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SHOCK SYNDROMES AND SEPSIS

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Learning Objectives

1. Distinguish between the various shock syndromes according to a patient's clinical and hemodynamic parameters.
2. Identify critical determinants affecting oxygen delivery.
3. Construct a hemodynamic monitoring plan that incorporates data from monitoring devices and markers of perfusion.
4. Devise a treatment strategy for a patient with shock.
5. Develop a treatment pathway for the care of patients with sepsis or septic shock that incorporates current evidence and the Surviving Sepsis Campaign guideline recommendations.

Abbreviations in This Chapter

4PCC	Four-factor prothrombin complex concentrate
CO	Cardiac output
CVP	Central venous pressure
Do ₂	Oxygen delivery
ICU	Intensive care unit
IVC	Inferior vena cava
LV	Left ventricular
LVOT VTI	Left ventricular outflow tract velocity time integral
MAP	Mean arterial pressure
O ₂ ER	Oxygen extraction ratio
PAC	Pulmonary artery catheter
PCC	Prothrombin complex concentrate
PCWP	Pulmonary capillary wedge pressure
PE	Pulmonary embolism
PH	Pulmonary hypertension
PLR	Passive leg raising (test)
PPV	Pulse pressure variation
PRBC	Packed red blood cell
PVR	Pulmonary vascular resistance
rFVIIa	Recombinant activated factor VIIa
RV	Right ventricular
SBP	Systolic blood pressure
Scvo ₂	Central venous oxygen saturation
SOFA	Sequential Organ Failure Assessment
SSC	Surviving Sepsis Campaign
SV	Stroke volume
Svo ₂	Venous oxygen saturation

SVR	Systemic vascular resistance
SVV	Stroke volume variation
TEG	Thromboelastogram
TSOAC	Target-specific oral anticoagulant
Vo ₂	Oxygen consumption

Self-Assessment Questions

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

Questions 1 and 2 pertain to the following case.

An 80-year-old woman presents to the intensive care unit (ICU) with septic shock caused by an *Escherichia coli* urinary tract infection. Pertinent vital signs on admission are as follows: blood pressure 80/40 mm Hg, heart rate 155 beats/minute with a rhythm of atrial fibrillation, respiratory rate 26 breaths/minute, and temperature 105.8°F (41°C). The heart rate is sinus tachycardia on rhythm strip. On physical examination, the patient is weak, lethargic, and confused. Pertinent laboratory values are as follows: sodium (Na) 155 mEq/L, potassium (K) 3.6 mEq/L, serum creatinine (SCr) 1.8 mg/dL, and lactate 4.2 mmol/L.

1. Which clinical symptoms and physiologic variables most likely indicate that this patient has a shock syndrome?
 - A. Fever, lethargy, and tachycardia.
 - B. Hypotension, fever, and tachypnea.
 - C. Hypotension, confusion, and hyperlactatemia.
 - D. Tachypnea, fever, and hyperlactatemia.
2. Which variable is most likely contributing to impaired oxygen delivery (Do₂) to her end organs?
 - A. Serum lactate.
 - B. Atrial fibrillation.
 - C. Acute kidney injury.
 - D. Fever.
3. A 62-year-old woman (weight 119 kg) develops ventilator-associated pneumonia in the setting of prolonged intubation after aortic valve replacement surgery. Her pneumonia is complicated by septic shock, and she is given 2 L of 0.9% sodium chloride and 1 L of 5% albumin for resuscitation and initiated on norepinephrine. Her laboratory values are as follows: Na 144 mEq/L, chloride (Cl) 110 mEq/L,

- K 3.8 mEq/L, bicarbonate 18 mEq/L, SCr 1.8 mg/dL, arterial pH 7.28, and albumin 3.2 g/dL. Having determined that the patient is still fluid responsive, you would like to give another fluid bolus. Which fluid is best for the fluid bolus?
- 0.9% sodium chloride.
 - 5% albumin.
 - 6% hydroxyethyl starch.
 - Lactated Ringer solution.
4. A 48-year-old man presents to the medical ICU for septic shock secondary to a urinary tract infection. His medical history is significant only for hypertension. The patient has an initial mean arterial pressure (MAP) of 58 mm Hg and a lactate concentration of 4.8 mmol/L. The patient is initiated on broad-spectrum antimicrobials, has a central venous catheter placed in his right subclavian vein, and is resuscitated with quantitative resuscitation. The patient receives 2 L of 0.9% sodium chloride total and 2 L of lactated Ringer solution, and he is initiated on norepinephrine. Three hours after presentation, his current pertinent vital signs, hemodynamic parameters, and laboratory values are as follows: MAP 68 mm Hg on norepinephrine 8 mcg/minute, central venous pressure (CVP) 10 mm Hg, central venous oxygen saturation (ScvO₂) 72%, urine output 0.2 mL/kg/hour, and lactate 4.6 mmol/L. Which is the next best step for the patient's hemodynamic therapy?
- Continue current therapy.
 - Increase the norepinephrine dose.
 - Give 1 L of 0.9% sodium chloride.
 - Initiate dobutamine.
5. An 82-year-old man is admitted to the surgical ICU after an exploratory laparotomy and small bowel resection for a small bowel obstruction that was complicated by fecal peritonitis and hypotension. The patient received 2 L of lactated Ringer solution, 500 mL of 5% albumin, and 500 mL of 6% hydroxyethyl starch in the operating room, but vasopressors were never initiated. He remains intubated and mechanically ventilated, requiring a 90% fraction of inspired oxygen (FIO₂), and has the following vital signs: heart rate 131 beats/minute in atrial fibrillation, MAP 62 mm Hg (by arterial blood pressure catheter), respiratory rate 22 breaths/minute, and temperature 100.8°F (38.2°C). An arterial blood gas reveals a lactate concentration of 5.2 mmol/L. An arterial pulse pressure waveform analysis monitor reveals a pulse pressure variation (PPV) of 18%. The patient has a central venous catheter in his right femoral vein. Which next step is best?
- Give 1 L of 0.9% sodium chloride.
 - Do a passive leg raising (PLR) test.
 - Measure CVP.
 - Send a blood gas for venous oxygen saturation.
6. A 19-year-old man is admitted to the medical ICU for hypotension after being stung by a bee. He was given intramuscular epinephrine by emergency medical services and transferred to the emergency department (ED). On arrival at the ED, his blood pressure was 78/42 mm Hg; he was given 1 L of 0.9% sodium chloride, diphenhydramine, famotidine, and methylprednisolone. The patient remained hypotensive but responded to an additional 2 L of 0.9% sodium chloride. He was transferred to the medical ICU for further treatment. On arrival in the medical ICU, his MAP is 62 mm Hg. A right internal jugular central venous catheter is placed, which reveals CVP 3 mm Hg, ScvO₂ 61%, venous lactate concentration 4.4 mmol/L, and hemoglobin (Hgb) 9.6 g/dL. Together with further fluid resuscitation, which agent would be best to initiate or administer?
- Packed red blood cells (PRBCs).
 - Dobutamine.
 - Milrinone.
 - Norepinephrine.
7. A 41-year-old man presents to the ED after a motorcycle accident. While the patient is being evaluated, it is apparent that he has broken ribs, a broken pelvis, and bilateral broken femurs. He is confused, and his vital signs are as follows: blood pressure 82/48 mm Hg, heart rate 125 beats/minute, respiratory rate 34 breaths/minute, and temperature 95°F (35°C). Which most accurately reflects this patient's class of hypovolemic shock?
- I.
 - II.
 - III.
 - IV.

8. A 66-year-old man with a medical history of non-small cell lung cancer presents to the ED with new-onset shortness of breath. A chest computed tomography (CT) scan reveals a pulmonary embolism (PE) at the bifurcation of the right and left pulmonary arteries. The patient is initiated on parenteral anticoagulation and transferred to the medical ICU. On admission to the medical ICU, the patient develops pulseless electrical activity. He is intubated and mechanically ventilated, with recovery of spontaneous circulation after one round of chest compressions and administration of epinephrine 1 mg. Which is the next best step to evaluate and/or treat this patient's PE?
- A. Administer alteplase 100 mg infused over 2 hours.
 - B. Check a troponin T concentration.
 - C. Check a brain natriuretic peptide concentration.
 - D. Do a transthoracic echocardiogram (TTE).
9. A 56-year-old man (weight 66 kg) presents to the ED with presumed community-acquired pneumonia. Blood cultures are obtained, and the patient is given ceftriaxone 1 g and levofloxacin 750 mg. His initial blood pressure is 83/47 mm Hg with a lactate concentration of 6.2 mmol/L, and he is given 1.5 L of 0.9% sodium chloride over 1 hour. Subsequently, his blood pressure is 92/54 mm Hg with a lactate concentration of 4.6 mmol/L and urine output of 30 mL/hour. A central venous catheter placed in his right internal jugular vein shows a CVP of 6 mm Hg, and a venous blood gas reading obtained from the central venous catheter shows an $ScvO_2$ of 63%, Hgb 9.2 g/dL, and hematocrit (Hct) 28%. Which would be the best therapy for this patient right now?
- A. 0.9% sodium chloride.
 - B. 5% albumin.
 - C. Phenylephrine.
 - D. PRBCs.
10. A 68-year-old woman (weight 88 kg) presents to the ED with a urinary tract infection. Her medical history is significant for paroxysmal atrial fibrillation. The patient's vital signs in the ED are as follows: blood pressure 83/47 mm Hg, heart rate 118 beats/minute in atrial fibrillation, respiratory rate 24 breaths/minute, and temperature 102°F (38.9°C). Her laboratory values of interest in the ED include white blood cell count (WBC) 19.6×10^3 cells/mm³, Hgb 9.3 g/dL, albumin 2.4 g/dL, lactate 4.9 mmol/L, and SCr 1.2 mg/dL. Blood and urinary cultures are obtained, and she receives levofloxacin 750 mg and 3 L of 0.9% sodium chloride. Thirty minutes after completing the 0.9% sodium chloride infusion, her blood pressure is 92/49 mm Hg with a lactate concentration of 4.6 mmol/L and urine output of 30 mL/hour. Which would be the best therapy for this patient right now?
- A. Norepinephrine.
 - B. Vasopressin.
 - C. Phenylephrine.
 - D. Dopamine.
11. A 34-year-old man is admitted to the surgical ICU with septic shock associated with necrotizing soft tissue infection of the right leg. He received 100% oxygen by high-flow mask; adequate broad-spectrum antibiotics with vancomycin, piperacillin/tazobactam, and clindamycin; and quantitative resuscitation. The patient has been resuscitated for the past 4 hours with 5 L of normal saline and currently is hemodynamically unstable on norepinephrine 14 mcg/minute with a corresponding blood pressure of 92/45 mm Hg and heart rate of 132 beats/minute in sinus rhythm. His CVP is 12 mm Hg, $ScvO_2$ 72%, urine output 0.3 mL/kg/hour, and lactate 7.4 mmol/L. Which would be best to initiate for this patient?
- A. 0.9% sodium chloride.
 - B. Vasopressin.
 - C. Phenylephrine.
 - D. Epinephrine.

