT 72-96 h: Liver necrosis, coagulation defects, jaundice, renal failure, hepatic encephalopathy 4 d to 2 wk: Resolution of liver dysfunction	Elimination: Gastric lavage (if <1 h after ingestion), activated charcoal (if <4 h after ingestion) (both longer if sustained-release product) Treatment: <i>N</i> -acetylcysteine for toxic ingestion based on Rumack-Matthew nomogram
Amphetamines	Hypertension, tachycardia, arrhythmias, myocardial infarction, vasospasm, seizures, paranoid psychosis, diaphoresis, tachypnea	Elimination: Activated charcoal for oral ingestion Agitation/seizures: Benzodiazepines Hypertension: Control agitation, α -antagonists (phentolamine), vasodilators (nitroglycerin, nitroprusside, nifedipine) Hyperthermia: Control agitation, external cooling
Iron	0.5-6 h: Nausea, vomiting, GI discomfort, GI bleeding, drowsiness, hypoglycemia, & hypotension 6-24 h: Latency/quiescence (may not occur in severe ingestions) 24-48 h: Shock, coma, seizures, coagulopathy, acidosis, cardiac failure 2-7 d: Hepatotoxicity & coagulopathy, metabolic acidosis, renal insufficiency 1-8 wk: GI disorders, achlorhydria	Elimination: Gastric lavage &/or whole bowel irrigation with polyethylene glycol-electrolyte solution, especially with tablets (radiopaque) present on KUB Shock: IV fluids & blood (if hemorrhage present); vasopressors if needed Antidote: Deferoxamine to chelate iron, when iron levels >500 mcg/dL or severe ingestion suspected (will change urine to "vin rosé" color)
Salicylate	Respiratory alkalosis (initially), metabolic acidosis (after substantial absorption), pulmonary edema, platelet dysfunction, nausea, vomiting, hearing loss, agitation, delirium	Elimination: Activated charcoal, hemodialysis (for severe poisoning), alkalization of urine Agitation/delirium: Alkalize blood (acidemia enhances transfer into tissue, especially brain) with IV bicarbonate
Tricyclic antidepressants	Wide-complex tachyarrhythmias, hypotension, seizures	Tachyarrhythmias: Alkalizing blood (pH 7.5-7.55) with IV bicarbonate reduces binding to sodium channel Seizures: Benzodiazepines Hypotension: Fluid resuscitation, vasopressors

Abbreviations: GI, gastrointestinal tract; IV, intravenous; KUB, radiograph of kidneys, ureters, bladder; LFT, liver function test; PT, prothrombin time; RUQ, right upper quadrant.

Critical Care Medicine Pharmacy Review (continued)**Overview of Drotrecogin Alfa^a (Activated Protein C)****Indication**

Known or suspected infection that is being treated

and

Patient meets ≥ 3 SIRS criteria:

1. Core temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
2. HR >90 beats per minute unless a medical condition causes tachycardia or patient is receiving treatment to prevent tachycardia (eg, β -blocker)
3. RR >20 breaths per minute, $\text{PaCO}_2 <32$ mm Hg, or the use of a mechanical ventilator
4. WBC $>12,000/\text{mL}$

and

APACHE II score ≥ 25

or

At least 1 organ or system dysfunction:

1. Cardiovascular dysfunction (shock, hypotension, or the need for vasopressor support despite adequate fluid resuscitation)
2. Respiratory dysfunction ($\text{PaO}_2/\text{FIO}_2$ ratio <250)
3. Renal dysfunction (oliguria despite adequate fluid resuscitation)
4. Thrombocytopenia (platelet count $<80,000/\text{mL}$ or 50% decrease from the highest value in the past 3 d)
5. Metabolic dysfunction with elevated lactic acid concentrations

Contraindications

Clinical situations in which bleeding could be associated with increased risk of death:

1. Active internal bleeding
2. Recent (within 3 mo) hemorrhagic stroke
3. Recent (within 2 mo) intracranial or intraspinal surgery or severe head trauma
4. Trauma with an increased risk of life-threatening bleeding
5. Presence of an epidural catheter
6. Intracranial neoplasm or mass lesion or evidence of cerebral herniation
7. Known hypersensitivity to drotrecogin alfa or any of its metabolites

Warnings

Patients with single-organ dysfunction & recent surgery (within 30 d) had higher mortality, but sample was too small for statistical significance; these patients may not be at high risk of death irrespective of APACHE II score—therefore, the drug may not be indicated; carefully consider the risks & benefits

Precautions

The following conditions are likely to increase the risk of bleeding; therefore, the risks & benefits should be considered:

1. Concurrent therapeutic dosing of heparin; platelet count $<30,000/\text{mL}$; INR >3.0
2. Recent (within 6 wk) GI bleeding
3. Recent (within 3 d) administration of thrombolytic therapy
4. Recent (within 7 d) administration of oral anticoagulants or glycoprotein IIb/IIIa inhibitors
5. Recent (within 7 d) administration of aspirin (>650 mg daily) or other platelet inhibitors
6. Recent (within 3 mo) ischemic stroke
7. Intracranial arteriovenous malformation
8. Known bleeding diathesis
9. Chronic severe hepatic disease
10. Any other condition in which bleeding constitutes a serious hazard

Adverse reactions

Serious bleeding occurred in 3.5% of patients in the drotrecogin alfa group compared with 2% in the placebo group

Dose

24 mcg/kg/h continuous infusion for 96 h

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; FIO_2 , fraction of inspired oxygen; GI, gastrointestinal tract; HR, heart rate; INR, international normalized ratio; RR, respiration rate; SIRS, systemic inflammatory response syndrome; WBC, white blood cell count.

^aXigris; Eli Lilly and Co., Indianapolis, Indiana.