Critical Care

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Learning Objectives:

1. Discuss strategies for preventing complications in intubated critically ill patients.
2. Recommend a regimen to provide optimal analgesia and sedation in critically ill patients.
3. Discuss the differences in treatment of hypovolemic and septic shock.
4. Discuss appropriate use of fluids, vasopressors, antibiotics, and corticosteroids in patients with severe sepsis or septic shock.
5. Recommend pharmacologic therapy to prevent stress ulcers, venous thromboembolism, and hyperglycemia in critically ill patients.

Self-Assessment Questions:

Answers and explanations to these questions may be found at the end of this chapter.

1. A 58-year-old woman remains intubated in the intensive care unit (ICU) after a recent abdominal operation. In the operating room, she receives more than 10 L of fluid and blood products but has received aggressive diuresis with furosemide postoperatively. In the past 3 days, she has generated 7.5 L of urine output, and her blood urea nitrogen (BUN) and serum creatinine (SCr) have steadily increased to 40 and 1.5 mg/dL, respectively. Her urine chloride (Cl) concentration was 9 mEq/L (24 hours after her last dose of furosemide. This morning, her arterial blood gas (ABG) reveals pH 7.50, $PaCO_2$ 46 mm Hg, and sodium bicarbonate (HCO_3^-) 34 mEq/L. Which one of the following actions is best to improve her acid-base status?

   A. 0.9% sodium chloride (NaCl) infusion.
   B. 5% dextrose (D_5W) infusion.
   C. Hydrochloric acid (HCl) infusion.
   D. Acetazolamide intravenously.

2. A 21-year-old, 80-kg man admitted 1 day ago after a gunshot wound to the abdomen is receiving mechanical ventilation and thrashing around in bed, pulling at his breathing tube. Using the Richmond Agitation Sedation Scale (RASS), he is rated a +3 (i.e., very agitated; pulls or removes tubes or catheters; aggressive). The patient is positive for delirium on the basis of the Confusion Assessment Method for the ICU (CAM-ICU). He is not ready for extubation, and the attending physician estimates that he will remain intubated for at least 48 hours. The medical team has decided that his RASS goal should be −1 (i.e., drowsy; not fully alert but with sustained awakening to voice). He is receiving a morphine 4-mg/hour infusion for pain control, which has been adequately controlling his pain. Vital signs include blood pressure (BP) 110/70 mm Hg and heart rate (HR) 110 beats/minute. His baseline QT interval is 440 milliseconds. In addition to nonpharmacologic interventions to treat delirium, which one of the following is the best intervention to achieve this patient's RASS goal?

   A. Initiate a dexmedetomidine 1-mcg/kg loading dose over 10 minutes, followed by 0.2 mcg/kg/hour.
   B. Initiate lorazepam 3-mg intravenous load, followed by a lorazepam 3-mg/hour infusion.
   C. Initiate propofol at 5 mcg/kg/minute and titrate by 5 mcg/kg/minute every 5 minutes as needed.
   D. Initiate haloperidol 1-mg intravenously and double the dose every 20 minutes as needed.

3. A patient is admitted to the ICU for a traumatic brain injury and several abdominal injuries. He is initiated on a high dose of propofol, morphine, and vecuronium for sedation, analgesia, and paralysis to help control his intracranial pressure. On day 3 of hospitalization, the patient develops pancreatitis and requires total parenteral nutrition (PN). He is initiated on 2-in-1 total PN and is given lipids 20% 250 mL/day. His electrolytes on day 5 are within normal limits, except for an elevated magnesium concentration. His train-of-four (TOF) is 0/4. His medications include piperacillin/tazobactam 4.5 g intravenously every 8 hours and tobramycin 350 mg/day intravenously for a possible pancreatic abscess. Which one of the following is the most appropriate concern in this patient?

   A. Vecuronium and propofol are having an additive effect on sedation.
   B. High magnesium concentrations and tobramycin can inhibit the effects of vecuronium.
   C. Propofol should be considered in his daily nutritional assessment.
   D. Morphine is antagonized by propofol; this may require a dosage increase.

4. A 62-year-old woman is admitted to your ICU for respiratory dysfunction requiring mechanical ventilation. Her medical history is nonsignificant, and she is taking no medications at home. Her chest radiograph shows bilateral lower lobe infiltrates, her white blood cell count (WBC) is 21,000, her temperature is 39.6°C, her BP is 82/45 mm Hg (normal for her is 115/70 mm Hg), and her HR is 110 beats/minute. After she receives a diagnosis of community-acquired pneumonia, she is empirically initiated on ceftriaxone 1 g/day intravenously and levofloxacin 500 mg/day intravenously. After fluid resuscitation with about 4 L of 0.9% NaCl, her BP is essentially unchanged. After initiation of dopamine 4 mcg/kg/minute, her BP is 96/58 mm Hg, and her HR is 128 beats/minute. She has made less than 100 mL of urine during the past 6 hours, and her Cr has increased from 0.9 mg/dL to 1.3 mg/dL. Her serum albumin concentration is 3.1 g/dL. Which one of the following drug therapies is best for this patient at this time?

   A. Administer 5% albumin 500 mL intravenously.
   B. Initiate hydrocortisone 50 mg intravenously every 6 hours and fludrocortisone 50 mcg by feeding tube once daily.
   C. Change dopamine to norepinephrine 0.01 mcg/kg/minute titrated to maintain a mean arterial pressure (MAP) of at least 65 mm Hg.
   D. Continue current antibiotic therapy and hemodynamic monitoring.

5. A 92-year-old woman is admitted to the ICU with urosepsis and septic shock. She lives in a long-term care facility and has a medical history significant for myocardial infarction, hypertension, and heart failure. Her BP is 72/44 mm Hg, HR 120 beats/minute, and O_2 saturation 99%; her laboratory values are normal, except for a BUN of 74 mg/dL and Cr of 2.7 mg/dL. Her urine output is about 20 mL/hour. Empiric antibiotics were initiated. Which one of the following therapies is most appropriate to initiate next?

   A. Dopamine 1 mcg/kg/minute.
   B. Furosemide 60 mg intravenously now.
   C. Normal saline 500-mL bolus.
   D. Albumin 5% 500-mL bolus.

6. A 46-year-old man had a witnessed cardiac arrest in an airport terminal. After about 5 minutes, emergency medical services arrived, and defibrillator pads were applied. The cardiac monitor showed ventricular tachycardia (VT), and the patient had no discernible pulse. He was defibrillated with 200 J without return of spontaneous circulation. He received an additional two shocks of 200 J with no improvement. Between shocks, the patient received CPR (cardiopulmonary resuscitation). An intravenous line was obtained, and an epinephrine 1-mg intravenous push was given; chest compressions and artificial respirations were initiated. Within 1 minute, the patient was reassessed. The cardiac monitor still showed VT, and he remained pulseless; therefore, another shock of 200 J, followed by an amiodarone 300-mg intravenous push, was administered. After this, the patient was converted to a normal sinus rhythm with an HR of 100 beats/minute. The patient was then transported to the hospital intubated and unresponsive. Which one of the following recommendations is most likely to improve this patient's outcomes?

   A. Administer HCO_3^- for a presumed metabolic acidosis.
   B. Administer vasopressin 40 units intravenously.
   C. Transport the patient immediately to a cardiac catheterization laboratory for possible percutaneous intervention.
   D. Initiate hypothermia protocol.

7. A 22-year-old man is admitted to the trauma ICU after a motor vehicle accident. He has several rib fractures, a ruptured spleen, and a small brain contusion. He is rushed to the operating room for an emergency splenectomy, and the trauma team places a postpyloric orogastric feeding tube (OGT) before returning to the ICU. The patient is unresponsive and mechanically ventilated. Which one of the following is best for stress ulcer prophylaxis (SUP)?

   A. Pantoprazole intravenous push.
   B. Famotidine suspension by OGT.
   C. Sucralfate slurry by OGT.
   D. No SUP indicated.

I. INTERPRETING HEMODYNAMIC PARAMETERS

A. Indicators of Intravascular Volume
   1. HR is normally 60–100 beats/minute.
   2. MAP = [(SBP − DBP)/3] + DBP, where SBP is systolic blood pressure and DBP is diastolic blood pressure. Note that MAP is largely based on DBP because perfusion (especially coronary) occurs during diastole.
      a. Normal MAP is 70–100 mm Hg.
      b. MAP is an indication of global perfusion pressure; need MAP of at least 60–65 mm Hg for organ perfusion
      c. BP or MAP usually directly correlates with volume status because:
         i. BP is the product of flow × resistance (i.e., cardiac output [CO] × systemic vascular resistance [SVR]).
         ii. CO is directly related to HR and stroke volume.
         iii. Stroke volume is directly related to preload.
         iv. Preload is a measure of volume.
   3. Central venous pressure (CVP) – Pressure in the thoracic vena cava near the right atrium; can reflect preload; CO is optimal at a CVP of 8–12 mm Hg. Note that using CVP as an indicator of preload and fluid responsiveness is controversial.
   4. Pulmonary capillary wedge pressure (PCWP) – This is an indirect measure of cardiac function as related to blood volume or left ventricular volume. Normal value is 5–12 mm Hg. Similar to CVP, use of PCWP as a predictor of preload and fluid responsiveness is controversial.
   5. Measures such as CVP and PCWP are referred to as "static" measures of intravascular volume because they are a "snapshot" and do not consider other variables such as venous tone, intrathoracic pressure, and ventricular compliance. "Dynamic" measures of intravascular volume such as stroke volume variation and pulse pressure variation are beyond the scope of this text, but they have been recently proposed as better assessments of an individual patient's position on the Starling curve and thus better predictors of intravascular volume.

B. Indicators of Bloodflow and Heart Function
   1. CO is the amount of blood the heart pumps in 1 minute (normally 4–8 L/minute).
   2. Cardiac index (CI) = CO/body surface area. Normally 2.5–4 L/minute
   3. CVP and PCWP: These pressures can be a measure of heart function because as the CO is reduced, the volume is increased because of a reduction in the forward flow of blood. As volume is increased, the pressure will increase. Thus, CVP and PCWP may be elevated in heart failure.

C. Indicators of Oxygen Transport and Use
   1. Lactic acid
      a. Lactic acid is formed during anaerobic metabolism.
      b. During states of hypoperfusion, the tissues receive less blood and therefore less oxygen.
      c. If there is less oxygen for the tissues, they will use anaerobic metabolism with the subsequent production of lactic acid.
   2. Venous saturation (Svo_2)
      a. Arterial saturation is ideally 95%–100%, and Svo_2 is normally 70%–75%.
      b. Thus, the extraction ratio from the arterial circulation to the venous circulation is normally 25%–30%.
      c. In situations of hypoperfusion, the extraction ratio may increase because of a lack of oxygen; thus the Svo_2 will be less than 70%.
      d. An Svo_2 less than 70% can indicate a reduction in CO, tissue perfusion, or arterial oxygen saturation. It can also be a sign of anemia or increased metabolic rate.
      e. A normal SvO_2 does not rule out hypoperfusion in patients with impaired extraction (e.g., sepsis). An elevated lactate concentration may indicate hypoperfusion in this scenario.

D. Indicators of Vascular Tone: SVR
   1. SVR is a measure of arteriolar tone and is normally 900–1400 dynes/second/cm^3.
   2. If resistance equals pressure/flow, then SVR is directly related to BP and indirectly related to CO.