I. INTRODUCTION

A. Shock

1. Shock is a heterogeneous group of syndromes best defined as “acute circulatory failure.” This arises when the tissues receive an insufficient supply of oxygen to be able to perform vital metabolic function.
2. The clinical presentation of shock may be subtle. The diagnosis of shock typically includes the interpretation of three variables: hemodynamic assessment, clinical presentation, and biochemical signs.
3. Shock is often categorized into four distinct etiology mechanisms: (1) hypovolemic, (2) obstructive, (3) distributive and vasodilatory, and (4) cardiogenic. It is important to recognize clinical scenarios in which various shock syndromes may be occurring at the same time.
4. In many cases, shock is first identified in the presence of arterial hypotension. However, it is important to recognize that the blood pressure limits used are arbitrary and may not be patient-specific (e.g., a patient with hypertension before critical illness). The typical value used for systolic blood pressure (SBP) is less than 90 mm Hg, or a MAP less than 70 mm Hg. These values may vary within a range to permit autoregulation, allowing acceptable perfusion in the setting of acute hypotension.
5. Clinical presentation of shock can manifest in many different ways. Usually, shock is identified through an assessment of mentation, skin, and kidney function.
 - a. Assessment of mentation should include a careful examination for signs of confusion and obtundation. These signs should be compared with those in the patient’s preexisting status. This may be challenging in a patient with a poor medical history or a diminished baseline status.
 - b. Evidence of an existing shock syndrome can manifest with decreased capillary refill and cold, clammy skin.
 - c. Altered kidney function in the setting of shock primarily presents with reduced urine output (e.g., less than 0.5 mL/kg/hour). Laboratory values such as SCr often lag behind the immediate observation of urine volume and quality.
6. Biochemical assessment reveals hyperlactatemia (greater than 2 mmol/L) or reduced Svo₂ (less than 70%). This usually indicates abnormal cellular oxygen metabolism.

B. Physiology

1. Hemodynamic parameters can either be directly measured from a monitoring device or calculated according to direct measurements (see Table 1).

Table 1. Hemodynamic and Oxygen Transport Parameters

Value	Equation (as applicable)	Normal Value
Systolic blood pressure (SBP)		90–140 mm Hg
Diastolic blood pressure (DBP)		60–90 mm Hg
Mean arterial blood pressure (MAP) ^a	$[SBP + (2 \times DBP)]/3$	70–100 mm Hg
Heart rate (HR)		60–80 beats/min
Cardiac output (CO) ^b	$HR \cdot SV$	4–7 L/min
Cardiac index (CI)	CO/BSA	2.5–4.2 L/min/m ²
Stroke volume (SV)	CO/HR	60–130 mL/beat
Pulmonary artery systolic pressure (PASP)		20–30 mm Hg
Pulmonary artery diastolic pressure (PADP)		8–12 mm Hg
Mean pulmonary artery pressure (mPAP)	$[PASP + (2 \times PADP)]/3$	12–15 mm Hg

Table 1. Hemodynamic and Oxygen Transport Parameters (*continued*)

Value	Equation (as applicable)	Normal Value
Pulmonary capillary wedge pressure (PCWP) or pulmonary arterial occlusion pressure (PAOP)		5–12 mm Hg
Central venous pressure (CVP) or right atrial pressure (RAP)		2–6 mm Hg
Pulmonary vascular resistance (PVR) ^c	$80 \times [(\text{mPAP} - \text{PCWP})/\text{CO}]$ (divide by 80 for Wood units)	20–120 dynes•s•cm ⁻⁵ (< 2 Wood units)
Systemic vascular resistance (SVR) ^c	$80 \times [(\text{MAP} - \text{CVP})/\text{CO}]$	800–1200 dynes•s•cm ⁻⁵
Oxygen delivery (Do ₂)	$10 \times \text{CO (L/min)} \times \text{CaO}_2$	520–570 mL/min/m ²
Arterial oxygen content (CaO ₂)	$(1.34 \times \text{Hgb} \times \text{Sao}_2) + (0.003 \times \text{Pao}_2)$	20 mL/dL
Venous oxygen content (CvO ₂)	$(1.34 \times \text{Hgb} \times \text{Svo}_2) + (0.003 \times \text{Pvo}_2)$	15 mL/dL
Resting oxygen consumption (Vo ₂)	$10 \times \text{CO (L/min)} \times (\text{CaO}_2 - \text{CvO}_2)$	110–160 mL/min/m ²
Oxygen extraction ratio (O ₂ ER)	$\text{Vo}_2/\text{Do}_2 \times 100$	20%–30%

^aMay be directly measured or calculated.

^bMay be measured using several mechanisms, including thermodilution with a pulmonary artery catheter. May also be calculated using the Fick equation (see later in the chapter).

^cMay also be expressed as an indexed value calculated by multiplying the value by body surface area.

BSA = body surface area in square meters.

Modified with permission from: Wittbrodt ET, Tietz KJ. Shock syndromes. In: Carter BL, Lake KD, Raebel MA, et al., eds. Pharmacotherapy Self-Assessment Program, 3rd ed. Module 2: Critical Care. Kansas City, MO: American College of Clinical Pharmacy, 1998:87-127.

2. MAP is the driving pressure for peripheral blood flow (and end-organ perfusion). Sufficient arterial pressure allows redistribution of cardiac output (CO) to vital organs.
3. Blood pressure is the product of CO and systemic vascular resistance (SVR).
4. CO is the product of heart rate and stroke volume (SV).
5. SV is determined by many factors, but predominantly preload, intrinsic contractility, and afterload.
 - a. Preload refers to ventricular end-diastolic volume and is proportionally related to SV (i.e., when preload increases, the SV increases) by the Frank-Starling mechanism (though the magnitude of the proportionality is reduced beyond a point of ventricular end-diastolic volume).
 - b. Intrinsic contractility is the ability of the myocardium to contract and may be reduced by several factors, including myocardial ischemia, cardiomyopathy, and sepsis.
 - c. Afterload is the force the ventricle must overcome to eject its volume and is inversely related to SV (i.e., when afterload increases, the SV decreases). Left ventricular (LV) afterload is predominantly influenced by aortic pressure, whereas right ventricular (RV) afterload is predominantly influenced by pulmonary artery pressure.
6. SVR (also termed *total peripheral resistance*) is the resistance to flow that must be overcome by the left ventricle.
 - a. SVR is the major determinant of LV afterload.
 - b. Systemic vasoconstriction increases SVR, whereas vasodilation decreases SVR.
 - c. Skin temperature may be used as an approximation (surrogate) of SVR, in which warm skin temperature suggests decreased SVR (vasodilation), and cold skin temperature suggests increased SVR (vasoconstriction).
7. The right ventricle better tolerates increases in ventricular volume (preload) than increases in afterload. Contrarily, the left ventricle better tolerates increases in afterload than increases in ventricular volume.

8. Coronary artery perfusion for the left ventricle occurs primarily in diastole, whereas coronary artery perfusion for the right ventricle occurs in both systole and diastole. Aortic diastolic pressure must be sufficient to ensure perfusion of the coronary arteries.

C. Oxygen Delivery and Consumption

1. The circulatory system delivers oxygen and vital nutrients to the tissue beds for homeostasis and end-organ function.
2. Oxygen is inspired and delivered to the alveoli, where it binds reversibly to hemoglobin.
3. Oxygen is then transported by CO to the tissues. The rate of DO_2 is the product of the CO and arterial oxygen content (CaO_2), as described in Table 1. Metabolic function of tissue beds requires consistent DO_2 .
4. At the tissues, oxygen dissociates from hemoglobin and is taken up by the mitochondria through systemic capillaries for aerobic metabolism. Oxygen uptake or oxygen consumption (VO_2) is the rate at which oxygen transfers from systemic capillaries into the tissues and is the by-product of CO, CaO_2 , and venous oxygen content (CvO_2).
5. The Fick equation states that $\text{CO} = \text{VO}_2 / (\text{CaO}_2 - \text{CvO}_2)$.
6. The oxygen extraction ratio (O2ER), or the ratio of $\text{VO}_2 / \text{DO}_2$, is 20%–30% at resting state, meaning that about 25% of oxygen delivered to the capillaries is taken up by the tissues. The O2ER is relatively stable and can accommodate temporary fluctuations in DO_2 or VO_2 . Sustained $\text{DO}_2 / \text{VO}_2$ mismatches contribute to tissue hypoxia and deranged metabolic function.
7. Treatment of shock syndromes should be rapid to minimize permanent tissue organ damage.
8. In the early stages of a shock state, blood pressure is preserved through stimulation of the sympathetic system, release of endogenous vasopressin, and vasoconstriction through the formation of angiotensin II. The synergy of these actions preserves blood flow and DO_2 to vital organs.
9. Blood flow is prioritized to maximize DO_2 to the heart and brain. Consequently, blood flow to extravital organs (e.g., skin, gut, kidneys) is redirected.
10. When the endogenous response to shock is insufficient, blood pressure declines, and overt shock develops.

II. MONITORING TECHNIQUES

A. Hemodynamic Monitoring Devices

1. Hemodynamic variables may be obtained through noninvasive or invasive monitoring devices (Table 2).
2. In general, less invasive devices are desired, but they often have limited accuracy in estimating hemodynamic parameters (compared with invasive devices).
3. Some ICU monitors can display additional hemodynamic parameters (e.g., automated PPV from an arterial catheter) without additional equipment or devices.