E. Interpreting Acid-Base Disturbances
   1. Normal values reported as pH/P_{CO_2}/P_{O_2}/HCO_3^-/Sa_{O_2}
      a. pH 7.40 (range 7.35–7.45)
      b. P_{CO_2} 35–45 mm Hg
      c. P_{O_2} 80–100 mm Hg
      d. HCO_3^- 22–26 mEq/L (or mmol/L)
      e. Sa_{O_2} 95%–100%
   2. Metabolic disorders
      a. Acidosis = decreased HCO_3^-
      b. Alkalosis = increased HCO_3^-
   3. Respiratory disorders
      a. Acidosis = increased P_{CO_2}
      b. Alkalosis = decreased P_{CO_2}
   4. Compensation will occur to normalize the pH in response to the primary problem.
      a. Respiratory compensation occurs *immediately* by changes in respiratory rate.
         i. The compensation for metabolic acidosis is a respiratory alkalosis (i.e., decrease in P_{CO_2}). This occurs by increasing the respiratory rate to blow off more CO_2, thus making pH more basic (i.e., higher pH).
         ii. The compensation for metabolic alkalosis is a respiratory acidosis (i.e., increase in P_{CO_2}). This occurs by slowing the respiratory rate to retain more CO_2, thus making pH more acidic (i.e., lower pH).
      b. Metabolic compensation occurs *slowly* in the kidneys by regulating the excretion and reabsorption of HCO_3^- and H^+.
         i. The compensation for a respiratory acidosis is metabolic alkalosis (i.e., an increase in HCO_3^-).
         ii. The compensation for a respiratory alkalosis is metabolic acidosis (i.e., a decrease in HCO_3^-).

Table 1. Blood Gas Changes in Acid-Base Disturbances

Normal Values **HCO_3^- = 24 mmol/L** **P_{CO_2} = 40 mm Hg**	**Primary Disturbance**	**Compensation**
Metabolic acidosis	↓ HCO_3^- by 1 mmol/L	↓ P_{CO_2} by 1 mm Hg
Metabolic alkalosis	↑ HCO_3^- by 1 mmol/L	↑ P_{CO_2} by 1–2 mm Hg
Respiratory acidosis Chronic (> 3 days) Acute	 ↑ P_{CO_2} by 10 mm Hg ↑ P_{CO_2} by 10 mm Hg	 ↑ HCO_3^- by 4 mmol/L ↑ HCO_3^- by 1 mmol/L
Respiratory alkalosis Chronic (> 3 days) Acute	 ↓ P_{CO_2} by 10 mm Hg ↓ P_{CO_2} by 10 mm Hg	 ↓ HCO_3^- = 2–5 mmol/L ↓ HCO_3^- = 1–3 mmol/L

   5. Steps to evaluate acid-base disorders
      a. Assess pH, P_{CO_2}, and HCO_3^-.
         i. Acidosis if pH less than 7.35
            (a) If P_{CO_2} is elevated, the primary disorder is respiratory acidosis.
            (b) If HCO_3^- is decreased, the primary disorder is metabolic acidosis.

ii. Alkalosis if pH is greater than 7.45
   (a) If P_{CO_2} is decreased, the primary disorder is respiratory alkalosis.
   (b) If HCO_3^- is elevated, the primary disorder is metabolic alkalosis.

b. Calculate the anion gap (AG) = [Na+] − [Cl^- + HCO_3^-].
   i. Normal AG = 140 − [105 + 24] = 11 (normal range is 6–12 mEq/L).
   ii. If AG is more than 12, there is a primary metabolic acidosis regardless of pH or HCO_3^-. Some patients have a mixed acid-base disorder in which they have more than one primary disorder.
   iii. Hypoalbuminemia will decrease the AG by 2.5–3 mEq/L for every 1-g/dL decrease in serum albumin less than 4 g/dL.

c. Calculate the excess AG = total AG − normal AG. Add excess AG to serum bicarbonate.
   i. If the sum is greater than a normal serum bicarbonate (i.e., more than 30 mEq/L), there is als an AG metabolic alkalosis (this can be in addition to other primary disorders).
   ii. If the sum is less than a normal serum bicarbonate (i.e., less than 23 mEq/L), there is an underlying non-AG metabolic acidosis.

Table 2. Acid-Base Disturbances

	Respiratory Acidosis	**Respiratory Alkalosis**	**Metabolic Acidosis**	**Metabolic Alkalosis**
Etiology	Pulmonary edema Cardiac arrest CNS depression Stroke Pulmonary embolus Pneumonia Bronchospasm Spinal cord injury Sedatives	Anxiety Pain CNS tumor Stroke Head injury Hypoxia Stimulant drugs	**Anion gap** >12 (MUDPILES) Methanol Uremia DKA Propylene glycol Intoxication/infection Lactic acidosis Ethylene glycol Salicylate/sepsis **Nonanion gap** (F-USED CARS) Fistula (Pancreatic) Uteroenteric conduits Saline excess Endocrine (Hyperparathyroid) Diarrhea Carbonic anhydrase inhibitors Arginine, lysine, chloride Renal tubular acidosis Spironolactone	**Urine Cl^- > 20** Hyperaldosteronism ↑ Mineralocorticoid **Urine Cl^- < 10** Vomiting NG suction Diuretic
Treatment	Oxygen Correct cause	Hypoventilation Sedation Correct cause	Correct cause (Sodium bicarbonate has traditionally been used, but evidence of clinical benefit is lacking)	Correct cause **If urine Cl^- < 10** 0.9% NaCl Consider HCl Consider acetazolamide

Cl^- = chloride; CNS = central nervous system; DKA = diabetic ketoacidosis; GI = gastrointestinal; HCl = hydrochloric acid; NaCl = sodiu chloride; NG = nasogastric.

Patient Cases

1. A 62-year-old woman has been hospitalized in the ICU for several weeks. Her hospital stay has been complicated by aspiration pneumonia and sepsis, requiring prolonged courses of antibiotics. For the past few days, she has been having high temperatures again, and her stool output has increased dramatically. Her most recent stool samples have tested positive for *Clostridium difficile* toxin, and her laboratory tests reveal serum Na 138 mEq/L, K 3.5 mEq/L, Cl 115 mEq/L, albumin 4.4 g/dL, pH 7.32, $PaCO_2$ 30 mm Hg, and HCO_3^- 15 mEq/L. Which one of the following is most consistent with this patient's primary acid-base disturbance?

   A. AG metabolic acidosis. - ND
   B. Normal AG metabolic acidosis.
   C. Saline-responsive metabolic alkalosis. - ND
   D. Acute respiratory acidosis.

2. A 27-year-old man with no medical history is admitted to the hospital after being "found down" at a party, where he reportedly ingested a fifth of whiskey during a 20-minute period. On arrival at the emergency department, he was neurologically unresponsive with the following ABG values: pH 7.23, $PaCO_2$ 58 mm Hg, PaO_2 111 mm Hg, HCO_3^- 24 mEq/L, and SaO_2 100% on 2 L/minute of oxygen by nasal cannula. Which one of the following actions is most appropriate?

   A. Administer albuterol 4 puffs every 20 minutes for 4 hours; then 2–4 puffs every 2–4 hours as needed.
   B. Administer 100% oxygen by face mask.
   C. Give $NaHCO_3^-$ 100 mEq intravenous piggyback over 30 minutes.
   D. Intubate and transfer to the ICU.

3. A 55-year-old woman with a history of severe chronic obstructive pulmonary disease is admitted to the hospital after several days of worsening shortness of breath. Recently, she was discharged from the hospital after a similar episode and was doing fine until 3 days before admission, when she developed a productive cough, requiring an increase in her home O_2 and more frequent use of her metered-dose inhalers. On admission to the medical ICU, she was anxious and markedly distressed, with rapid, shallow breaths. She was hypertensive (160/80 mm Hg), tachycardic (140 beats/minute), and tachypneic (28). Her ABG showed a pH of 7.30, $PaCO_2$ 59 mm Hg, PaO_2 50 mm Hg, HCO_3^- 28 mEq/L, and SaO_2 83% on 6 L/minute of oxygen by face mask, and she was immediately intubated. Which one of the following primary acid-base disturbances is most consistent with this patient's presentation and laboratory data?

   A. Metabolic acidosis.
   B. Metabolic alkalosis.
   C. Respiratory acidosis.
   D. Respiratory alkalosis.

II. SHOCK

A. Diagnosis of Shock on the Basis of Hemodynamic Parameters

Table 3. Definitions of Shock

Hemodynamic Subset	CI (2.5–4.0 L/minute/m^2)	PCWP (8–12 mm Hg)	SVR (800–1400 dynes/second/cm^2)	Translation
Septic	High	Low	Low	Patients with septic shock are hyperdynamic (high CI), with vasodilation (low SVR) and increased vascular permeability ("leaky capillaries"), causing intravascular fluid to shift into the interstitial spaces (thus, low PCWP). The vasodilation and vascular permeability are attributable to cytokines and inflammatory mediators
Hypovolemic	Low	Low	High	To understand why patients with hypovolemia have a low CI, refer to the Starling curve (see the chapter titled "Fluids, Electrolytes, and Nutrition"), which illustrates reduced cardiac function as intravascular volume is reduced. The reduced intravascular volume is indicated by a low PCWP, with a reflex increase in SVR to maintain tissue perfusion. Remember that resistance (SVR) is inversely related to flow (CI)
Cardiogenic	Low	High	High	Patients with cardiogenic shock have acute heart failure (low CI). The insufficient forward flow of blood causes venous congestion (high PCWP) and an underfilled arterial blood volume. The subsequent reduced tissue perfusion causes a reflex vasoconstriction (which, although it can improve bloodflow to vital organs, can worsen heart function by increasing afterload) and reduced renal excretion of Na^+ and wate

CI = cardiac index; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance.

B. Hypovolemic Shock

1. Treatment centers on the restoration of intravascular volume.
   a. Crystalloids and colloids are discussed in the chapter titled "Fluids, Electrolytes, and Nutrition"
   b. Blood products should be administered if clinically indicated in patients with hemorrhagic shock
2. Patients may require vasopressors if hypotension is not rapidly reversed with fluid resuscitation. See below for vasopressor options.
   a. The efficacy of vasopressors will be reduced in patients who have not received adequate fluid resuscitation.
   b. The risks of vasopressors (e.g., arrhythmias, ischemia) will be greater in patients who have not received adequate fluid resuscitation.

3. Fluid resuscitation is typically guided by a target CVP of at least 8 mm Hg (or at least 12 mm Hg, if mechanically ventilated), improvement in MAP, evidence of improved organ function (e.g., increased urine output), and clinical examination.

C. Stages of Sepsis and Subsequent Organ Dysfunction
   1. Definitions and clinical signs

Table 4. Definitions of Sepsis

Terminology	Definition	Signs
Sepsis	Documented or suspected infection plus a systemic inflammatory response	Temperature > 38°C or < 36°C Heart rate > 90 beats/minute Tachypnea Altered mental status Hyperglycemia WBC > 12,000 or < 4000 cells/mm^3 Immature leukocytes (bands) > 10% Edema
Severe sepsis	Sepsis complicated by organ dysfunction or hypoperfusion	SBP < 90 mm Hg or MAP < 70 mm Hg Venous saturation (Svo_2) < 70% Pao_2/Fio_2 < 300 CI > 3.5 Lactate > 1 mmol/L Decreased capillary refill (press finger until turns white; time for color to return is refill time and normally less than 2 seconds) Mottling Creatinine increase > 0.5 mg/dL Urine output < 0.5 mL/kg/hour for ≥ 2 hours INR > 1.5 or aPTT > 60 seconds Platelet count < 100,000 Ileus Plasma total bilirubin > 4 mg/dL
Septic shock	Sepsis-induced hypotension persisting despite adequate fluid resuscitation	See all signs listed above

aPTT = activated partial thromboplastin time; CI = cardiac index; INR = international normalized ratio; MAP = mean arterial pressure; SBP = systolic blood pressure; WBC = white blood cell count.

Table 5. Organ Dysfunction

Organ System	Some (not all) Signs of Dysfunction
Cardiovascular	SBP < 90 or MAP < 70 mm Hg Persistently hypotensive despite adequate fluid resuscitation
Pulmonary	Need for mechanical ventilation because of respiratory failure
Kidney	Abrupt decrease in urine output (i.e., less than 0.5 mL/kg/hour for at least 2 hours) or increased creatinine
Hematologic or coagulation	Reduced platelet count or white blood cell count or an increase in INR

INR = international normalized ratio; MAP = mean arterial pressure; SBP = systolic blood pressure.