Table 2. Hemodynamic Monitoring Devices

Device or Category	Obtainable Parameters	Advantages	Limitations
Noninvasive BP monitoring ^a	SBP, DBP, MAP	• Noninvasive • Bedside practitioner familiarity	• Limited accuracy in shock • Does not provide continuous monitoring • Less sensitive in predicting end-organ dysfunction

Table 2. Hemodynamic Monitoring Devices (*continued*)

Device or Category	Obtainable Parameters	Advantages	Limitations
Arterial BP catheter	SBP, DBP, MAP	• More accurate BP measurement in shock than noninvasive methods • Ready access for arterial blood gas sampling • Continuous monitoring	• Invasive • Inaccurate damping influences SBP and DBP measurements (MAP still accurate) • Catheter-related infection • Brachial site lacks collateral circulation (may result in decreased arterial perfusion)
Left atrial catheter	Measured left atrial pressures	• More accurate measurement of LV preload	• Risk of air embolus
Central venous catheter (CVC)	CVP/RAP, Scvo ₂	• Easier and safer to insert than a PAC • Scvo₂ may be available as a continuous measurement • Access for administration of highly osmotic and caustic agents	• CVP/RAP not a true estimate of LV end-diastolic pressure • CVP/RAP does not accurately predict fluid responsiveness • Scvo₂ not equivalent to Svo₂ (see later in the chapter)
Pulmonary artery catheter (PAC)	Measured: PASP, PADP, mPAP, CVP/RAP, PCWP/PAOP, CO, and CI by thermodilution or continuous measurement (copper filament-adapted catheter), Svo₂ Calculated: PVR, SVR, CO, and CI by Fick equation, SV	• Only method available to directly measure pulmonary artery pressures • Direct measurement of CO and Svo₂ (may be available as continuous variables)	• Outcomes data supporting superiority to CVC lacking • May cause arrhythmias • Assumes right heart function approximates left heart function (usually, but not always, true) • Fick CO calculation typically uses an estimated value for oxygen consumption, which may be falsely low in a patient with septic shock (and underestimate CO) • Valvular abnormalities may make values inaccurate (particularly mitral stenosis, mitral regurgitation, tricuspid regurgitation, or aortic regurgitation) • Correct catheter tip location (lung zone 3) needed for accurate readings

Table 2. Hemodynamic Monitoring Devices (*continued*)

Device or Category	Obtainable Parameters	Advantages	Limitations
Echocardiography	Cardiac chamber size and function, pericardial appearance (and presence of fluid), inferior vena cava (IVC) collapsibility, ejection fraction, RVSP (an estimate of PASP), LVOT VTI (to calculate CO/CI)	• Noninvasive (transthoracic) • Visualization of ventricular function instead of presumed function based on CO • IVC collapsibility can predict fluid responsiveness	• Subjectivity of user assessment • Not done continuously; therefore, cannot detect acute changes or must be repeated when the patient's status changes
Esophageal Doppler (ODM II, CardioQ, HemoSonic 100)	CO and CI	• Ease of use • Bedside practitioner familiarity	• Assumptions used by the device may not be valid in the setting of hemodynamic instability (fixed partition of blood flow to cephalic vessels and descending aorta, constant aortic cross-sectional area) • Accuracy depends on position (need for frequent repositioning)
Arterial pulse pressure waveform analysis (FloTrac/Vigileo, PiCCOplus, PulsioFlex, LiDCO plus, PRAM-MostCare, Nexfin)	CO and CI, SV, SVR (calculated), SVV, PPV Continuous ScvO ₂ measurement may also be available with a separate module attached to a CVC	• Continuous measurement of values • Allows for assessment of SVV and PPV, which are dynamic markers of fluid responsiveness in mechanically ventilated patients (see later in the chapter) • Minimally invasive (Nexfin is noninvasive)	• Accuracy relies on optimal arterial waveform from arterial catheter • Inaccurate in patients with mitral or aortic valve disease or when used concomitantly with an intra-aortic balloon pump • Arrhythmias reduce the accuracy of reported CO and CI (though this may be accounted for by internal software with some devices) • Accuracy may be limited during rapid changes in vascular resistance • Some devices require a CVC in addition to an arterial pressure catheter • Interpretation of SVV and PPV is limited by the need for positive pressure ventilation and relatively large tidal volumes • SVV and PPV are not accurate predictors of fluid responsiveness in the setting of arrhythmias

Table 2. Hemodynamic Monitoring Devices (*continued*)

Device or Category	Obtainable Parameters	Advantages	Limitations
Bioimpedance/bioreactance (NICOM, BioZ, ECOM)	Continuous CO and CI, SV, SVR SVV (NICOM)	• Noninvasive • NICOM CO correlates well with CO values from thermodilution and pulse pressure waveform analysis	• Conflicting validation results with BioZ and ECOM, particularly in patients with septic shock • ECOM requires endotracheal intubation

*Includes manual sphygmomanometry and automated oscillometric (cuff) techniques.

BP = blood pressure; CI = cardiac index; DBP = diastolic blood pressure; LV = left ventricular; LVOT VTI = left ventricular outflow tract velocity time integral; PAOP = pulmonary arterial occlusion pressure; PPV = pulse pressure variation; RAP = right atrial pressure; RVSP = right ventricular systolic pressure; SVV = stroke volume variation.

Information from: Alhashemi JA, Cecconi M, Hofer CK. Cardiac output monitoring: an integrative perspective. Crit Care 2011;15:214.

B. Markers of Perfusion

1. Global perfusion

- a. End-organ function (altered mental status, low urine output, and mottled skin, as noted earlier)
- b. Elevated blood lactate concentration (above 2 mmol/L)
 - i. Lactate is produced from pyruvate by lactate dehydrogenase as an end product of glycolysis under anaerobic conditions.
 - ii. Most lactate is cleared by the liver (by conversion back to pyruvate in the Cori cycle), with a small amount cleared by the kidneys. Severe liver dysfunction may impair lactate clearance and accentuate lactate concentration elevations in shock.
 - iii. Elevated lactate concentrations may be the result of increased production, decreased clearance, or both.
 - (a) Type A lactic acidosis occurs in the setting of DO_2/VO_2 mismatch (oxygen demand exceeds supply).
 - (b) Type B lactic acidosis is not related to tissue hypoxia and typically occurs in the setting of impaired lactate clearance or medication-related causes (e.g., metformin, epinephrine, linezolid, or toxic alcohols).
 - iv. Arterial and venous lactate concentrations are slightly different in value but may be used interchangeably.
- c. Venous oximetry (ScvO_2 and SvO_2)
 - i. ScvO_2 and SvO_2 are the oxyhemoglobin saturation of venous blood obtained from a central vein and the pulmonary artery, respectively, and are expressed as a percentage.
 - ii. ScvO_2 is obtained from a subclavian or internal jugular central venous catheter where the catheter tip terminates in the superior vena cava. As such, ScvO_2 is more reflective of oxygen extraction in the brain and upper body than is systemic oxygen extraction. Of importance, the oxyhemoglobin saturation of blood obtained from a femoral central venous catheter cannot be used interchangeably with an ScvO_2 obtained from a thoracic central venous catheter and should not be used as a marker of perfusion.
 - iii. SvO_2 is a better representation of systemic oxygen extraction because it represents the mixing of venous blood from the superior vena cava, inferior vena cava (IVC), and coronary sinus.
 - iv. In normal physiology, ScvO_2 is about 2%–3% lower than SvO_2 because the upper body and the heart extract more oxygen than the lower body.
 - v. In the setting of shock, ScvO_2 exceeds SvO_2 by about 5%–8% because of increased mesenteric and renal oxygen extraction (with a similar cerebral extraction ratio).
 - vi. The difference between ScvO_2 and SvO_2 decreases in low CO states.

- vii. Although $ScvO_2$ and SvO_2 are not equivalent, they have a good (albeit not perfect) correlation, and $ScvO_2$ may be a reasonable approximation of SvO_2 .
 - viii. An $ScvO_2$ obtained from a central venous catheter with the tip terminating at the entrance or in the right atrium gives a better approximation of SvO_2 than an $ScvO_2$ obtained from a central venous catheter with the tip terminating in the superior vena cava far from the right atrium.
 - ix. A decreased $ScvO_2$ or SvO_2 is a sign that tissue oxygen demands are not completely met by Do_2 (more discussion on this topic later in this chapter).
 - x. Rearrangement of the Fick equation shows that a decrease in SvO_2 indicates a decrease in CO , whereas an increase in SvO_2 indicates an increase in CO .
 - xi. In general, SvO_2 values above 70% are considered adequate, whereas SvO_2 values less than 40% are considered critically low and approach the critical O_2ER (where anaerobic metabolism will occur and lactate concentrations will increase). SvO_2 values of 50%–70% by themselves do not lead to firm conclusions about the O_2ER ; they must be interpreted in the context of other markers of tissue perfusion (e.g., lactate concentrations).
 - xii. SvO_2 values above 80% likely indicate poor tissue oxygen extraction capacity.
 - (a) This may occur because of the heterogeneity of microvascular and macrovascular blood flow (i.e., microcirculatory dysfunction), peripheral shunting of oxygen past the tissues, or impaired mitochondrial oxygen use.
 - (b) Patients with septic shock and venous hyperoxia ($ScvO_2$ greater than 89%) within the first 6 hours of their treatment had a higher mortality than those with normoxia ($ScvO_2$ 71%–89%).
2. Regional tissue perfusion
- a. Microcirculatory blood flow
 - i. The microcirculation consists of arterioles, capillaries, and venules and is where oxygen release to the tissues occurs.
 - ii. Traditional resuscitation strategies have focused on hemodynamic and Do_2 end points (the “macrocirculation”), but the microcirculation plays a key role in tissue oxygenation in shock (particularly in septic shock) and has historically been overlooked.
 - iii. Of importance, microcirculatory blood flow (and Do_2) cannot be predicted by global (macrocirculatory) hemodynamics.
 - iv. Microcirculatory blood flow can be visualized with orthogonal polarization spectral imaging or sidestream darkfield imaging. These devices use green light to illuminate tissue, which is absorbed by the hemoglobin of red blood cells. This allows the microcirculation to be visualized because of its red blood cell content.
 - v. The sublingual microcirculation has been studied most often because of its accessibility.
 - vi. Studies have shown that the microcirculation is often altered in patients with sepsis, persistent microvascular alterations are associated with multisystem organ failure and death, alterations are more severe in non-survivors than in survivors, and improvements in microcirculatory blood flow correspond with improved patient outcomes.
 - vii. Decreased vascular density, decreased capillary perfusion, and a decreased percentage of perfused small vessels are the most commonly described microcirculatory alterations. The proportion of perfused small vessels seems to be the strongest microcirculatory blood flow predictor of patient outcomes. In one study of patients with sepsis and septic shock, this was a stronger predictor of mortality than global hemodynamic markers.
 - viii. Heterogeneity in observations of microcirculatory blood flow in the same tissue bed (with as little as a few millimeters between observations) and between different tissue beds has been observed.