2. Treatment
   a. Ideally, initial resuscitation should be completed in the first 6 hours.
      i. Achieving the following resuscitation goals is referred to as *early goal-directed therapy*; meeting these goals within the first 6 hours after onset of severe sepsis or septic shock is associated with an improvement in survival.
         (a) CVP of 8–12 mm Hg (12–15 mm Hg if intubated on ventilator)
         (b) MAP of 65 mm Hg or more
         (c) Urine output 0.5 mL/kg/hour or more
         (d) Central venous oxygen saturation (Svo_2) more than 70% or mixed venous oxygen saturation ($Scvo_2$) more than 65%
      ii. Protocol for achieving goals
         (a) Fluid resuscitation using 1000 mL of crystalloids (i.e., normal saline or lactated Ringer's) or 300–500 mL of colloids (albumin, hetastarch, Voluven) administered over 30 minutes
            (1) Continue as long as hemodynamic parameters improve and CVP is within goal; recheck CVP after each fluid challenge; patients may require aggressive fluid resuscitation during the first 24 hours.
            (2) There is no evidence that colloids are superior to crystalloids in improving outcomes, and they are more costly.
         (b) If Svo_2 target is not achieved, consider further fluid resuscitation, packed red blood cells (to hematocrit of more than 30%), and/or dobutamine infusion.
         (c) Vasopressors (see Table 6) may be necessary to maintain MAP of 65 mm Hg or greater if a fluid challenge fails to restore BP and organ perfusion.
            (1) Vasopressors improve tissue perfusion by increasing BP and/or CO. Very few studies have evaluated an improvement in clinical outcomes. Therefore, drug selection is largely based on expert opinion, practitioner experience, and patient response.
            (2) Although norepinephrine or dopamine is the initial vasopressor of choice, there is no high-quality evidence to recommend one over the other. Norepinephrine and dopamine have similar efficacy; however, dopamine has been associated with an increased incidence of arrhythmias.
            (3) Vasopressin efficacy is similar to norepinephrine and, when added to norepinephrine, vasopressin can have a vasopressor-sparing effect, although mortality is not improved with the combination.
            (4) Use of arterial catheter for BP measurements is preferred.
            (5) Vasopressors should be administered through a central line as soon as possible to reduce the risk of extravasation and subsequent tissue ischemia. If extravasation occurs, phentolamine (an α-receptor antagonist) can be used to reduce tissue necrosis.
            (6) Use caution with calculations and avoid unit errors (e.g., mcg/kg/min, mcg/kg/hour, mcg/min, units/min)
         (d) Inotropes (i.e., dobutamine, milrinone) may be necessary to improve cardiac function in patients with low CO after fluid resuscitation. Because the mechanism of action of milrinone does not rely on catecholamines, phosphodiesterase inhibitors may be theoretically preferred in patients who have received chronic treatment with β-adrenergic antagonists.
         (e) Begin appropriate intravenous antibiotics as early as possible and always within the first hour of recognizing severe sepsis and septic shock.

Table 6. Vasopressors and Inotropes

Drug	Dose	α_1	β_1	β_2	Dopa	Cautions/Clinical Effects
Dopamine	1–3 mcg/kg/minute	+/–	++	+/-	++++	Lower doses cause renal, coronary, mesenteric, and cerebral arterial vasodilation and a natriuretic response Lower "inotropic" doses can complement the vasoconstrictive effects of norepinephrine Do not use low-dose dopamine for renal protection because evidence does not support this practice Moderate doses can ↑ contractility and SVR Any dose can induce arrhythmias Any dose can cause endocrine changes (e.g., decreased prolactin, growth hormone, thyroid hormone); however, the clinical significance is unknown Immediate precursor of norepinephrine Prolonged infusions can deplete endogenous norepinephrine stores, resulting in a loss of vasopressor response Effects on renal bloodflow may be lost at higher doses because of predominant α_1-vasoconstrictive effects
	3–10 mcg/kg/minute	++	+++	+	++	
	10–20 mcg/kg/minute	++++	+++	0	+	
Norepinephrine	0.01–3 mcg/kg/minute for septic shock	++++	+++	0	0	↓ Renal perfusion ↑ SVR, ↑ BP 0 – ↓ cardiac output (at high doses) Peripheral ischemia Can induce tachyarrhythmias and myocardial ischemia Extravasation produces ischemic necrosis and sloughing (treatment: phentolamine 5–10 mg IV diluted)
Epinephrine	0.04–1 mcg/kg/minute for refractory hypotension	+++	+++	++	0	Positive inotropic and chronotropic effects can induce arrhythmias and myocardial ischemia Low doses primarily β-adrenergic; escalating doses primarily α-adrenergic Some evidence of reduced splanchnic circulation which can lead to gut ischemia Extravasation produces ischemic necrosis and sloughing (treatment: phentolamine 5–10 mg diluted) Increases blood glucose and lactate concentrations

Table 6. Vasopressors and Inotropes *(continued)*

Drug	Dose	α_1	β_1	β_2	Dopa	Cautions/Clinical Effects
Phenylephrine	0.5–8 mcg/kg/minute for septic shock (or a common maximum amount is 300 mcg/min)	++++	0	0	0	↓ Renal perfusion Pure α-adrenergic agonist with minimal cardiac activity Rapid ↑ SBP and DBP can cause a reflex bradycardia and reduction in CO Can be administered as a rapid bolus for acute hypotension (e.g., intraoperative), or as a continuous infusion. Extravasation produces ischemic necrosis and sloughing (treatment: phentolamine 5–10 mg diluted)
Vasopressin	0.03–0.04 unit/minute (physiologic replacement dose)	0	0	0	0	Direct stimulation of smooth muscle V1 receptors; peripheral vasoconstriction, no adrenergic activity Theoretically beneficial because of an apparent relative vasopressin deficiency in septic shock, but no evidence to show efficacy over other vasopressors Effective during acidosis and hypoxia because does not rely on adrenergic receptors Doses ≥ 0.04 unit/minute associated with coronary vasoconstriction and peripheral necrosis Not titrated like traditional vasopressors Prone to dosing errors because of "unit/minute"
Dobutamine	2–20 mcg/kg/minute	+	+++	+	0	Positive inotrope to ↑ cardiac output Can cause hypotension because of β_2-stimulation Higher doses can cause tachyarrhythmias and changes in BP, which can lead to myocardial ischemia
Milrinone (Primacor)	50-mcg/kg load over 10 minutes, followed by 0.375–0.75 mcg/kg/minute	0	0	0	0	Noncatecholamine, phosphodiesterase inhibitor Positive inotrope Vasodilation/hypotension, arrhythmias possible Use lower doses in renal failure Loading doses often omitted especially if patient hypotensive

BP = blood pressure; DBP = diastolic blood pressure; IV = intravenously; SBP = systolic blood pressure; SVR = systemic vascular resistance.

b. Appropriate use of antimicrobials in patients with sepsis
   i. Empiric antimicrobials should cover likely pathogens on the basis of suspected origin of infection.
      (a) Common sources of infection are lung, abdomen, blood, and urinary tract.
      (b) Consider empiric fungal therapy if patients have several risk factors including recent abdominal surgery, chronic PN, or indwelling central venous catheter or if patients are immunocompromised (i.e., chronic corticosteroids or other immunosuppressants, neutropenia, malignancy, organ transplant).
   ii. Begin intravenous antimicrobials as early as possible, at least within the first hour, but after at least two blood cultures (one drawn percutaneously) are obtained.
      (a) If several antibiotics are prescribed, administer the broadest coverage first and infuse as quickly as possible.
      (b) Mortality is increased for each 1-hour delay in administering appropriate antimicrobials.
   iii. Appropriate antimicrobials do not preclude the importance of emergency source control by drainage, debridement, or device removal as needed.
   iv. Deescalation should occur on the basis of culture data and/or clinical judgment.
   v. Consider discontinuing antimicrobials in 7–10 days unless there is slow response, undrainable foci, immunosuppression, or multidrug-resistant pathogens.
   vi. Discontinue antimicrobials if no infectious cause is found.

c. Indication for and use of corticosteroids
   i. In a study by Annane et al, intravenous hydrocortisone improved short-term survival in adult patients with septic shock defined as a systolic blood pressure less than 90 mm Hg for greater than 1 hour. The recommendation from the Surviving Sepsis Campaign is broadened slightly by defining eligible patients as adults with "septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors."
      (a) The use of hydrocortisone in this instance is a grade 2C recommendation of the Surviving Sepsis Campaign guidelines (i.e., a weak recommendation based on low-quality evidence; the study in question was significantly underpowered).
      (b) This underscores the importance of categorizing the severity of sepsis on the basis of the definitions listed above.
      (c) The risks (hyperglycemia, infection) of corticosteroids outweigh the benefits in patients who do not have septic shock.
      (d) The typical dose of hydrocortisone is 50 mg intravenously every 6 hours. The total daily dose should not exceed 300 mg.
      (e) Fludrocortisone 50 mcg orally once daily may optionally be added to hydrocortisone, but it is unnecessary in theory because hydrocortisone has mineralocorticoid activity.
      (f) Adrenocorticotrophic hormone stimulation testing and cortisol concentrations are not necessary and do not correlate with the efficacy of hydrocortisone.
      (g) Patients should be weaned off steroid therapy once vasopressors are no longer required.
   ii. The CORTICUS trial evaluated hydrocortisone 50 mg intravenously every 6 hours in patients with sepsis requiring vasopressors, but not necessarily with persistent hypotension. Corticosteroids were not associated with a mortality benefit; however, they were associated with an increased risk of hyperglycemia, new sepsis, or septic shock. For this reason, corticosteroids are not recommended in patients with septic shock who have been stabilized with fluid and vasopressor therapy.

d. Recombinant human activated protein C (rhAPC, or drotrecogin alfa) has been withdrawn from the market because PROWESS-SHOCK, a randomized controlled trial, showed that it did not result in improved 28-day mortality compared with placebo.

3. The Surviving Sepsis Campaign and the Institute for Healthcare Improvement have developed a treatment bundle for sepsis that should include the following:
   a. Measure serum lactate (a sign of hypoperfusion).
   b. Obtain blood cultures before antibiotics.
   c. Timely administration of broad-spectrum antibiotics
   d. Early goal-directed therapy
   e. Consider corticosteroids.
   f. Consider rhAPC (recently withdrawn from the market).
   g. Glucose control (to be discussed later)

D. Cardiogenic Shock – See ADHF in "Acute Care Cardiology."

Patient Cases

4. A 65-year-old woman is admitted to the coronary care unit after suffering a myocardial infarction and requiring mechanical ventilation. On the fourth day of hospitalization, she is found to be hypotensive (BP 80/50 mm Hg), tachycardic (HR 125 beats/minute), tachypneic (respiratory rate 30 breaths/minute), hypoxemic (Pao_2 55 mm Hg), febrile (102°F), and confused. The patient is given two 1000-mL boluses of normal saline and then is intubated and initiated on piperacillin/tazobactam 4.5 g intravenous piggyback every 8 hours and ciprofloxacin 400 mg intravenous piggyback every 8 hours for possible nosocomial pneumonia. After fluid boluses fail to improve her hemodynamic and clinical status, a pulmonary artery catheter is placed, which reveals a PCWP of 14 mm Hg, CI of 3.8 L/minute/m^2, and SVR of 515 dynes/second/cm^2. Her chest radiograph shows diffuse interstitial infiltrates, and she still requires 100% FIO_2. Which one of the following actions is best?

   A. Add clindamycin 600 mg intravenous piggyback every 8 hours for possible aspiration pneumonia.
   B. Administer a dobutamine infusion titrated to achieve a MAP of at least 65 mm Hg.
   C. Administer a norepinephrine infusion titrated to achieve a MAP of at least 65 mm Hg.
   D. Administer hydrocortisone 50 mg intravenously every 6 hours.

5. A 70-kg patient is to receive a continuous infusion of dopamine for BP support. The nurse has a 250-mL bag of D_5W containing 400 mg of dopamine. Which one of the following rates is most appropriate to infuse the dopamine drip at a dose of 5 mcg/kg/minute?

   A. 13 mL/hour.
   B. 13 mL/minute.
   C. 22 mL/hour.
   D. 22 mL/minute.

6. A 42-year-old man was found unresponsive at his group home covered in vomit. He was intubated by the paramedics. On arrival to the emergency department, his BP is 72/30 mm Hg and HR is 122 beats/minute. During the next couple of hours, he receives 5 L of normal saline, 500 mL of 5% albumin, and norepinephrine infusing at 40 mcg/minute. With these interventions, his BP is 87/56 mm Hg and HR is 100 beats/minute. Pertinent laboratory values include a WBC of 20,000 cells/mm^3, lactic acid 15 mmol/L, AST 78, creatinine 2 (baseline 1) mg/dL, platelet count 118,000, INR 1.4, and urine output of about 15 mL/hour. The patient is initiated on piperacillin/tazobactam to cover for presumed aspiration pneumonia. Which one of the following is most appropriate?

   A. Add hydrocortisone 50 mg intravenously every 6 hours.
   B. Check a random cortisol concentration to determine whether hydrocortisone is indicated.
   C. Add low-dose dopamine.
   D. Add enoxaparin 40 mg subcutaneously daily.

III. ACUTE RESPIRATORY FAILURE

A. Causes of Respiratory Failure

Table 7. Respiratory Failure

Indication for Mechanical Ventilation	Examples
Hypoventilation (hypercapnic respiratory failure)	Drug overdose Neuromuscular disease Cardiopulmonary resuscitation Central nervous system injury or disease
Hypoxemia (hypoxic respiratory failure)	Pulmonary injury or disease Pneumonia Pulmonary edema Pulmonary embolus Acute respiratory distress syndrome
Airway protection	Loss of airway patency (mechanical obstruction, tracheal/chest wall injury) Loss of gag/cough reflex with large-volume aspiration risk (central nervous system injury, central nervous system depression, cardiovascular accident, seizures, cardiac arrest, etc.)

B. Complications Associated with Mechanical Ventilation (see individual sections later in text for prevention of these complications)
   1. Ventilator-associated pneumonia
   2. Stress ulcer
   3. Venous thrombosis

IV. CARDIAC ARREST

A. Training: Any pharmacist who participates in codes should complete basic life support and advanced cardiac life support training. In general, basic life support training requires 3–5 hours to complete, and advanced cardiac life support training requires 2 days. The information presented in this section consists of selected highlights from these training sessions and should not be used in place of a comprehensive training program.

B. Major Changes to the 2010 American Heart Association Guidelines:
   1. Change from "A-B-C" (i.e., Airway, Breathing, Chest compressions) to "C-A-B," which will reduce time to first chest compressions, a critical element of cardiopulmonary resuscitation; airway management is no longer recommended until after the first cycle of chest compressions (i.e., 30 compressions).
   2. Atropine is no longer recommended for routine use in pulseless electrical activity or asystole because of a lack of therapeutic benefit; atropine is still recommended as first-line drug therapy for patients with symptomatic bradycardia at a dose of 0.5 mg bolus repeated every 3–5 minutes up to a maximum of 3 mg; an infusion of dopamine or epinephrine is an alternative for patients unresponsive to atropine.

C. Medications Used During a Code – See chapter titled "Acute Care Cardiology" for information on drugs, indications, and dosages.

D. Medication Administration
   1. Central venous administration is preferred.
      a. Intraosseous administration is preferred over endotracheal if intravenous administration is not possible because of more predictable drug delivery and pharmacologic effect.
      b. Endotracheal drug administration can be used by administering 2–2.5 times the standard intravenous dose and diluting in 5–10 mL of sterile water. The following drugs can be administered through an endotracheal tube (Naloxone, Atropine, Vasopressin, Epinephrine, Lidocaine … acronym is NAVEL).
   2. If medications are administered through a peripheral vein, it is important to follow the medication with 20 mL of intravenous fluid to facilitate drug flow from the extremity to the central circulation.
   3. Chest compressions and defibrillation should not be significantly interrupted for vascular access, medication administration, or airway placement.

E. Role of Hypothermia
   1. New proposed terminology is "targeted temperature management."
   2. Hypothermia (32°C–34°C) for 12–24 hours beginning as soon as possible after cardiac arrest can improve neurologic recovery and mortality. Although most evidence of benefit involves patients with ventricular fibrillation or pulseless VT, hypothermia is recommended for adult survivors of cardiac arrest regardless of the initial rhythm.
   3. Consider hypothermia in patients who have been successfully resuscitated after a cardiac arrest but who remain comatose (usually defined as a lack of meaningful response to verbal commands).
   4. Hypothermia is induced as soon as possible and no later than 10 hours after cardiac arrest.
   5. Hypothermia is typically induced using ice packs (to armpits, neck, torso, and groin), cooling blankets, and infusion of cold normal saline.
   6. Patients will need sedation and analgesia during periods of hypothermia.
   7. Complications during hypothermia
      a. Shivering causes excess heat production, increased oxygen consumption, and a general stress response and thus should be treated and prevented.
         i. Shivering can be treated with sedatives (midazolam, dexmedetomidine), anesthetics, opiates (e.g., meperidine 50 mg; fentanyl 50 mcg), buspirone 30 mg enterally, magnesium 2 g intravenously, and paralytics.
         ii. Note that shivering can be treated without the use of paralytics in many patients. Thus, paralytics are not mandatory and should be avoided if possible (see disadvantages of paralytics below). Paralytics may be most beneficial during the induction of hypothermia; however, they should be continually reevaluated and discontinued if possible once goal temperature is achieved.
      b. Drug clearance is typically reduced during hypothermia.
         i. Use bolus dosing during the induction of hypothermia.
         ii. Reduce maintenance doses of sedatives, opiates, paralytics, and other drugs as needed.
      c. Increased renal excretion of water and subsequent volume depletion
      d. Electrolyte disorders
         i. Reductions in potassium, magnesium, and phosphate during cooling
         ii. Hyperkalemia during rewarming
      e. Increased risk of infection
      f. Hyperglycemia during hypothermia, but hypoglycemia during rewarming – Monitor blood glucose frequently (i.e., every 1–2 hours) and adjust insulin accordingly.
      g. Bedsores

h. Impaired bowel function
i. Systemic inflammation upon rewarming; should rewarm slowly
j. Seizures (consider continuous EEG monitoring)

Patient Case

7. A 51-year-old woman collapsed in front of her family, who called 911 and began CPR. The paramedics arrive and find the victim unresponsive with an electrocardiogram showing bradycardia and an HR of 20 beats/minute. In the emergency department, the patient's MAP is 68 mm Hg after fluids and norepinephrine, but the patient remains unresponsive. She is initiated on the hypothermia protocol. After 24 hours of hypothermia (temperature 33°C), the patient is in the ICU, and the rewarming process has recently begun. The pharmacist arrives in the ICU about 30 minutes into the rewarming process. The patient has been receiving a continuous infusion of insulin throughout the period of hypothermia at an average rate of 15 units/hour, with blood glucose testing every 6 hours. The patient has been sedated with a continuous infusion of propofol and is paralyzed with a continuous infusion of cisatracurium. The patient's vital signs are stable, and her laboratory values are normal. Which one of the following pharmacist recommendations is most appropriate at this time?

A. Increase blood glucose testing to now and every 1–2 hours during rewarming.
B. Adjust cisatracurium to achieve a TOF of zero 0/4 impulses.
C. Discontinue propofol to facilitate extubation.
D. Increase insulin infusion to prevent hyperkalemia.

V. ANALGESICS, SEDATIVES, ANTIPSYCHOTICS, AND PARALYTICS

A. Develop a Protocol with a Patient-Focused Strategy.
   1. Nonpharmacologic strategies to improve patient comfort include lighting, music, massage, verbal reassurance, avoidance of sleep deprivation, and patient positioning based on patient preferences.
   2. Determine patient goals using validated scales, and routinely assess pain and sedation.
      a. Routine assessment of pain and sedation is associated with a reduction in ICU length of stay and duration of mechanical ventilation.
      b. To assess pain, the Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT) are recommended because, compared with other scores, they are more valid and reliable for monitoring pain in adult ICU patients (except those with brain injury).
         i. The BPS score can range from 3 (no pain) to 12 (maximal pain). A score of 6 or higher is generally considered to reflect unacceptable pain.
         ii. The CPOT score can range from 0 to 8.

Table 8. The Behavioral Pain Scale (Payen JF, et al. Crit Care Med 2001;29:2258–63)

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Table 9. Critical Care Pain Observation Tool (Gelinas et al. Am J Crit Care 2006;15:420–7)

Indicator	Description	Score
Facial expression	No muscular tension observed	Relaxed, neutral: 0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense: 1
	All of the above facial movements plus eyelid tightly closed	Grimacing: 2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements: 0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection: 1
	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness: 2
Muscle tension	No resistance to passive movements	Relaxed: 0
	Resistance to passive movements	Tense, rigid: 1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid: 2
Compliance with the ventilator	Alarms not activated, easy ventilation	Tolerating ventilator or movement: 0
	Alarms stop spontaneously	Coughing but tolerating: 1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator: 2
OR Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound: 0
	Sighing, moaning	Sighing, moaning: 1
	Crying out, sobbing	Crying out, sobbing: 2

c. Vital signs (e.g., elevated HR or BP) are cues that indicate further assessment of pain is necessary (i.e., using a scale described above).

d. To assess sedation, the Richmond Agitation-Sedation Scale (RASS) and Sedation-Agitation Scale (SAS) are recommended because, compared with other sedation scores, they have been shown to be more valid and reliable for monitoring the quality and depth of sedation in adult ICU patients.

Table 10. Richmond Agitation-Sedation Scale (RASS)

Scale	Term	Description
+4	Combative	Combative, violent, immediate danger to staff
+3	Very agitated	Pulls to remove tubes or catheters; aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive
0	Alert and calm	Spontaneously pays attention to caregiver
−1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening/eye contact for at least 10 seconds)
−2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
−3	Moderate sedation	Movement or eye opening to voice but no eye contact
−4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Table 11. Sedation-Agitation Scale (SAS)

Score	Term	Description
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side
6	Very agitated	Requiring restraint and frequent verbal reminding of limits, biting endotracheal tube
5	Agitated	Anxious or physically agitated, calms to verbal instructions
4	Calm and cooperative	Calm, easily roused, follows commands
3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

3. Treat pain first and add a sedative if needed.
   a. Use analgesics or nonpharmacologic interventions before potentially painful procedures.
   b. Opioid analgesics are considered first line for the treatment of nonneuropathic pain (gabapentin or carbamazepine can be considered for neuropathic pain).
   c. Nonopioid analgesics (e.g., acetaminophen, ibuprofen, ketorolac, ketamine) can be used in conjunction with opioids to optimize pain control and avoid dose-related adverse effects.
   d. Non-benzodiazepine sedatives may be preferred over benzodiazepines to improve clinical outcomes in mechanically ventilated patients.
4. Dosing strategies for analgesics and sedatives
   a. Analgesics and sedatives should be dosed to achieve pain and sedation goals. Titrate sedative medications to achieve a light level of sedation (i.e., capable of being roused and able to follow simple commands).
   b. Goals may be achieved using intermittent dosing administered routinely or as needed.
   c. If unable to achieve goals with intermittent dosing, use a combination of bolus dosing with a continuous infusion.

i. In patients receiving a continuous infusion, use a bolus dose before or instead of increasing the infusion rate (a bolus dose has a faster onset and can eliminate the need for an increase in the infusion rate). Exception is with drugs such as propofol or dexmedetomidine, which can cause hypotension and/or bradycardia when bolused.
ii. Use bolus dosing proactively (e.g., before dressing changes, suctioning, repositioning).
iii. Protocols should specify times or prompts for regular reductions in sedative infusion rates.

d. A scheduled daily interruption of continuous infusions is associated with several important benefits:
i. Assess patient neurologic function.
ii. Prevent drug accumulation and overdose.
iii. Reduce time on the ventilator.
iv. Reduce ICU length of stay.
v. Reduce symptoms of posttraumatic stress disorder.

e. Careful attention to minimize infusion rates of longer-acting analgesics and sedatives can be effective at achieving sedation and analgesia goals and can be more cost-effective than short-acting medications (e.g., propofol, remifentanil, dexmedetomidine).

5. Use laxatives and stool softeners proactively to prevent opioid-induced constipation.
6. Evaluate and manage delirium.