- ix. Evaluation of the microcirculation is not commonly used in clinical practice because it requires extensive user experience to obtain proper measurements and time to analyze the results. However, this is an attractive marker of tissue perfusion that, with technical advances, may be used more commonly in the future.
- b. Gastric tonometry
 - i. As a non-vital organ, the gut has blood flow diverted away from it in the setting of shock. As such, the gut is very sensitive to changes in perfusion and oxygenation.
 - ii. Gastric tonometry is a technique to indirectly assess gastric mucosal perfusion by placing a balloon tonometer in the lumen of the stomach.
 - iii. Gastric luminal PCO_2 is measured by the tonometer.
 - iv. Increases in gastric PCO_2 and in the difference (gap) between gastric and arterial PCO_2 suggest splanchnic hypoperfusion.
 - v. Although theoretically helpful as a resuscitation target for tissue perfusion, clinical studies comparing resuscitation with gastric tonometry goals have not consistently shown patient outcome benefits over conventional resuscitation goals.
 - vi. Gastric tonometry is subject to many sources of measurement error and is not widely available or widely used.
- c. Near-infrared spectroscopy (NIRS)
 - i. NIRS is a noninvasive method of measuring tissue oxygen saturation (StO_2) in a skeletal muscle.
 - ii. The method uses spectroscopy to detect the fractions of oxygenated and deoxygenated hemoglobin in the microcirculation, which is then expressed as StO_2 . Because most blood in a skeletal muscle is venous, StO_2 mainly represents local venule oxygen saturation.
 - iii. StO_2 is the aggregate of (venule) oxygen saturation in the muscle sampled and does not represent microcirculatory blood flow. As such, NIRS cannot identify heterogeneous blood flow. In addition, a change in StO_2 cannot differentiate the cause between a change in DO_2 and consumption.
 - iv. The correlation between StO_2 and SvO_2 is poor in patients with septic shock, and StO_2 cannot be used as a surrogate for SvO_2 .
 - v. Low StO_2 (less than 75%) has been associated with the development of organ dysfunction in patients with trauma, but this marker is better used for its negative predictive value (91%) than for its positive predictive value (18%).
 - vi. NIRS may also be used with a vascular occlusion test to assess microvascular reserve (it is not an assessment of microvascular perfusion). Alterations in the slope of the increase in StO_2 measurements after reperfusion have been associated with survival in patients with septic shock.
 - vii. The accuracy of measurements from NIRS is influenced by the thickness of adipose tissue and tissue edema. As such, NIRS is not useful for many patients with shock.
 - viii. Interventional studies showing the benefit of incorporating StO_2 into resuscitation protocols are lacking, and use of this marker in clinical practice cannot currently be recommended.
- d. Elevated lactate concentrations may also indicate regional tissue hypoperfusion (e.g., mesenteric ischemia or critical limb ischemia).

Patient Case

1. A 77-year-old man presents to the ED with light-headedness and fatigue. He reports increasing melena during the past 24 hours. His medical history is significant for hypertension, asthma, and gastroesophageal reflux disease. Vital signs in the ED are as follows: blood pressure 88/54 mm Hg, heart rate 124 beats/minute, respiratory rate 18 breaths/minute, and temperature 102.2°F (39°C). While interviewing the patient, you note that he appears lethargic and confused. His serum chemistry panel results are as follows: Na 138 mEq/L, K 3.8 mEq/L, Cl 105 mEq/L, carbon dioxide 22 mEq/L, blood urea nitrogen (BUN) 25 mg/dL, SCr 1.1 mg/dL, and glucose 78 mg/dL. Results of the complete blood cell count (CBC) are as follows: WBC 10.2×10^3 cells/mm³, Hgb 6.6 g/dL, Hct 19.2%, and platelet count (Plt) 180,000/mm³. Which value is most likely contributing to compromised Do₂ to the end organs in this patient?
 - A. Medical history of hypertension.
 - B. Reduced hemoglobin.
 - C. Tachycardia.
 - D. Leukocytosis.

III. DIFFERENTIATION OF SHOCK STATES

- A. Typically based on assessments of preload (CVP or pulmonary capillary wedge pressure [PCWP]), CO (Scvo₂ or Svo₂ may serve as a surrogate), and afterload (SVR) (see Table 3)
- B. Values to describe this hemodynamic profile have historically been obtained from a pulmonary artery catheter (PAC), but use of bedside echocardiography is now recommended as the preferred modality to initially evaluate the type of shock.
- C. As such, evaluation of echocardiography results is key, with surrogates for preload (LV size) and CO (ventricular function and left ventricular outflow tract velocity time integral [LVOT VTI]) able to be obtained.

Table 3. Hemodynamic Profiles of Shock States

Shock State	CVP	PCWP	CO	SVR
Hypovolemic	↓ ^a	↓ ^a	↓	↑
Cardiogenic	↑	↑	↓ ^a	↑
Obstructive				
Impaired diastolic filling (e.g., cardiac tamponade)	↑	↑	↓ ^a	↑
Impaired systolic contraction (e.g., massive PE)	↑	↓ or ↔	↓ ^a	↑
Vasodilatory/distributive				
Pre-resuscitation	↓	↓	↓	↓ ^a
Post-resuscitation	↑	↑	↑	↓ ^a

^aPathophysiologic hallmark of shock state.

PE = pulmonary embolism; SVR = systemic vascular resistance.

Information from: Vincent JL, De Backer D. Circulatory shock. N Engl J Med 2013;369:1726-34, Dellinger RP. Cardiovascular management of septic shock. Crit Care Med 2003;31:946-55, and Weil MH, Shubin H. Proposed reclassification of shock states with special reference to distributive defects. Adv Exp Med Biol 1971;23:13-23.

- D. The hemodynamic profiles in Table 3 are observed exclusively in the stated shock state, which often does not occur in practice. Indeed, patients often have features of combined shock states.

IV. RESUSCITATION PARAMETERS AND END POINTS

- A. The approach to treating a patient with circulatory shock can be divided into four phases, each having different (and sometimes overlapping) treatment goals and therapeutic strategies.
1. The first phase is focused on salvage, in which a minimum perfusion pressure and CO must be achieved to maintain the patient's survival. Treatment of the underlying cause of the patient's shock, which consists of life-saving measures, should be undertaken at this time. Examples of these measures include antimicrobials for sepsis, revascularization for acute myocardial infarction, and surgical hemostasis for trauma.
 2. Optimization is the second phase, with the goal to ensure adequate Do_2 .
 3. In the third phase, patient stabilization is targeted, with the goal of preventing (further) end-organ dysfunction.
 4. The fourth phase is de-escalation, where the goals of therapy include vasoactive medications weaning (or cessation) and fluid elimination (e.g., diuresis or ultrafiltration).
 5. Although the rest of this chapter will focus on the first two phases, understanding the phase of a patient's circulatory shock is essential for establishing treatment goals and subsequent therapeutic approaches.
- B. Blood Pressure
1. As noted earlier, blood pressure is the driving pressure for peripheral blood flow. As such, an adequate blood pressure is vital to ensure end-organ perfusion.
 2. MAP is the true driving pressure for peripheral blood flow (and end-organ perfusion) and is preferred to SBP as a therapeutic target.
 3. The perfusion pressure of any organ can be calculated by subtracting the pressure within the organ or anatomic space from the MAP (e.g., cerebral perfusion pressure = MAP – intracranial pressure).
 4. The target blood pressure for a patient in shock is usually a MAP greater than 65 mm Hg or an SBP greater than 90 mm Hg, but this must be individualized according to perfusion.
 5. MAP is an insensitive hemodynamic resuscitation parameter because it is influenced by many hemodynamic variables (e.g., blood pressure may be at goal when CO is inadequate). Therefore, additional resuscitation parameters should be used to ensure the optimization of all hemodynamic components that may influence end-organ perfusion and Do_2 .
 6. These additional resuscitation goals typically include ensuring (1) adequate end-organ perfusion, (2) lack of fluid responsiveness, and (3) adequate Do_2 .
- C. Adequate End-Organ Perfusion
1. Each organ has a critical perfusion pressure that must be exceeded to maintain adequate perfusion. This critical perfusion pressure is organ- and patient-specific (because of adaptation for chronic conditions).
 2. As the MAP decreases, the perfusion pressure of the organ decreases, and subsequently, organ function decreases.
 3. Adequate organ perfusion is best assessed clinically on a per-patient basis.
 4. General goals of therapy include resolution of altered mental status and adequate urine output (above 0.5 mL/kg of body weight per hour). These goals may be challenging to assess, though, in patients who are given medications that mask the ability to assess the organ function (e.g., sedatives) or in patients with chronic organ dysfunction (e.g., end-stage renal disease).

D. Lack of Fluid Responsiveness

1. Intravenous fluids are given to increase preload and subsequently increase SV, increase CO, and increase DO_2 .
2. Fluids should be given only if there is inadequate effective organ perfusion caused by inadequate CO (presumably because of inadequate SV) and if the patient is fluid responsive.
 - a. Fluid responsiveness is defined as at least a 10%–15% increase in CO after fluid administration.
 - b. This is best assessed by giving a fluid challenge and evaluating the response.
 - c. A change in blood pressure is not a reliable indicator of CO response to a fluid challenge; an assessment of CO (or SV) change should instead be used.
 - d. In one systematic review, only 57% of hemodynamically unstable patients were fluid responsive.
3. Patients given additional fluid when they are no longer fluid responsive will not have the beneficial effects of fluid (increased CO)—only the detrimental effects (e.g., pulmonary edema). Although an argument could be made to determine fluid responsiveness in each patient, it is most critical in patients for whom detrimental fluid effects cannot be tolerated (e.g., those with refractory hypoxemia in the setting of shock).
4. Fluid responsiveness may be predicted by either static markers or dynamic markers.
 - a. Static markers of fluid responsiveness include the cardiac filling pressures CVP and PCWP.
 - b. Dynamic markers of fluid responsiveness include stroke volume variation (SVV), systolic pressure variation, PPV, and IVC variation.
5. Although CVP and PCWP may help differentiate shock states, they are not reliable predictors of fluid responsiveness.
 - a. In one study of patients with severe sepsis and septic shock, a CVP less than 8 mm Hg and a PCWP less than 12 mm Hg had fluid responsiveness positive predictive values of 47% and 54%, respectively.
 - b. Systematic reviews and meta-analyses suggest that CVP should not be used as a resuscitation parameter.
6. Fluid responsiveness is better predicted by dynamic markers of fluid responsiveness than by static markers of fluid responsiveness.
7. The areas under the receiver operating characteristic curve (with the optimal area of 1) for predicting fluid responsiveness are as follows: PPV 0.94 (95% confidence interval [CI], 0.93–0.95), systolic pressure variation 0.86 (0.82–0.90), and SVV 0.84 (0.78–0.88). In contrast, the area under the receiver operating characteristic curve for predicting fluid responsiveness for CVP is 0.55 (0.48–0.62).
8. Because of their ability to be obtained from monitoring devices, PPV and SVV are more commonly used in practice than is systolic pressure variation.
9. The dynamic markers PPV, SVV, and IVC collapsibility are based on heart-lung interactions in mechanically ventilated patients.
 - a. In mechanically ventilated patients, a controlled positive pressure breath increases pleural pressure. This increase in intrathoracic pressure leads to a decrease in venous return, decreased RV preload, and decreased RV SV. LV preload is subsequently decreased, which may lead to a decrease in LV SV.
 - b. Patients who are preload (fluid) responsive (on the steep rather than the flat portion of the Frank-Starling curve) will have relatively large changes in LV SV with positive pressure breaths. This leads to variation in the LV SV between periods with and without positive pressure breaths.
 - c. Some ICU monitors can display automated PPV from an arterial catheter without additional monitoring equipment or devices.
 - d. The specific values of PPV and SVV used to predict fluid responsiveness vary by study, specific conditions (e.g., the use of vasopressors), and assessment method or device. In a systematic review, thresholds to predict fluid responsiveness were PPV greater than 12.5% and SVV greater than 11.6%.

- e. IVC variation (also termed *IVC collapsibility* or *IVC distensibility*) uses echocardiography to visualize the diameter of the IVC during positive pressure ventilation. With a positive pressure breath, venous return is impaired, and the diameter of the IVC increases. The change in IVC diameter during inspiration is higher in patients who are fluid responsive than in those who are not fluid responsive.
 - i. In one study, an IVC diameter change above 12% predicted fluid responsiveness with a positive predictive value of 93% and a negative predictive value of 92%.
 - ii. In another study, the area under the receiver operating characteristic curve for predicting fluid responsiveness for IVC distensibility was 0.84 (95% CI, 0.63–1.0), and the best cutoff was 16% (sensitivity 67%, specificity 100%).
- 10. The PLR test measures the hemodynamic effects of a positional change in the patient's legs. Lifting the legs passively from the horizontal position to a 45-degree angle (or a change in position of the patient's bed) leads to a transfer of blood from the abdominal compartment and lower extremities to the intrathoracic compartment.
 - a. This increase in venous return may subsequently increase SV and CO (if the patient is preload responsive).
 - b. The benefit of the PLR test is that it can be used in spontaneously breathing, nonintubated patients. In addition, it does not require the administration of fluid (which may be detrimental if the patient is not fluid responsive) and can easily be reversed by returning patients to their previous position.
 - c. A caveat to the use of the PLR test is that a method of determining CO is required to determine response (or lack thereof). A change in blood pressure is not an adequate surrogate for CO, as noted earlier. The CO measurement may be obtained from an arterial pulse pressure waveform analysis monitor (minimally invasive approach) or from a bioimpedance device, bioreactance device, or TTE LVOT VTI (noninvasive approach).
- 11. Several caveats exist for using dynamic markers of fluid responsiveness.
 - a. PPV and SVV assume the following: sinus cardiac rhythm, the absence of significant valvular dysfunction, intubation and mechanical ventilation without spontaneous breaths, and tidal volume of 8 mL/kg or more of predicted body weight. Values for PPV and SVV above the noted thresholds do not reliably predict fluid responsiveness in the setting of arrhythmias (e.g., atrial fibrillation). If these assumptions are not fulfilled, PPV and SVV are not reliable in predicting fluid responsiveness.
 - b. IVC collapsibility also requires intubation and mechanical ventilation without spontaneous breaths and is not conducive to continuous monitoring.
 - c. The real-time response of CO (or lack thereof) with PLR must be assessed using a CO monitoring device. In addition, intra-abdominal hypertension reduces the ability of PLR to detect fluid responsiveness.
- 12. The best dynamic marker of fluid responsiveness to use in practice is unclear.
 - a. In the previously mentioned study, the area under the receiver operating characteristic curve for predicting fluid responsiveness was higher for PPV than for SVV.
 - b. In one study of postoperative patients, IVC distensibility was not noninferior to PPV (noninferiority $p=0.28$), considering a noninferiority margin of 15%.
 - c. These data suggest that PPV is the best dynamic marker to predict fluid responsiveness, but larger comparative studies are needed.
- 13. Despite the superiority of dynamic markers to static markers in predicting fluid responsiveness, dynamic markers incorporated into a resuscitation strategy that improves patient outcomes in the ICU is still lacking.
 - a. A randomized controlled trial of patients with septic shock and/or acute respiratory distress syndrome randomized patients to treatment on the basis of pulse index continuous cardiac output (PiCCO)-derived parameters or a control group with parameters obtained by a central venous catheter (e.g.,

CVP). In both groups, the MAP was maintained above 60 mm Hg with norepinephrine or below 100 mm Hg with nitroglycerin. In the PiCCO group, circulatory volume was managed with diuretics or fluid administration according to intrathoracic blood volume and extravascular lung water index, and dobutamine was initiated if the cardiac index was less than 2.5 L/minute/m². There was no difference in 28-day mortality between the PiCCO and control groups (odds ratio [OR] 1.00; 95% CI, 0.66–1.52; p=0.993).

- b. A pilot study of using protocol-guided assessments of fluid responsiveness after initial resuscitation in patients with septic shock requiring vasopressors found that this approach is feasible and appears to be safe, paving the way for larger trials using this approach.

Patient Case

Questions 2 and 3 pertain to the following case.

A 59-year-old man with a medical history of cirrhosis complicated by ascites was transferred from the ward to the medical ICU for gross hematemesis, with a hemoglobin drop from 9.2 g/dL to 7.3 g/dL, a blood pressure of 82/36 mm Hg, and new-onset confusion. After 2 L of lactated Ringer solution and 2 units of PRBCs, the patient's hemoglobin increased to 9.1 g/dL, but he remained hypotensive. The medical team placed a PAC and an arterial blood pressure catheter, which revealed the following: CVP 8 mm Hg, PCWP 14 mm Hg, CO 7.4 L/minute, and MAP 58 mm Hg.

2. With which shock state are the patient's hemodynamic parameters most consistent?
 - A. Hypovolemic.
 - B. Obstructive.
 - C. Vasodilatory.
 - D. Cardiogenic.
 3. After further resuscitation, the patient developed hypoxemia requiring intubation and mechanical ventilation. A post-intubation radiograph revealed diffuse bilateral alveolar opacities. The patient remained hypoxemic with an FIO₂ of 90% and was subsequently deeply sedated and given atracurium. The patient also remained hypotensive with low urine output. Which value best predicts that the patient will respond favorably to a fluid bolus?
 - A. CVP 7 mm Hg.
 - B. PCWP 11 mm Hg.
 - C. SVV 16%.
 - D. MAP 62 mm Hg.
- E. Adequate Do₂
1. CO, ScvO₂, and Svo₂
 - a. Historically, CO was monitored and used as a therapeutic target in most patients with a PAC.
 - i. Because treatment of general ICU patients with a PAC has not been shown to improve patient outcomes, routine use of a PAC has declined substantially.
 - ii. Use of venous oximetry (ScvO₂ and Svo₂) and echocardiographic findings have largely replaced use of a PAC (and CO monitoring or use of CO as a therapeutic target).