B. Analgesics

Table 12. Analgesics

	Morphine	Fentanyl	Hydromorphone	Remifentanil
Trade name	Various	Sublimaze	Dilaudid	Ultiva
Pharmacokinetics				
Onset (minutes)	5–10	1–2	5–10	1–3
Duration of effect (hours)	2–4	1–5	2–6	0.3–0.6
Prolonged in renal failure	Yes	No	Yes	No
Prolonged in hepatic failure	Yes	Yes	Yes	No
Elimination half-life (hours)	1–4	2–5	2–3	0.05–0.17
Active metabolites	Yes	No	No	No
Adverse effects				
Hypotension	Yes	No	Yes	Yes
Flushing	Yes	No	Yes	No
Bronchospasm	Yes	No	No	No
Constipation	Yes	Yes	Yes	Yes

C. Sedatives

1. Benzodiazepines should be titrated or avoided to prevent adverse outcomes including prolonged duration of mechanical ventilation, increased ICU length of stay, and development of delirium.
a. Lorazepam
i. Intermittent dosing 1–4 mg every 2–6 hours
ii. Continuous infusion: Start at 1 mg/hour and titrate to goal (e.g., RASS, SAS).
b. Midazolam
i. Intermittent dosing 1–4 mg every 15 minutes to 1 hour
ii. Continuous infusion: Start at 1 mg/hour and titrate to goal (e.g., RASS, SAS).

Table 13. Benzodiazepines

	Diazepam	Lorazepam	Midazolam
Trade name	Valium	Ativan	Versed
Pharmacokinetics			
Onset (minutes)	2–5	5–20	2–5
Duration of effect (hours)	2–4	4–6	1–2
Prolonged in renal failure	Yes	No	Yes
Prolonged in hepatic failure	Yes	No	Yes
Elimination half-life (hours)	24–120	10–20	1–10
Active metabolite	Yes	No	Yes
CYP 450 3A4 interactions	Yes	No	Yes
Adverse effects			
Hypotension	Yes	No	No
Thrombophlebitis	Yes	Maybe	No
Propylene glycol toxicity	No	Yes	No

2. Propofol (Diprivan)
   a. Rapid onset (1–2 minutes) and short duration (3–5 minutes or longer if prolonged infusion)
   b. Initiate at 5 mcg/kg/minute and titrate to achieve sedation goals by 5 mcg/kg/minute every 5 minutes. Avoid prolonged infusions greater than 50 mcg/kg/minute.
   c. Avoid loading doses because of risk of hypotension.
   d. In general, used in intubated patients because of risk of respiratory depression
   e. Propofol has no significant analgesic activity. If a patient has pain, will need to combine propofol with an analgesic
   f. Monitoring
      i. Blood pressure
      ii. Triglycerides
      iii. Calories provided from 10% lipid emulsion (1 kcal/mL). May need to adjust lipid or calories provided by nutrition support (i.e., EN or PN)
      iv. Propofol-related infusion syndrome is more likely to occur with prolonged infusions greater than 50 mcg/kg/minute and is associated with metabolic acidosis, cardiac failure, arrhythmias (e.g., bradycardia), cardiac arrest, rhabdomyolysis, hyperkalemia, and kidney failure.
   g. Propofol is more commonly used than benzodiazepines, most likely because it has a shorter duration, is easily titratable, and is more predictable.
3. Dexmedetomidine (Precedex)
   a. Sedative and analgesic properties through central and peripheral α_2-receptor agonist activity
   b. Extent of analgesic activity is not well described, and surgical patients will typically need additional medications for adequate pain control.
   c. Does not cause respiratory depression or drug dependency
   d. Rapid onset (5–15 minutes if bolus, longer without bolus) and short duration (2-hour half-life)
   e. A loading dose is suggested for patients undergoing surgery; however, loading doses are NOT recommended for ICU patients because of the risk of bradycardia and hypotension.
   f. Maintenance dose of 0.2–0.7 mcg/kg/hour is FDA approved for a maximum of 24 hours, although there is evidence showing the safety and efficacy of prolonged infusions at doses up to 1.5 mcg/kg/hour.
   g. Compared with benzodiazepines, dexmedetomidine is associated with a lower prevalence of ICU delirium in some studies; need comparative studies with propofol
   h. Monitoring: Primary adverse effects are dose-related bradycardia and hypotension.

D. Assessment and Management of Delirium
   1. Delirium is an acute change in cognitive function characterized by disorganized thought, altered level of consciousness, and inattentiveness.
   2. Delirium is associated with increased mortality and prolonged length of stay in the ICU.
   3. Use a validated tool to proactively identify and assess delirium (e.g., the CAM-ICU or the Intensive Care Delirium Screening Checklist).
   4. Nonpharmacologic interventions include maintaining communication with the patient, maximizing uninterrupted sleep, providing access to natural lighting (rooms with windows), removing unnecessary equipment from room, and encouraging patient autonomy and early mobility.
   5. Delirium may also be prevented by avoiding or using the minimal dose necessary of benzodiazepines and other medications that may cause delirium, such as opiates and anticholinergic medications.
   6. Pharmacologic treatment of delirium
      a. Haloperidol
         i. There is no evidence that haloperidol reduces the duration of delirium.
         ii. Effective dose is generally 1–10 mg. To determine the patient-specific dose, start with 1 mg intravenously and double the dose every 20 minutes. Once the patient is calm, add the total milligrams administered and divide into four daily doses given intravenously at 6-hour intervals.
         iii. Monitoring
            (a) Hypotension
            (b) Assess QT interval at baseline and daily during administration of haloperidol. In addition, monitor for other drugs that could potentially prolong QT interval.
            (c) Extrapyramidal effects including laryngeal dystonia and dysphagia are more common with oral administration than with intravenous administration.
            (d) Seizures
      b. Atypical antipsychotics (olanzapine [Zyprexa], risperidone [Risperdal], quetiapine [Seroquel], and ziprasidone [Geodon]) are potential alternatives to haloperidol.

E. Therapeutic Paralysis in ICU Patients
   1. Therapeutic paralysis is used for intubated patients with persistent hypoxia despite adequate sedation and analgesia; although it is usually used in patients with acute respiratory distress syndrome, this has not been shown to improve mortality. Paralytic agents are also used as adjunct agents to control severe intracranial hypertension in patients with neurologic injury (e.g., traumatic brain injury).
      a. Point of emphasis: Paralysis should only be used once efforts to sedate the patient using a combination of analgesia and sedation have failed (i.e., patient continues to have poor oxygenation).
      b. NEVER paralyze a patient who is not completely sedated.
      c. Paralytic agents should only be used in conjunction with a continuously infused sedative. Of importance, sedatives should have amnestic properties (e.g., benzodiazepines). Analgesics can also be used as needed in patients with pain. Many practitioners will insist on the combination of a sedative and analgesic in paralyzed patients.

2. Paralytic agents

Table 14. Paralytics

Recommendation	Pancuronium	Vecuronium	Atracurium	Cisatracurium
Trade name	Pavulon	Norcuron	Tracrium	Nimbex
Duration of effect (hours)	0.75–1.5	0.5–0.75	0.25–0.5	0.5–1
Prolonged in renal failure	Yes	Yes	No	No
Prolonged in hepatic failure	Yes	Yes	No	No
Loading dose	0.08 mg/kg	0.1 mg/kg	0.4 mg/kg	0.1 mg/kg
Maintenance dose	0.02–0.04 mg/kg	0.02–0.04 mg/kg/hour	0.4 mg/kg/hour	2–10 mcg/kg/minute
Adverse effects				
Tachycardia	Yes	No	No	No
Hypotension	No	No	Dose-dependent	No
Daily drug cost per 70 kg	$5–$15	$100–$200	$100–$200	$200–$400

3. Disadvantages of paralysis
   a. Paralytics may mask seizure activity.
   b. Prolonged paralysis is associated with critical illness polyneuromyopathy, characterized by prolonged muscle weakness or paralysis.
   c. Paralysis can mask insufficient analgesia and sedation.
   d. Increased risk of venous thromboembolism (VTE)
   e. Skin breakdown and decubitus
   f. Corneal abrasions caused by eye dryness; prevent by applying Lacri-Lube ophthalmic ointment to eyes every 8 hours
4. Monitoring paralysis
   a. Paralytic agents need to be monitored to prevent overdose and thus prolonged paralysis.
   b. Even with appropriate individualized dosing and monitoring of paralytic agents, a principal adverse effect is prolonged muscle weakness after discontinuation. This can dramatically slow patient recovery, requiring considerable health care resources (e.g., physical therapy, rehabilitation). For this reason, it must be emphasized that the need for therapeutic paralysis must be carefully considered and reevaluated every day.
   c. The simplest way to assess the appropriateness of the paralytic is as follows: regularly (once daily), but temporarily, discontinue the drug to determine the time needed for the patient to move or breathe spontaneously. This "drug holiday" can also be useful for the following reasons:
      i. Assess sedation and titrate sedatives as needed (i.e., if the patient is agitated after the paralytic is discontinued, he or she is not receiving adequate sedation or analgesia).
      ii. Assess the need for continued paralysis (i.e., if the patient is able to maintain oxygenation, then perhaps the paralytic is no longer necessary).
      iii. Assess the dose of the paralytic (i.e., Did the paralysis "wear off" within the expected time frame based on the expected drug duration?); this is especially important for drugs such as vecuronium and pancuronium because of the long half-life and dependence on end-organ clearance.
   d. A peripheral nerve stimulator can be used in conjunction with the drug holidays described previously to assess the level of paralysis and guide drug dosing.
      i. The TOF refers to peripheral nerve stimulation using 4 electrical impulses usually applied to the ulnar or facial nerves.
      ii. Obtain a baseline TOF before initiating paralysis to determine patient sensitivity to impulses. Patients who are not paralyzed should exhibit 1 twitch for each impulse (for 4/4 twitches).

iii. During paralysis, patients should be maintained at 1–2 twitches, which indicate the extent of receptor blockade.
iv. Technical problems that limit the accuracy of TOF monitoring include the presence of perspiration or tissue edema.

e. In addition to the monitoring described, clinical assessment involves adjusting the paralytic dosing to prevent patient-ventilator dyssynchrony (e.g., "bucking" the ventilator, elevated peak airway pressures).
f. Avoid other medications or electrolyte abnormalities that can potentiate or inhibit paralysis.

Table 15. Interactions with Paralytics

	Potentiate Block	Antagonize Block
Drugs	Corticosteroids	Aminophylline
	Aminoglycosides	Theophylline
	Clindamycin	Carbamazepine
	Tetracyclines	Phenytoin (chronic)
	Colistin	
	Calcium channel blockers	
	Type Ia antiarrhythmics	
	Furosemide	
	Lithium	
Electrolyte disorders	Hypermagnesemia	Hypercalcemia
	Hypocalcemia	Hyperkalemia
	Hypokalemia	

Patient Cases

8. An elderly woman is admitted to the ICU for acute decompensated heart failure and kidney failure with an ejection fraction of less than 30%. She was administered a continuous infusion of bumetanide; however, the benefit was limited because of her kidney failure. She was intubated on ICU day 2 because of worsening pulmonary edema and hypoxia. After intubation, she scored a +2 (agitated; frequent nonpurposeful movement, fights ventilator) on the RASS, and her CAM-ICU is positive for delirium. She denies pain. Her BP is 120/70 mm Hg and HR is 88 beats/minute. Which of the following is the best recommendation for achieving her sedation goal of RASS equals zero (i.e., alert and calm)?

A. Initiate propofol at 5 mcg/kg/minute and titrate as needed.
B. Administer haloperidol 5 mg intravenously and double the dose every 20 minutes as needed.
C. Administer lorazepam 1 mg every 20 minutes as needed.
D. Initiate morphine 4 mg intravenously every 4 hours as needed.

9. A 42-year-old woman with acute respiratory distress syndrome, having a significant history of alcohol and tobacco abuse, is transferred to the medical ICU from an outside hospital. She presented to the outside hospital after 1 week of productive cough, fever, chills, and increased shortness of breath. On admission to the medical ICU, she is hypotensive (80/60 mm Hg), tachycardic (130 beats/minute), and febrile (39.0°C). Her ABG shows pH 7.1, $PaCO_2$ 56 mm Hg, PaO_2 49 mm Hg, HCO_3^- 16 mEq/L, and SaO_2 76% on 100% FIO_2. The only other significant laboratory results are an SCr of 1.5 mg/dL and WBC 16,000. She is achieving her sedation goals with continuous infusions of midazolam 3 mg/hour and fentanyl 250 mcg/hour. After several nonpharmacologic attempts to improve her oxygenation fail, she is paralyzed, and her ventilator settings are adjusted accordingly. Which one of the following statements about therapeutic paralysis is most appropriate?

A. Opioids should be discontinued after paralysis is initiated to avoid prolonged paralysis.
B. Once paralysis is initiated, do not discontinue it abruptly.
C. Depth of paralysis should be monitored by discontinuing the sedation once daily and assessing the patient's response.
D. The goal of monitoring paralysis using a peripheral nerve stimulator is to observe 2/4 twitches on a TOF.

Patient Cases

10. The patient above was paralyzed as instructed and appeared to being doing well until about 8 hours after starting an infusion of cisatracurium (currently infusing at 2 mcg/kg/minute), when she began to move around violently in her bed. At this time, she was tachycardic (120 beats/minute) and appeared very agitated; her SaO_2 fell to 80%. Which one of the following actions is best?

    A. Increase the infusion rate of cisatracurium to a maximum of 10 mcg/kg/minute as needed until the patient stops moving.
    B. Administer a midazolam bolus and increase the infusion rate as needed to achieve sedation goals.
    C. Increase the fentanyl infusion rate as needed to achieve sedation goals.
    D. Check the TOF.

11. After that event, the patient above did poorly the rest of the night. A Swan-Ganz catheter was placed, confirming the diagnosis of sepsis (i.e., high CO and low SVR). The patient was initiated on a dopamine infusion at 10 mcg/kg/minute to maintain an adequate BP. Other medications included clindamycin, cefepime, and gentamicin. By morning, her SCr has increased to 2.8 mg/dL, and the night shift nurse reports that the patient has had 0/4 twitches on TOF for the past 8 hours. Pertinent electrolyte values include K^+ 3.0 mEq/L, Ca^{++} 9 mg/dL, and Mg^{++} 2 mg/dL. Which one of the following is most likely to potentiate the effects of cisatracurium?

    A. Clindamycin.
    B. Gentamicin.
    C. Hypokalemia.
    D. All of the above.

VI. PREVENTING HYPERGLYCEMIA AND HYPOGLYCEMIA

A. History of Blood Glucose Control
    1. 2001: Study by van den Berghe et al of primarily cardiac surgical ICU patients showed a mortality benefit of maintaining blood glucose in the range of 80–110 mg/dL despite an increased risk of hypoglycemia (5.1% vs. 0.8%).
    2. Subsequent investigators could not duplicate the mortality benefit of tight blood glucose control. Furthermore, there were concerns about increased incidence and consequences of hypoglycemia.
    3. 2006: Study by van den Berghe et al of primarily medical ICU patients showed no mortality benefit associated with maintaining blood glucose in the range of 80–110 mg/dL. The study did show a reduction in ventilator time and length of stay. The high incidence of hypoglycemia (18%) was alarming.
    4. The 2007 Surviving Sepsis Campaign guidelines suggested maintaining blood glucose less than 150 mg/dL (grade 2C, indicating a weak recommendation based on a low grade of evidence).
    5. 2009: Results of a large, international, randomized study (NICE-SUGAR) involving more than 6000 critically ill medical and surgical patients showed increased mortality and increased risk of hypoglycemia (blood glucose 40 mg/dL or less) in patients receiving intensive blood glucose control (goal glucose 81–108 mg/dL) compared with patients having a goal of 180 mg/dL or less.

B. Treatment Strategies to Maintain Blood Glucose in Target Range (less than 180 mg/dL)
    1. Use a validated dosing protocol that considers blood glucose concentration, rate of change, and insulin infusion rate.
    2. If unable to maintain blood glucose in target range with subcutaneous insulin, consider using a continuous infusion of intravenous insulin.

3. Regularly scheduled administration of insulin is a proactive approach to preventing hyperglycemia and is preferable to a reactive administration of insulin in response to an elevated glucose concentration (e.g., "sliding-scale" insulin).
4. A sliding-scale insulin regimen can be used in conjunction with the regularly scheduled doses; however, the baseline of insulin administered should be adjusted every day to prevent hyperglycemia and the need for additional doses of insulin.

C. Monitoring Blood Glucose
1. Monitor blood glucose every 1–2 hours until glucose values are stable and then every 4 hours thereafter.
2. Interpret point-of-care testing of capillary blood with caution because it can overestimate plasma glucose values.

VII. PREVENTING STRESS ULCER

A. Signs and Symptoms: Hematemesis, gross blood in gastric tube aspirates, "coffee ground" emesis or aspiration from gastric tube, and melena

B. Drug Therapy Is Recommended for Any One of the Following Major Risk Factors:
1. Respiratory failure requiring mechanical ventilation (likely for greater than 48 hours)
2. Coagulopathy defined as platelet count less than 50,000, international normalized ratio (INR) greater than 1.5, or activated partial thromboplastin time more than 2 times control. (Note: Prophylactic or treatment doses of anticoagulants do not constitute a coagulopathy.)

C. Drug Therapy Is Recommended for Two or More of the Following Risk Factors:
1. Head or spinal cord injury
2. Severe burn (more than 35% of body surface area)
3. Hypoperfusion
4. Acute organ dysfunction
5. History of gastrointestinal (GI) ulcer/bleeding within 1 year
6. High doses of corticosteroids. (Note: Corticosteroid use alone is not a risk factor.)
7. Liver failure with associated coagulopathy
8. Postoperative transplantation
9. Acute kidney injury
10. Major surgery
11. Multiple trauma

D. Prevention Strategies/SUP
1. Efficacy of intravenous histamine-2 (H_2)-blockers in preventing stress-related upper GI bleeding is clearly shown in clinical trials. These are commonly administered enterally when possible because of excellent bioavailability; however, evidence of efficacy has primarily been shown with intravenous administration of H_2-blockers.
2. Despite limited evidence in preventing stress-related mucosal bleeding, enterally administered proton pump inhibitors (PPIs) are also often used. Furthermore, the intravenous route is common, despite a lack of evidence.
3. Regardless of the drug choice or route, it is important to discontinue therapy when risk factors are no longer present to avoid unnecessary drug interactions, adverse effects (pneumonia), and increased costs. This is easily overlooked, with the result that patients are discharged from hospitals and continued on acid-suppressive therapy with no indication.

E. Not Recommended for Prevention

1. Antacids are not used to prevent stress ulcers because of several limitations including large and frequent dosing (30–60 mL every 1–4 hours), fluctuating gastric pH, electrolyte abnormalities (especially in patients with kidney disease), diarrhea, constipation, a propensity to clog enteral feeding tubes, and a requirement for gastric access.
2. Sucralfate is inferior to H_2-blockers and is therefore not recommended for prevention of stress ulcers. In addition, it can clog enteral feeding tubes.

F. Safety: The benefits of preventing stress ulcers by increasing the stomach pH must be weighed against an increased risk of infection including *C. difficile*, hospital-acquired pneumonia, and community-acquired pneumonia (for patients discharged on a PPI).

Table 16. H_2-Receptor Blockers

Action	Competitive Blocker of H_2-Receptors on Parietal Cells
Available agents/dose (dose based on clinical data, not FDA label approved for SUP)	Ranitidine 150 mg PO every 12 hours or 50 mg IV every 8 hours Famotidine 20 mg IV/PO every 12 hours Nizatidine 150 mg PO every 12 hours Cimetidine 300 mg PO/IV every 6 hours or continuous infusion 37.5–50 mg/hour *(only H_2-blocker FDA label approved agent for SUP)*
Adverse effects	Mental status changes, thrombocytopenia (cimetidine)
Advantages	Ease of administration Cost
Disadvantages	Drug interactions (cimetidine) Potential for reduced efficacy over time (tachyphylaxis) Dose adjustment for renal dysfunction Risk of nosocomial pneumonia

FDA = U.S. Food and Drug Administration; H_2 = histamine-2; IV = intravenously; PO = by mouth; SUP = stress ulcer prophylaxis.

Table 17. Proton Pump Inhibitors

Action	**Prodrugs that are activated in the acidic environment of the parietal cell that then bind to and inhibit active proton pumps. Oral formulations are designed to dissolve at a pH > 5.6 to protect from degradation and premature activation in the stomach**
Available agents/dose *(NOTE: Appropriate dose is unknown because of lack of data in preventing stress ulcers; doses are based on clinical data, not FDA label approved for SUP; exception is omeprazole suspension)*	PO Omeprazole (Prilosec) Capsules 20 mg/day PO Capsules 20 mg/day by tube Open capsule and suspend granules in a syringe with 40 mL of apple juice and give by NGT/OGT; flush with 10 mL of apple juice (DO NOT CRUSH GRANULES; delayed release) Omeprazole suspension: By NGT/OGT, dissolve granule content of a 20-mg capsule in 10 mL of 8.4% sodium bicarbonate and flush with 10 mL of sodium bicarbonate or water Powder for oral suspension (Zegerid) 20 mg/day PO (only FDA-approved PPI for prevention of stress ulcers) Esomeprazole (Nexium) Capsules 40 mg/day PO Capsule content 40 mg through a tube Suspend granules in a syringe with 50 mL of water and give by NGT/OGT; flush with 10 mL of water so that all granules are delivered (DO NOT CRUSH GRANULES; delayed release) Lansoprazole (Prevacid) Capsules 30 mg/day PO Capsules 30 mg by tube Open capsule and suspend granules in a syringe with 40 mL of apple juice and give by NGT/OGT; flush with 20 mL of apple juice (DO NOT CRUSH GRANULES; delayed release) Lansoprazole suspension: Dissolve granules in 10 mL of 8.4% sodium bicarbonate and flush with 10 mL of sodium bicarbonate or water Delayed-release orally disintegrating tablets (Prevacid SoluTab) 30 mg: Dissolve in 10 mL of water and give PO/NGT/OGT; flush NGT/OGT with 5 mL of water (NGT/OGT ≥ 8 French) Delayed-release suspension: DO NOT USE by NGT/OGT; Xanthan gum in formulation will likely clog the NGT/OGT Pantoprazole (Protonix) Enteric-coated tablet 40 mg/day PO Enteric-coated tablet 40 mg by tube Crush and dissolve tablet in 10 mL of 4.2% sodium bicarbonate; add 10 mL for a total volume of 20 mL; and flush with 10 mL of sodium bicarbonate or water IV (ONLY for patients who CANNOT tolerate PO/NG administration) Pantoprazole 40 mg/day IV (caution with multiple incompatibilities) No filter required (flush before and after administration); administer over 2–5 minutes Esomeprazole 20–40 mg/day IV; administer over 3 minutes; little compatibility information
Adverse effects	Headache, diarrhea, constipation, abdominal pain, nausea
Advantages	No adjustment needed for renal or liver dysfunction
Disadvantages	Drug interactions: impaired conversion of clopidogrel to active form Cost Administration issues Risk of pneumonia Risk of *Clostridium difficile* infection (nosocomial or community acquired)

FDA = U.S. Food and Drug Administration; IV = intravenously; NGT = nasogastric tube; OGT = orogastric tube; PO = orally; SUP = stress ulcer prophylaxis.

Patient Cases

12. A 73-year-old woman weighing 84 kg is admitted to the ICU after an episode of cardiac arrest with successful resuscitation. She was intubated during the code, and she is being mechanically ventilated. Her BP is 104/65 mm Hg, HR is 88 beats/minute, and O_2 saturations are 98% on 40% F_{IO_2} and PEEP 5; her Glasgow Coma Scale score is 11. Other laboratory values are normal. An OGT is in place, she is being fed enterally, and she has no gastric residuals. Her medications include amiodarone 400 mg 2 times/day, simvastatin 20 mg every night, clopidogrel 75 mg/day, aspirin 81 mg/day, metoprolol 25 mg twice daily, heparin 5000 units subcutaneously every 8 hours, and 0.9% NaCl intravenously at 75 mL/hour. The physicians would like to initiate SUP. Which one of the following is the best recommendation for this patient?