- b. ScvO₂ may be used as a component of an early resuscitation strategy (although it is not a mandatory component).
 - i. A decreased ScvO₂ or Svo₂ is a sign that tissue oxygen demands are not completely met by Do₂.
 - ii. Strategies to increase Do₂ (and subsequently increase ScvO₂ or Svo₂) include fluids to optimize preload, red blood cell transfusion to increase Cao₂, and inotropes to increase CO. Because Pao₂ does not contribute significantly to Cao₂, it should not be used as a therapeutic target.
 - c. If ScvO₂ or Svo₂ is used as a resuscitation goal, it may be more important to use predefined targets in the early resuscitation period (first 6 hours after presentation) than in the later resuscitation periods.
 - d. Caution must be taken with using ScvO₂ or Svo₂ in isolation as a resuscitation goal for the following reasons.
 - i. The assumption that decreased ScvO₂ or Svo₂ is synonymous with Do₂ and oxygen demand mismatch is not true because, by definition, tissue oxygen demand exceeds Vo₂ in shock.
 - ii. During resuscitation, Vo₂ depends on Do₂, and increasing Do₂ will result in an increase in Vo₂ without substantial changes in ScvO₂ or Svo₂ until the critical Do₂ threshold is reached.
 - iii. Svo₂ and CO are not directly proportional and are better described by a hyperbolic relationship. As such, in hyperdynamic states where the CO is already high, the Svo₂ will not increase substantially with increases in CO.
 - iv. Venous hyperoxia may indicate mitochondrial dysfunction and impaired tissue oxygen use (achieving a high ScvO₂ or Svo₂ is not always best).
 - e. It is likely best to interpret CO, ScvO₂, or Svo₂ as either adequate or inadequate (not high or low).
 - i. Adequacy is best determined by assessing end-organ perfusion and lactate concentrations.
 - ii. If CO, ScvO₂, or Svo₂ is inadequate, interventions to raise Do₂ should be undertaken.
 - f. A strategy of systematically increasing CO to predefined “supranormal” values was not associated with a mortality benefit; hence, it is not recommended. The decision to augment CO must be individualized according to organ perfusion.
2. Lactate clearance and normalization
- a. Lactate clearance (a decline in lactate concentration from the initial value) suggests improvement in global tissue perfusion and is associated with a decreased mortality rate.
 - b. Significant discordance between lactate clearance and ScvO₂ may occur. In one study, 79% of patients with a lactate clearance of less than 10% had a concomitant ScvO₂ of 70% or greater.
 - c. A protocol-based approach to resuscitating patients with sepsis or septic shock targeting a lactate clearance of at least 10% was noninferior to an approach targeting an ScvO₂ above 70%.
 - d. Lactate normalization (to a concentration below 2 mmol/L) is a strong independent predictor of survival and may be an even better predictor of outcome than lactate clearance.
 - e. Targeting lactate clearance or normalization is an attractive end point because it does not require invasive hemodynamic monitoring.
 - f. Use of both lactate clearance and ScvO₂ above 70% as resuscitation goals may be best.
 - g. A further discussion of lactate clearance as a resuscitation target in patients with sepsis or septic shock is included later in the chapter.

V. AGENTS USED TO TREAT SHOCK – FLUIDS AND VASOACTIVE AGENTS

- A. See the Fluids, Electrolytes, and Nutrition chapter for a further discussion of fluid components.
- B. Pharmacology of Vasoactive Agents
1. Vasoactive agents can be broadly differentiated to (1) vasopressors, (2) inotropes, or (3) vasodilators. Vasoactive agents may have several of these properties.
 2. Vasopressor agents are indicated if hypotension is refractory to fluid administration (the patient is no longer fluid responsive) or in the setting of severe hypotension while fluids are being administered. Although objective criteria exist, a lack of fluid responsiveness is often assessed subjectively in practice. In addition, if a patient is severely hypotensive, vasopressors may be initiated (together with additional fluid administration), even if a patient is still fluid responsive, in order to ensure adequate end-organ perfusion. Because there are no definitive criteria for when vasopressors should be initiated, bedside clinicians often need to make a patient-specific assessment and decision.
 3. Vasopressor agents primarily exert pharmacologic benefit by augmenting SVR. Some vasopressors may have an additional benefit of increasing CO. Table 4 highlights the receptor pharmacology of the various agents.
 - a. Once the decision to start a vasoactive agent is made, selection of a vasoactive agent or inotrope is largely based on choosing the agent that best achieves the desired pharmacodynamic effect(s) (e.g., increase in SVR or increase in CO). In most shock syndromes, limited literature exists to guide optimal vasoactive agent selection.
 - b. Vasopressor agents should be administered through central venous access to minimize the risk of extravasation and tissue necrosis.
 4. Inotropes exert a pharmacodynamic effect that increases CO after adequate fluid administration.
 - a. Dobutamine is a β -agonist and improves cardiac function by improving SV and CO. Because of its β_1 activity, dobutamine may induce tachyarrhythmias as well as hypotension, given its β_2 activity.
 - b. Milrinone is a phosphodiesterase type 3 (PDE3) inhibitor. PDE3 inhibition potentiates cyclic adenosine monophosphate, leading to increased ventricular contractility and vasodilation.
 - i. Milrinone may be desirable for patients receiving β -antagonists before critical illness or for patients experiencing tachyarrhythmias while receiving dobutamine.
 - ii. May be favored in patients with pulmonary hypertension (PH) because it decreases cardiac filling pressures and pulmonary vascular resistance (PVR)
 - iii. Milrinone may cause an increase or a decrease in blood pressure, depending on the individual patient's SVR and CO when it is administered. In general, a decrease in blood pressure is more common with milrinone than with dobutamine.
 5. Levosimendan is a calcium channel sensitizer that also activates adenosine triphosphate (ATP-sensitive potassium channels)
 - a. The agent's pharmacodynamic effects are similar to those of milrinone.
 - b. Like milrinone, levosimendan may be preferred in patients receiving β -antagonists before critical illness or in those with PH.
 - c. Levosimendan is not available for use in the United States.

Table 4. Vasoactive Pharmacology

	DA	α_1	β_1	β_2	Other Mechanism	HR	CVP	CO	SVR	PVR
Vasopressors										
Dopamine ^a	+++++	+++	++++	++		↑	↔ or ↑	↑	↔ or ↑	↔ or ↑
Epinephrine ^a		++++	++++	+++		↑	↔ or ↑	↑	↑	↑
Norepinephrine ^a		+++++	+++	++		↔ or ↑	↔ or ↑	↔ or ↑	↑	↑
Phenylephrine		+++++				↔ or ↓	↔ or ↑	↔ or ↓	↑	↑
Vasopressin	N/A				V ₁ R and V ₂ R agonism	↔ or ↓	↔ or ↑	↔	↑	↔ or ↓
Inotropes										
Dobutamine		+	++++	++		↑	↔ or ↓	↑	↔ or ↓	↔ or ↓
Isoproterenol			+++++	+++++		↑	↔ or ↓	↑	↔ or ↓	↔ or ↓
Levosimendan	N/A				Ca ²⁺ sensitization and K ^{ATP} activation	↔	↔ or ↓	↑	↓	↓
Milrinone ^b	N/A				PDE3 inhibition	↔ or ↑	↔ or ↓	↑	↓	↓

^aHigh doses associated with increasing α_1 activity.

^bNormal half-life is 2.5 hr, but milrinone is eliminated renally. Loading dose rarely used in routine management.

DA = dopaminergic; K^{ATP} = adenosine triphosphate-sensitive potassium channels; N/A = not applicable; PDE3 = phosphodiesterase type 3.

Information from: Bangash MN, Kong ML, Pearse RM. Use of inotropes and vasopressor agents in critically ill patients. *Br J Pharmacol* 2012;165:2015-33; and Hollenberg SM. Vasoactive drugs in circulatory shock. *Am J Respir Crit Care Med* 2011;183:847-55.

C. Outcomes Studies

1. Studies of therapies in patients with sepsis and septic shock will be discussed in section IX, Sepsis.
2. Fluids
 - a. Resuscitation fluids are commonly given for patients in the ICU, with 25%–37% of patients receiving this therapy in a 24-hour period in cross-sectional studies.
 - b. The Saline versus Albumin Fluid Evaluation (SAFE) study enrolling almost 7000 patients with varied shock types requiring fluid resuscitation, with 90% power, found no difference in 28-day mortality between treatment with 0.9% sodium chloride and 4% albumin (20.9% vs. 21.1%, $p=0.87$). However, this was not a study of strictly initial fluid resuscitation because the allocated study fluid was used for all fluid resuscitation in the ICU until death, discharge, or 28 days after randomization. In light of this study, crystalloids are usually preferred to albumin for the initial resuscitation of patients with shock because of their lower cost.
 - c. A pragmatic open-label randomized study of crystalloids compared with colloids for resuscitation detected no difference between groups in 28-day mortality (27.0% vs. 25.4%, $p=0.26$) but did find a difference in 90-day mortality favoring the colloid group (34.2% vs. 30.2%, $p=0.03$). Because 90-day mortality was a secondary (not primary) outcome, the results must be interpreted with caution. In addition, the open-label nature (which may bias toward finding a difference between groups) and use of many different resuscitation fluids within each study group make this study challenging to implement into practice.

- d. The type of crystalloid fluid that should be used for resuscitation, whether chloride rich (i.e., 0.9% sodium chloride) or chloride poor (i.e., lactated Ringer solution), is an area of increasing interest.
 - i. Administration of chloride-rich fluids may lead to afferent renal arteriole vasoconstriction (leading to a decrease in renal perfusion and kidney injury) and may cause a metabolic acidosis by lowering the strong ion difference. As such, crystalloids that better approximate the electrolyte composition of plasma (“chloride-poor,” “balanced salt,” or “balanced crystalloid” solutions) have been evaluated.

Table 5. Sodium, Chloride, and Lactate Content of Commonly Used Resuscitation Fluids

Fluid	Sodium (mmol/L)	Chloride (mmol/L)
“Chloride rich” ^a		
0.9% sodium chloride	154	154
5% albumin	130–160 ^b	0–128 ^b
Hydroxyethyl starch 6% (130/0.4)	154	154
Hydroxyethyl starch 6% (670/0.75)	143	124
“Chloride poor” ^a		
25% albumin	130–160 ^b	0–19 ^b
Lactated Ringer solution	131	111
Plasma-Lyte 148	140	98
Normosol-R	140	98

^aDistinction of “chloride rich” and “chloride poor” is based on chloride content above or below 120 mmol/L.

^bDiffers according to manufacturer because of differences in buffer type (e.g., sodium bicarbonate or sodium chloride) and amount used. Reported chloride content of 4% Albumex (CSL Bioplasma) is 128 mmol/L, and that of 20% Albumex (CSL Bioplasma) is 19 mmol/L (products used in Australia/New Zealand), which led to the distinction of “chloride rich” and “chloride poor” for 4%–5% albumin and 20%–25% albumin, respectively. However, neither 5% Flexbumin (Baxter, Westlake Village, CA) nor 25% Flexbumin (Baxter; products available in the United States) contains chloride.

Information from: Guidet B, Soni N, Della Roca G, et al. A balanced view of balanced solutions. *Crit Care* 2010;14:325; Frazee EN, Leedahl DD, Kashani KB. Key controversies in colloid and crystalloid fluid utilization. *Hosp Pharm* 2015;50:446-53; and Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012;308:1566-72.