A. Famotidine 20 mg per OGT every 12 hours.
B. Esomeprazole 40 mg per OGT daily.
C. Sucralfate 1 g by OGT 4 times/day.
D. Ranitidine 50 mg intravenously every 8 hours.

13. One week later, the patient from above is extubated. Her Glasgow Coma Scale score is 15, BP 112/70 mm Hg, and HR 75 beats/minute, but her appetite is poor. Which one of the following statements is most appropriate regarding SUP for this patient?

A. SUP should continue until the patient is discharged from the ICU.
B. SUP should be discontinued now.
C. Continue SUP until patient is eating.
D. SUP should be discontinued at hospital discharge.

VIII. PHARMACOLOGIC THERAPY FOR PREVENTING VTE OR PULMONARY EMBOLISM

A. Risk Factors for VTE: Surgery, major trauma, lower extremity injury, immobility, malignancy, sepsis, heart failure, respiratory failure, venous compression, previous VTE, increasing age, pregnancy, erythropoiesis-stimulating agents, obesity, and central venous catheterization

B. Nonpharmacologic Treatment: Mechanical prophylaxis with intermittent pneumatic compression or graduated compression stockings is recommended for medical patients at risk of VTE who have a contraindication to pharmacologic anticoagulation.

C. Special Populations:
   1. Kidney function should be assessed before using low-molecular-weight heparin (LMWH) and fondaparinux. If estimated creatinine clearance is 20–30 mL/minute, reduce enoxaparin to 30 mg subcutaneously daily (rather than 40 mg subcutaneously daily); if creatinine clearance is less than 20 mL/minute or patient is on dialysis, dosing information is limited for LMWH; anti-Xa monitoring may not be reliable in dialysis patients. Fondaparinux is contraindicated in patients with an estimated creatinine clearance less than 30 mL/minute.
   2. For obese patients, some experts recommend increasing LMWH prophylaxis doses by 30% if body mass index is less than 40 kg/m^2; peak (4 hours postdose) anti-Xa of 0.2–0.4 IU/mL is recommended.

D. Contraindication with Neuraxial Anesthesia/Analgesia:
   1. Combination of antithrombotic drugs with neuraxial anesthesia/analgesia is associated with increased risk of spinal or epidural hematoma, leading to spinal cord ischemia and paraplegia.

2. Avoid this combination in patients with known systemic bleeding disorders.
3. Avoid insertion or removal of spinal needles while patients are anticoagulated; wait until anticoagulant effect is minimal.
4. Delay anticoagulant thromboprophylaxis for at least 2 hours after spinal needle or catheter is removed.
5. Delay anticoagulant thromboprophylaxis in patients with a "bloody tap."
6. Because of the long duration of effect, avoid fondaparinux in patients with continuous epidural analgesia.

E. Prevention of VTE Pharmacologic Options

Table 18. Prevention of VTE Pharmacologic Options

	LMWH	LDUH	Dosing Examples
Major trauma	x		Enoxaparin 30 mg SC q12h[a]
Acute spinal cord injury	x		Enoxaparin 30 mg SC q12h
Medical patients with risk factor for VTE	x	x	Enoxaparin 40 mg SC q24h Dalteparin 5000 units SC q24h UFH 5000 units SC q8h–q12h[b]

[a]Recent evidence questions the efficacy of this dose because of low anti-Xa levels and an increased risk of VTE (Malinoski et al. J Trauma 2010;68:874–80), suggesting that dosing needs to be individualized and adjusted on the basis of appropriate monitoring.
[b]Choosing between q8h and q12h should be individualized and based on the patient's risk of bleeding and thrombosis.
h = hours; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; q = every; SC = subcutaneously; UFH = unfractionated heparin; VTE = venous thromboembolism.

IX. PREVENTING VENTILATOR-ASSOCIATED PNEUMONIA

A. Minimize Duration of Ventilation.
1. Daily sedation interruption
2. See above for appropriate use of sedatives and analgesics to avoid oversedation.
3. Daily assessment for readiness to wean from the ventilator

B. Maintain the Head of the Bed Elevated (about 30–45 degrees) to Limit Aspiration Risk.

C. Perform Daily Antiseptic Oral Care (e.g., chlorhexidine).

D. Avoid Gastric Overdistention.
1. Use promotility agents as needed (e.g., metoclopramide, erythromycin).
2. Avoid opioid-induced constipation.
3. Monitor gastric residuals in patients receiving enteral nutrition (EN).

E. Avoid Unplanned Extubation and Reintubation: See suggestions above for optimal use of sedatives and analgesics.

F. Unresolved Issues
1. Selective digestive tract decontamination
2. Use of antiseptic-impregnated endotracheal tubes
3. Intensive glycemic control
4. Avoidance of H_2-antagonists or PPIs, although evidence of an association between pneumonia and acid-suppressive therapy is primarily observational and has not been shown in prospective controlled trials.

X. OPTIMIZING NUTRITION SUPPORT

A. Enteral Nutrition
   1. Enteral nutrition is preferred to PN in patients with a functional GI tract. Benefits of EN include the following:
      a. Reduced risk of infectious complications
      b. Improved wound healing
      c. Less expense
      d. Maintained integrity of gut mucosa and reduction in bacterial translocation
   2. Preventing aspiration in patients receiving tube feedings
      a. Tube feedings should be interrupted if gastric residual volume is greater than 250–500 mL.
      b. Keep head of bed at least 30–45 degrees.
      c. Placing the feeding tube past the pylorus may reduce the risk of aspiration (although controversial). A one-time dose of erythromycin can facilitate small bowel feeding tube placement.
      d. Prokinetic agents such as metoclopramide and erythromycin promote GI motility and reduce gastric residuals; they can also improve tolerance of EN.
   3. Specific caloric goals provided from EN in critically ill patients are unknown. A recent study (Rice TW, et al. Crit Care Med 2011;39:967–74) of patients with respiratory failure during the first 6 days of ventilation showed that, compared with traditional infusion rates, EN infusion rates of 10–30 mL/hour (referred to as "trickle" or trophic feeds), providing about 16% of goal calories, had similar clinical outcomes (i.e., duration of ventilation, ICU stay) but fewer episodes of elevated gastric residual volume. See below for more discussion on predictive equations for determining caloric goals. This evidence needs to be balanced with other evidence showing caloric deficits are associated with prolonged ventilator dependence, pressure ulcers, increased length of stay, and mortality.
   4. Protein is needed for wound healing and immune function. See protein requirements in Fluids, Electrolytes, and Nutrition chapter. Many EN products will not meet protein requirements at normal infusion rates; therefore, additional protein supplements may be needed.

B. Parenteral Nutrition
   1. PN is indicated in patients who have a contraindication to EN or who do not tolerate EN.
   2. PN should be considered in patients with a contraindication to or intolerance of EN for at least 7 days. A recent study compared early (within 48 hours) with late (after 1 week) initiation of PN in more than 2300 critically ill patients (who were not malnourished) as a supplement to EN. The late-initiation group had a significant reduction in ICU stay by 1 day, as well as reductions in hospital stay, infection, cholestasis, and total health care costs. Benefits of late initiation were evident in the subgroup of more than 500 patients with a contraindication to EN, despite receiving essentially no nutrition for the first week.
   3. EN may be poorly tolerated or contraindicated in the following conditions:
      a. Massive bowel resection, perforated bowel, bowel obstruction
      b. Severe diarrhea or emesis
      c. Substantial abdominal distention
      d. Severe GI bleeding
      e. Severe hemodynamic instability
   4. Some trials have shown that glutamine supplementation in PN enhances immune function and reduces the rate of infectious complications.

C. Estimating Caloric Needs
   1. Indirect calorimetry is the gold standard for measuring metabolic rate in critically ill patients; however, it is expensive, requires trained professionals, and is unavailable in most intensive care settings.

2. When indirect calorimetry is unavailable, several predictive equations for determination of caloric goals have been used (e.g., Harris-Benedict, Penn State, Ireton-Jones, and Swinamer equations). See the reference by Walker and Heuberger for a review of the usefulness of predictive equations in critically ill patients. The authors do not recommend the commonly used Harris-Benedict equation f use in critically ill patients.
3. The American College of Chest Physicians 1997 consensus statement suggests a goal of 25 kcal/kg using usual body weight (or ideal body weight if body mass index is greater than 25 kg/m^2); however, this equation poorly predicts measured energy expenditure and may lead to underfeeding o overfeeding.
4. As stated above in EN, previous evidence shows worse morbidity and mortality with underfeeding. More evidence is needed to determine the caloric goals required in different patient populations (e.g. elderly, malnourished, obesity) to improve clinical outcomes in critically ill patients.

D. See Chapter Titled "Fluids, Electrolytes, and Nutrition" for Further Guidance.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

This ABG is consistent with a metabolic acidosis. The pH is less than 7.40 (indicating an acidosis), and the HCO_3^- and $PaCO_2$ are decreased from normal. In a metabolic acidosis, the decrease in HCO_3^- is the primary disorder. When a metabolic acidosis is present, the AG should be calculated to provide additional insight regarding the potential cause of the disorder. The AG is calculated by subtracting the sum of measured anions (Cl^- and HCO_3^-) from cations (Na^+). This patient's AG (8 mEq/L) is within the reference range of 6–12 mEq/L; thus, it is referred to as a "normal anion gap metabolic acidosis" or "non–anion gap metabolic acidosis." *C. difficile*–induced diarrhea is the most likely cause of this patient's acid-base disorder.

2. Answer: D

Given this patient's neurologic status and his elevated $PaCO_2$, he should be intubated and transferred to the ICU. In patients without chronic obstructive pulmonary disease, a $PaCO_2$ greater than 50 mm Hg is usually an indication for mechanical ventilation regardless of oxygenation status (this patient was oxygenating well: PaO_2 111 mm Hg, SaO_2 100%). Albuterol (Answer A) or oxygen (Answer B) therapy alone is unlikely to correct this patient's cause of respiratory failure (i.e., hypoventilation). Likewise, his acid-base disturbance is consistent with a pure acute respiratory acidosis (elevated $PaCO_2$, normal HCO_3^-) and is therefore unlikely to respond to HCO_3^- (Answer C), which is usually reserved for a severe metabolic acidosis.

3. Answer: C

This ABG is consistent with a respiratory acidosis. The pH is below 7.40 (indicating an acidosis), and the $PaCO_2$ (an acid) is higher than normal (about 40 mm Hg). In chronic respiratory acidosis, the kidneys will conserve HCO_3^- (a base) in an attempt to maintain a normal pH. This compensatory metabolic alkalosis is obvious in this patient, whose serum HCO_3^- is 28 mEq/L (which is about 4 mEq/L higher than normal). The elevated HCO_3^- concentration in this patient confirms the diagnosis of respiratory acidosis (because the HCO_3^- would be expected to be less than 24 mEq/L if the acidemia were attributable to a metabolic cause).

4. Answer: C

This patient's hemodynamic profile is most consistent with sepsis (i.e., high CI, low SVR). Her PCWP is also relatively low considering the degree of fluid challenge she has received. Because she remains hypotensive despite receiving an adequate fluid load, an α-adrenergic agent such as dopamine or norepinephrine (Answer D) should be initiated. Norepinephrine is a more potent vasoconstrictor than phenylephrine and provides less β-stimulation than dopamine. If she became more tachycardic while receiving norepinephrine, phenylephrine could be tried. Dobutamine (Answer B) is an inotropic agent that increases CI and lowers PCWP. Dobutamine is usually avoided when the SBP is less than 100 mm Hg. The goals of treatment are to improve BP (typically MAP) and restore adequate organ perfusion. Piperacillin/tazobactam and ciprofloxacin will provide adequate gram-positive, gram-negative, and anaerobic coverage for nosocomial pneumonia, eliminating the need for clindamycin (Answer A). If the patient continues to be hypotensive despite adequate fluid resuscitation and use of vasopressors, then hydrocortisone (Answer D) can be considered.