- ii. An open-label sequential period study evaluated outcomes between a control period in which chloride-rich fluids were routinely administered (n=760) and an intervention period in which chloride-rich fluids were restricted to attending physician approval and chloride-poor fluids were routinely used (n=773). In the intervention period, the incidence of acute kidney injury (8.4% vs. 14%, p<0.001) and use of renal replacement therapy were significantly lower (6.3% vs. 10%, p=0.005). Because the study was not blinded or randomized, the results should be considered hypothesis generating.
- iii. A retrospective cohort study of patients undergoing open major abdominal surgery compared 0.9% sodium chloride (n=30,994) with a balanced crystalloid solution (Plasma-Lyte; n=926) administered on the day of surgery. In a propensity-matched analysis, the balanced crystalloid solution was associated with a lower risk of major postoperative complications (odds ratio [OR] 0.79; 95% CI, 0.66–0.97) but no difference in mortality (OR 0.77; 95% CI, 0.48–1.22) on multivariable analysis. Because the study was retrospective and uncontrolled (though an attempt was made to control for channeling bias with propensity scores), these data should be considered hypothesis generating.

- iv. A large, double-blind, cluster randomized, double-crossover trial allocated four ICUs in New Zealand to either 0.9% sodium chloride (n=1025) or a balanced crystalloid solution (Plasma-Lyte; n=1067) for the treatment of all patients requiring crystalloid fluid therapy. Two crossovers occurred with 7-week intervals such that each ICU used each fluid twice during the 28-week study. A total of 2278 patients were enrolled, with 2092 patients having data available for analysis of the primary outcome of the incidence of acute kidney injury within 90 days. The balanced crystalloid solution group had no lower risk of acute kidney injury than did the 0.9% sodium chloride group (9.6% vs. 9.2%, relative risk [RR] 1.04; 95% CI, 0.80–1.36; p=0.77). There was also no difference between groups in the use of renal replacement therapy (RR 0.96; 95% CI, 0.62–1.50; p=0.91) or hospital mortality (RR 0.88; 95% CI, 0.67–1.17; p=0.40). Critiques of this study include the use of the study fluid for all crystalloid fluid therapy needs (not just as a resuscitation fluid for circulatory shock), relatively low volumes of fluid administered (2 L in each group), significant heterogeneity (p=0.05) of the treatment effect on acute kidney injury by specific ICU study site (suggesting center-related treatment differences [although the authors attributed this heterogeneity to chance]), and debatable widespread external validity in light of the predominantly surgical population (72% of patients were admitted to the ICU postoperatively, with 49% overall admitted after cardiovascular surgery) and the relatively low severity of patient illness (mean APACHE II [Acute Physiology and Chronic Health Evaluation II] scores of 14.1).
 - v. Balanced crystalloid solutions may lead to hyponatremia (with lactated Ringer solution) or cardiotoxicity (with acetate-containing solutions) when administered in large volumes (the incidence of these adverse effects was not reported in the previously mentioned randomized trial).
 - vi. At this time, the influence of balanced crystalloid solutions on patient outcomes is unclear.
 - e. Hydroxyethyl starch solutions should not be used for fluid resuscitation in the ICU.
 - i. A study of 7000 critically ill patients requiring fluid resuscitation compared a low-molecular-weight, low-molar-substitution (130/0.4) hydroxyethyl starch solution with 0.9% sodium chloride. There was no difference in 90-day mortality between the hydroxyethyl starch and 0.9% sodium chloride groups (18.0% vs. 17.0%, p=0.26), but patients allocated to hydroxyethyl starch had a greater need for renal replacement therapy (7.0% vs. 5.8%, p=0.04) and a higher incidence of adverse events (5.3% vs. 2.8%, p<0.001).
 - ii. A systematic review and meta-analysis that analyzed only unbiased trials found an association between hydroxyethyl starch use and increased patient mortality (RR 1.09; 95% CI, 1.02–1.17; p=0.02) and need for renal replacement therapy (RR 1.32; 95% CI, 1.15–1.50; p<0.001).
3. Vasopressors
- a. A multicenter randomized trial included patients requiring vasopressors for shock of any type and excluded those requiring vasopressors for more than 4 hours before enrollment. Enrolled patients were allocated to either blinded norepinephrine or dopamine. There was no difference in 28-day mortality between patients receiving dopamine and those receiving norepinephrine (52.5% vs. 48.5%, p=0.10), but patients receiving dopamine more commonly developed an arrhythmia (24.1% vs. 12.4%, p<0.001), required open-label norepinephrine (26% vs. 20%, p<0.001), and required more days with vasopressor support.
 - i. A predefined subgroup analysis evaluated the influence of shock type on the outcome. Patients with cardiogenic shock allocated to dopamine had a higher mortality rate than those allocated to norepinephrine (log-rank p=0.03). However, the overall effect of treatment did not differ among the shock subgroups (interaction p=0.87), suggesting that the reported differences in mortality according to subgroup are spurious.
 - ii. These data suggest that although norepinephrine does not improve mortality compared with dopamine, it is safer and more effective to increase a patient's blood pressure. Given these data, a case could be made for norepinephrine as the first-line vasoactive medication of choice in all shock types.

- b. A multicenter randomized trial comparing norepinephrine with epinephrine for patients with undifferentiated shock found no difference between agents in the time to achievement of a goal MAP (median 40 hours vs. 35.1 hours, $p=0.26$) or median number of vasopressor-free days at day 28 (25.4 days vs. 26.0 days, $p=0.31$). Patients allocated to epinephrine, though, had higher heart rates and lactic acid concentrations on the first study day (but not on subsequent days) and were more often withdrawn from the study by the treating clinician (12.9% vs. 2.8%, $p=0.002$). These data suggest that epinephrine offers no efficacy benefits over norepinephrine and is associated with an increased incidence of adverse effects.
- c. In a recent systematic review and meta-analysis of vasopressors for patients with circulatory shock of all types, there was no difference in all-cause mortality in any comparison of different vasopressor agents or combinations.
 - i. Single vasopressors evaluated included norepinephrine (reference group), dopamine, epinephrine, terlipressin, vasopressin, and phenylephrine. Vasopressor combinations included norepinephrine plus dobutamine and norepinephrine plus dopexamine (which were compared with epinephrine).
 - ii. More arrhythmias were observed in participants treated with dopamine than with norepinephrine. The authors concluded that major changes to clinical practice are not needed but that selection of vasopressors could be better individualized and could be based on clinical variables reflecting hypoperfusion. This systematic review is limited by the small number of patients enrolled in randomized studies of some agents (e.g., phenylephrine) and few studies with combination therapy.

Patient Case

Questions 4 and 5 pertain to the following case.

J.B. is a 28-year-old man (weight 92 kg) who presented to the surgical ICU with shock after an appendectomy was complicated by appendiceal perforation. In the operating room, the patient received 2 L of lactated Ringer solution and 500 mL of 5% albumin, and he was initiated on norepinephrine. The patient is still receiving norepinephrine 12 mcg/minute with a lactate of 6.8 mmol/L and had a CO increase of 18% with a PLR.

- 4. Which would best meet J.B.'s fluid needs?
 - A. 5% albumin.
 - B. 6% hydroxyethyl starch.
 - C. 0.9% sodium chloride.
 - D. No fluids necessary.
- 5. After 12 hours in the surgical ICU, J.B. remains hypotensive with a lactate concentration of 5.2 mmol/L. He currently requires norepinephrine 14 mcg/minute and has a MAP of 64 mm Hg and an $ScvO_2$ of 61%. The ICU team did a bedside echocardiogram, which revealed large ventricles with poor contractility. Which action is best?
 - A. Start phenylephrine.
 - B. Start vasopressin.
 - C. Increase norepinephrine.
 - D. Start epinephrine.

VI. HYPOVOLEMIC SHOCK

A. Etiology and Epidemiology

1. Patients with hypovolemic shock constitute about 16% of the cases of shock requiring vasoactive medications.
2. In the United States, the most common form of shock experienced after trauma is hypovolemic shock.
3. Exsanguination is estimated to be the direct cause of 2 million deaths from trauma in the United States.
 - a. Responsible for up to 30%–40% of trauma-related mortality
 - b. Leading cause of death in patients younger than 45 years; thus, burden to society is even larger
4. Although commonly associated with trauma, hypovolemic shock can occur in other clinical scenarios (e.g., acute gastrointestinal [GI] bleeding, surgical, obstetric, pharmacologic toxicity).

B. Pathophysiology

1. Hemorrhagic shock is observed when intravascular volume loss impairs DO_2 .
2. The estimated blood volume for a patient weighing 70 kg is 5 L.
3. A reduction in intravascular volume leads to a reduction in tissue perfusion.
4. Can be categorized as:
 - a. Whole blood loss: Whole blood loss from an open wound or into a body compartment (e.g., limb, retroperitoneal space)
 - b. Plasma loss: Loss of extracellular fluid (e.g., burns, pancreatitis, peritonitis, vomiting, diarrhea)
5. Clinical features of hypovolemic shock: Hypotension, tachycardia, diaphoresis, altered mentation, decreased urine output (Table 6)

Table 6. Classification of Trauma Hemorrhage^a

	Class I	Class II	Class III	Class IV
Blood loss (mL)/%	< 750 < 15%	750–1500 15%–30%	1500–2000 30%–40%	> 2000 > 40%
Heart rate (beats/min)	< 100	> 100	> 120	> 140
Respiratory rate (breaths/min)	14–20	20–30	30–40	> 35
Urine output (mL/hr)	> 30	20–30	5–15	< 5
CNS symptoms	Normal	Anxious	Confused	Lethargic

^aEstimated blood loss is based on a man weighing 70 kg. Classification system is intended to serve only as a guide to initial therapy, as the physiologic response to hemorrhage represents a continuum. Confounding factors that influence the physiologic response to hemorrhage include patient age, severity of injury, time from injury, prehospital interventions, and medications for chronic conditions. Therefore, it is not intended to wait for a patient to fit each precise physiologic classification before initiating volume resuscitation.

CNS = central nervous system.