5. Answer: A

Calculating an infusion rate is a very important role for the pharmacist in code situations. The infusion pump is set to run in milliliters per hour, so your answer should always be in these units. To determine the rate (in milliliters per hour) needed to achieve a 5-mcg/kg/minute dose, use the following calculation:

concentration of dopamine drip: 400 mg/250 mL = 1.6 mg/mL or 1600 mcg/mL. Therefore, 70 kg × 5 mcg/kg/minute × 60 minutes/1 hour × 1 mL/1600 mcg = 13 mL/hour

6. Answer: D

This patient is at risk of developing a VTE and should receive prophylaxis with either enoxaparin (Answer D) or unfractionated heparin. An elevated INR of 1.4, likely caused by hypoperfusion of the liver, is no reason to withhold prophylaxis for VTE. Hydrocortisone (Answer A) is not necessary in this case because the patient is responding to fluid resuscitation and the infusion of norepinephrine, as evidenced by the increase in MAP from 44 mm Hg on arrival to the emergency depart-

ment to 66 mm Hg after initial resuscitation. A random cortisol concentration (Answer B) is not recommended because it does not predict patient responsiveness to corticosteroids.

The addition of dopamine (Answer C) is not necessary at this time because the MAP is greater than 65 mm Hg, thus allowing global organ perfusion. In addition, there is no evidence that a low dose of dopamine will prevent acute kidney injury, and it increases the risk of arrhythmias compared with norepinephrine.

7. Answer: A

During rewarming, patients can become hypoglycemic. Therefore, a reduction in the insulin infusion is likely, and the blood glucose should be monitored more often (Answer A). Paralysis is generally only needed during the cooling process if other measures fail to prevent shivering. Once the patient is at goal temperature, and during the rewarming process, continued use of a paralytic agent should be reassessed. Paralytic assessment can include titrating to a TOF goal; however, a more applicable goal would be the presence of shivering in this patient when the paralytic is briefly interrupted. If the patient is not shivering, consideration should be given to discontinuing the paralytic. Of note, the TOF goal is 2/4 twitches, rather than 0/4 (Answer B), to avoid overparalysis. Although discontinuing propofol (Answer C) can facilitate extubation, this should not be done until the patient is no longer paralyzed, at a normal body temperature, and ready for ventilator weaning. Finally, although rewarming can cause hyperkalemia, it is appropriate to monitor potassium concentrations and treat as needed. It is not appropriate to increase the infusion of insulin (Answer D) to prevent hyperkalemia because this could precipitate hypoglycemia during the rewarming process.

8. Answer: A

Propofol (Answer A) is the most logical starting point for achieving the RASS goal for this patient because it has not been shown to worsen delirium. Haloperidol (Answer B) is an option; however, nonpharmacologic strategies should be attempted first, and the starting dose should be lower at 1 mg instead of 5 mg to avoid adverse effects. Benzodiazepines (Answer C) can worsen delirium and should thus be avoided in this patient. This illustrates the importance of using a validated tool to assess delirium (e.g., CAM-ICU) so that medications associated with worsening delirium can be avoided. Morphine (Answer D) is incorrect because the patient denies pain, and although opioids can be effective sedatives, morphine should be avoided if possible in patients with kidney injury because of active metabolites that are renally eliminated.

9. Answer: D

Although not universally accepted, there is a consensus among experts that peripheral nerve stimulation should be used to guide therapeutic paralysis in the ICU. This is usually accomplished with the TOF sequence. The goal response on TOF is typically 1 or 2 twitches (Answer D). It is imperative for clinicians to recognize that neuromuscular-blocking agents do not cross the blood-brain barrier and are not useful as either sedatives or analgesics. For this reason, sedatives and analgesics should not be discontinued while patients are paralyzed (Answer C). Adequate sedation and analgesia must be achieved before initiating a paralytic agent and should continue throughout the paralysis. In addition, the paralytic should be allowed to dissipate at least once daily to assess the adequacy of sedation/analgesia. This explains why Answer B is incorrect; it is appropriate to discontinue the paralytic agent day by day to reassess the need for continued paralysis. Answer A is incorrect because analgesics and sedatives should be continued during paralysis.

10. Answer: B

Although this patient is no longer paralyzed, it would be inappropriate to re-paralyze an obviously agitated patient (Answer A) because he or she should first be adequately sedated. Likewise, performing a TOF test using a peripheral nerve stimulator (Answer D) is unnecessary because it is obvious from the patient's movement that she is not paralyzed. It is possible that the patient is agitated and tachycardic because she was paralyzed without adequate sedation or analgesia. Before adjusting the paralytic, the patient should be given a sedative bolus (Answer B). In paralyzed patients, it is generally better to err on the side of oversedation rather than undersedation, so an increase in the sedative drip rates would also be appropriate in this patient. Answer C is incorrect because increasing the infusion rate of fentanyl will not have an immediate effect. It would be an acceptable option if the increased infusion rate were accompanied by a fentanyl bolus.

11. Answer: D

Clindamycin (Answer A) and gentamicin (Answer B) have pharmacodynamic effects (i.e., inhibit release of acetylcholine at the nicotinic receptor), which may potentiate the action of neuromuscular-blocking agents. Hypokalemia (Answer C) may also result in significantly prolonged effects.

12. Answer: A

Although this patient had hypotensive episodes during her resuscitation period, she currently has a functioning GI system, as noted by her tolerance of tube feeds. Therefore, SUP should be given by her OGT, if possible, making the best choice for this patient famotidine administered enterally (Answer A). Ranitidine (Answer D) is incorrect because it is administered intravenously. Esomeprazole (Answer B) is incorrect because it inhibits cytochrome P450 (CYP) 2C19 and may interact with clopidogrel. Clopidogrel is a prodrug that is metabolized to its active form through the CYP2C19 hepatic enzymes. Inhibition of this enzyme can result in a reduction in the efficacy of clopidogrel, although evidence showing the clear clinical significance of this interaction is lacking. Regardless, the interaction should be avoided if possible. Sucralfate (Answer C) is incorrect because it has not been shown to be effective at preventing a stress ulcer.

13. Answer: B

This patient's risk factors for SUP (mechanical ventilation and hypoperfusion) are no longer present, so SUP should be discontinued (Answer B). There is no reason to continue SUP until ICU (Answer A) or hospital (Answer D) discharge, and this practice just increases the risk of continuing the SUP as an outpatient without an appropriate indication. Answer C is incorrect because a poor appetite is not a risk factor for developing stress-related mucosal disease (SRMD).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

This patient's ABG and urine Cl are consistent with a saline-responsive metabolic alkalosis. In critically ill patients, the most common cause of metabolic alkalosis is volume contraction. In this case, the volume contraction is probably caused by overly aggressive diuresis. In patients receiving diuretics, the urine Cl should be measured at least 12–24 hours after the last dose. This patient should receive a normal saline infusion. Hydrochloric acid infusions (Answer C) are typically reserved for severer alkalosis (pH more than 7.55) that is not responding to conventional therapy. Administering D_5W (Answer B) will provide hydration but will not correct intravascular volume depletion. Acetazolamide (Answer D) would be a consideration if the metabolic alkalosis persisted after correction of the underlying problem (i.e., volume contraction).

2. Answer: C

Assuming that analgesia with morphine is adequate, this patient requires a sedative to achieve the RASS goal. Propofol is a sedative that is easily titrated and cost-effective. Dexmedetomidine (Answer A) is another option that is safe and effective even when used for longer than 24 hours, but it has not been shown superior to propofol in randomized controlled trials. Furthermore, the cost of dexmedetomidine is greater than that of propofol. Lorazepam (Answer B) should be avoided in patients with (or at high risk of) delirium. Use of benzodiazepines is associated with an increased risk of delirium. Haloperidol (Answer D) is incorrect because it should be avoided in patients with a prolonged QT interval. Haloperidol can cause further prolongation of the QT interval and could lead to torsades. Regardless of the QT interval, nonpharmacologic strategies to avoid delirium (e.g., uninterrupted sleep, natural lighting, early mobility) should be used before antipsychotic medications.

3. Answer: C

Propofol is formulated in a 10% lipid emulsion, which will contribute to the total calories the patient is receiving. In addition, triglycerides should be monitored, especially in patients with pancreatitis and those receiving high doses or prolonged infusions of propofol. Vecuronium (Answer A) is a paralytic with no sedative properties. Tobramycin and elevated magnesium concentrations (Answer B) both potentiate paralysis and should be avoided in this patient if possible. Morphine and propofol (Answer D) can have additive central nervous system effects when used in combination, so routine neurologic assessments should be conducted and doses titrated accordingly.

4. Answer: C

This patient meets the criteria for severe sepsis as defined by the American College of Chest Physicians/Society of Critical Care Medicine consensus guidelines. Treatment with 5% albumin (Answer A) is incorrect; it is unlikely to offer benefit because the patient's BP did not respond to a bolus of 0.9% NaCl. Furthermore, colloids are not more effective than crystalloids for fluid resuscitation, and a serum albumin concentration does not predict the efficacy of albumin administration. Hydrocortisone (Answer B) is incorrect because the patient is not persistently hypotensive after receiving fluids and vasopressors. Although this patient's BP is responding to the infusion of dopamine, the HR has increased. Norepinephrine (Answer C) is correct because it has similar efficacy but with fewer tachyarrhythmias than dopamine. The patient is taking the appropriate empiric antibiotics (Answer D); however, this regimen should be reevaluated when culture and sensitivity results become available.

5. Answer: C

The Surviving Sepsis Campaign guidelines recommend adequate fluid resuscitation with either crystalloids or colloids before the addition of vasopressor agents in patients with severe sepsis. This patient's BP, HR, and BUN/Cr ratio indicate that she has intravascular volume depletion and needs immediate volume replacement. Therefore, intravenous fluids with either crystalloid or colloid should be the next therapy added to this patient's regimen. Given the lack of evidence supporting one type of fluid over another and the substantial increase in cost associated with colloids, most experts would choose Answer C (a bolus of normal saline) over Answer D (albumin). Patients with a history of heart failure can still be administered a fluid bolus. In these patients, an initial bolus of 500 mL instead of 1000 mL is appropriate with close monitoring for worsening heart failure. Dopamine (Answer A) is incor-

because fluid resuscitation should be attempted before adding vasopressors, and there is no evidence that dopamine is renal-protective. Furosemide (Answer B) is incorrect because although it may increase urine output, it will worsen the intravascular volume depletion.

6. Answer: D

Hypothermia improves neurologic recovery and mortality in patients who have suffered a cardiac arrest. Although the patient likely has a metabolic acidosis, the administration of HCO_3^- (Answer A) has not been shown to improve outcomes. Vasopressin (Answer B) is an acceptable option during a cardiac arrest for patients with ventricular fibrillation or pulseless VT, but it does not have a role after cardiac arrest. Although acute coronary syndrome is a common cause of cardiac arrest, information was not provided in this case to suggest that the patient should be transported immediately to the cardiac catheterization laboratory (Answer C). After hypothermia is induced, it is likely that the patient will undergo cardiac catheterization. Of note, the induction of hypothermia does not necessarily interfere with plans for cardiac catheterization.

7. Answer: B

Mechanical ventilation and coagulopathy are independent risk factors for SRMD; therefore, Answer D is incorrect because the patient has a considerable risk of developing a stress ulcer. This patient is critically ill and may be intubated for an extended time; therefore, he is at risk of SRMD, and he will require SUP. The patient has an OGT, meaning that EN and medications administered by the tube will go directly into the stomach. Sucralfate (Answer C) was shown to be inferior to H_2RAs in preventing clinically significant bleeding from SRMD in a large randomized controlled trial (Cook DJ, et al. N Engl J Med 1998;338:791–7), and it is generally not recommended for SUP. Proton pump inhibitors such as intravenous pantoprazole (Answer A) have not been shown to prevent SRMD better than H_2RAs and have been associated with an increased risk of hospital-acquired pneumonia. Thus, famotidine (Answer B) administered enterally is the best agent for SUP in this patient. Of note, studies showing the efficacy of H_2RAs in preventing SRMD have used injectable drugs, rather than enteral administration. Regardless, given the extensive bioavailability with enteral administration, many practitioners will use the enteral route for administering H_2RAs to prevent SRMD.