Modified from: Committee on Trauma: Advanced Trauma Life Support Manual. Chicago: American College of Surgeons, 2012:62–78.

6. Physiologic response

- a. Compensatory responses try to restore the volume deficit.
- b. Neural response is immediate, occurring within minutes.

- i. Sympathetic response: Activation of the low-pressure receptors within the right and left atria and high-pressure receptors within the aortic arch and carotid sinus lead to increased secretion of epinephrine and norepinephrine, resulting in an increase in heart rate, myocardial contractility, and arteriolar/venous tone. Blood flow is preserved to critical organs.
 - ii. Parasympathetic response: Reduction in vagal tone leads to increased heart rate.
 - iii. Often, tachycardia is the earliest sign of circulatory shock from acute blood loss.
 - c. Intrinsic response compensates for acute blood loss within hours.
 - i. Reduced capillary pressure leads to fluid redistribution from the interstitium to the vascular compartment as albumin shifts into the plasma from the interstitium.
 - ii. The transcapillary refill can recruit up to 1 L into the intravascular compartment.
 - d. Humoral response is delayed, developing over hours to several days. After decreased renal perfusion, secretion of antidiuretic hormone, aldosterone, and renin increases sodium and volume retention to restore the interstitial deficit from the transcapillary refill.
- C. Acute Traumatic Coagulopathy (ATC)
- 1. Present in 25%–35% of injured civilian trauma patients on arrival to the ED and associated with a 40%–70% mortality rate
 - 2. Likely has a significant role in preventable deaths caused by hemorrhage
 - 3. Pathophysiology of ATC is multifactorial.
 - a. Inadequate tissue perfusion because of the resulting hypovolemia
 - b. Subsequent cell hypoxia, anaerobic respiration, and metabolic acidosis
 - c. Thrombin–thrombomodulin–complex generation caused by the tissue injury and the activation of anticoagulant and fibrinolytic pathways
 - d. Hyperfibrinolysis plays a central role in the initial coagulopathy.
 - e. Coagulopathy, acidosis, and hypothermia—known as the “lethal triad”—exacerbate one another, rapidly leading to death if not reversed.
 - 4. Characterization of ATC
 - a. Defined as an increase in standard plasma-based coagulation tests above normal limits (activated partial thromboplastin time [aPTT], partial thrombin time [PTT], prothrombin time [PT], and international normalized ratio [INR], fibrinogen). In a multicenter, observational study, an INR-based definition of acute coagulopathy (INR greater than 1.5) was significantly associated with death (OR 1.88; $p < 0.001$), venous thromboembolism (OR 1.73; $p < 0.001$), and multiple organ failure (OR 1.38; $p = 0.02$).
 - b. Viscoelastic tests have an emerging role in screening for coagulopathy in hemorrhagic shock.
 - i. Whole blood coagulation tests that represent global clot function, including clot initiation, formation, stabilization, and fibrinolysis
 - ii. Correlate well with standard plasma coagulation studies
 - iii. May be available as point-of-care tests with a faster turnaround time than standard plasma coagulation studies
 - iv. Available tests include thromboelastogram (TEG) and ROTEM (more common in Europe).
 - v. Outputs from TEG include a graphical representation of clot kinetics, including:
 - (a) Reaction time (R time), which represents factor initiation and function
 - (b) α , which represents clot strengthening, predominantly fibrinogen
 - (c) Maximum amplitude, which represents clot strength, predominantly platelets but also fibrinogen
 - (d) Estimated percent lysis, which represents fibrinolysis
 - vi. Standard coagulation laboratory or viscoelastic tests are recommended as monitoring techniques to characterize ATC (grade 1C recommendation).

D. Resuscitation

1. Rapid identification and correction of source of bleeding (e.g., surgical exploration, angiographic embolization, stabilization of the pelvic ring, damage control surgery)
2. Fluids
 - a. Indications: Diminished mental status or absent radial pulse (SBP less than 90 mm Hg)
 - b. Benefit: Fluids restore intravascular volume, reverse tissue hypoperfusion, and correct oxygen debt.
 - c. Risk: Fluids do not increase oxygen-carrying capacity, can precipitate dilutional coagulopathy, and lead to tissue edema, including the development of acute respiratory distress syndrome.
 - d. Crystalloids: Balanced crystalloids (e.g., lactated Ringer) and isotonic saline are both recommended as resuscitation fluids. Isotonic saline is the most commonly used, but it can cause hyperchloremic metabolic acidosis and resultant acute kidney injury. Balanced crystalloids are associated with less hyperchloremia in trauma patients, but it is unknown whether this improves morbidity and mortality. Hypertonic saline resuscitation has failed to improve outcomes.
 - e. Colloids, which confer no incremental benefit over crystalloids, were associated with increased mortality in a subgroup analysis of patients with severe brain injury in the SAFE trial, likely secondary to hypo-osmolality in patients with traumatic brain injury. Synthetic colloids (e.g., hydroxyethyl starches) contribute to coagulopathy and risk of acute kidney injury; they should therefore be avoided.
 - f. Recommendations: Isotonic crystalloids are indicated in hemorrhagic shock. In trauma, restricted volume replacement, usually less than 1.5 L, should be used initially, and hypotonic solutions (e.g., lactated Ringer) should be avoided in patients with head trauma to minimize fluid shifts into the cerebral tissue.
3. PRBCs and blood products
 - a. Indicated when estimated blood loss is greater than 30% of total blood volume
 - b. Amount of blood products to transfuse is based on clinical examination, given that the initial hemoglobin or hematocrit reading may not reflect blood loss because of compensatory mechanisms.
 - c. Although there are no randomized controlled trials of trauma, the European guidelines recommend maintaining a hemoglobin of 7–9 g/dL after initial resuscitation.
 - d. In the setting of acute upper GI bleeding, a restrictive transfusion threshold (Hgb less than 7 g/dL) compared with a liberal transfusion threshold (Hgb less than 9 g/dL) was associated with a higher 6-week survival rate (95% vs. 91%, hazard ratio [HR] 0.55 [95% CI, 0.33–0.92; p=0.02]) and lower rates of further bleeding (10% vs. 16%, p=0.01) and adverse effects (40% vs. 48%, p=0.02). Notable limitations: Single-center, exclusion of patients with cardiovascular disease, and unique processes of care
 - e. A randomized controlled trial of cardiac surgery patients compared a restrictive transfusion threshold (less than 7.5 g/dL) with a liberal transfusion threshold (less than 9 g/dL). There was no difference between groups with respect to the composite primary end point of serious infection or ischemic event (at 3 months) (35.1% vs. 33.0%; OR 1.11; 95% CI, 0.91–1.34; p=0.30). However, there were more deaths in the restrictive transfusion group (4.2% vs. 2.6%; HR 1.64; 95% CI, 1.00–2.67; p=0.045). Therefore, a restrictive transfusion strategy after cardiac surgery cannot be recommended.
4. Vasopressors
 - a. Attractive adjunct in hemorrhagic shock to minimize the amount of fluid required to reverse tissue hypoperfusion, but can increase cardiac afterload and are independently associated with increased mortality in trauma
 - b. May be used as a temporizing measure in the setting of profound hypoperfusion despite ongoing volume resuscitation
 - c. In life-threatening hypotension, vasopressors may be recommended only after hypovolemia has been corrected or when cardiac arrest is imminent.

5. End points of resuscitation
 - a. General recommendations include permissive hypotension, defined as SBP 80–90 mm Hg, and urine output greater than 30 mL/hour. Up to 85% of patients may be under-resuscitated using SBP and urine output.
 - b. In patients with traumatic brain injury, SBP less than 90 mm Hg should be avoided. The European guidelines on managing hemorrhage after trauma recommend that MAP be maintained greater than 80 mm Hg in patients with severe (Glasgow Coma Scale score of 8 or lower) traumatic brain injury (grade 1C).
 - c. Oxygen transport variables may be more patient-specific. Lactate, DO_2 , and cardiac index may be more sensitive.
- E. Burn Resuscitation
 1. Acute thermal injury triggers an inflammatory state that ultimately leads to third spacing of intravascular fluid shifts.
 2. Fluid resuscitation is initiated to maintain perfusion to tissue beds and end-organ function. A concomitant concern is to avoid over-administration of fluids, leading to abdominal compartment syndrome, acute respiratory distress syndrome, and further third spacing.
 3. Guideline recommendations promote fluid resuscitation to target a urine output greater than 0.5 mL/kg/hour in adults (greater than 1 mL/kg/hour in children), titrated to the total body surface area.
 4. Administration of crystalloid fluid using lactated Ringer solution by the Parkland formula is recommended: 4 mL/kg/% total body surface area, with half administered over the first 8 hours and the remaining half over the next 16 hours.
 5. The use of colloids for burn resuscitation is controversial. No consensus exists for fluid type, timing, and re-dosing.
- F. Management of Coagulopathy
 1. Lethal triad: Hypothermia, acidosis, and coagulopathy
 - a. Hypothermia, severe acidemia (pH less than 7.20), and hypocalcemia inhibit the procoagulant enzyme function.
 - b. Therefore, treatment of the acutely bleeding patient should prioritize warming the patient to a temperature greater than 93.2°F (34°C), correcting acidosis to a pH greater than 7.20, and administering calcium to an ionized calcium greater than 4.4 mg/dL (1.1 mmol/L).
 2. Initial bleeding and coagulopathy should be managed with blood component therapy (e.g., plasma, platelet count, cryoprecipitate) in an attempt to build whole blood.
 3. Blood component therapy will replete individual components but will not address other parts of hemostasis (e.g., fibrinolysis).
 - a. Standard massive transfusion protocols include at least a 1:1:1 strategy of PRBCs/plasma/platelets.
 - b. A recent trial compared a balanced 1:1:1 damage control resuscitation transfusion strategy of plasma/platelets/PRBCs with a ratio 1:1:2 in adult trauma patients in a multicenter, randomized trial (PROPR trial).
 - i. 1:1:1 group received 6 units of plasma, one dose of platelets (6 units of platelets), and 6 units of PRBCs. Transfusion order of platelets first, followed by alternating plasma and PRBC units
 - ii. 1:1:2 group received an initial container (and all subsequent odd-numbered containers) with 3 units of plasma, no doses of platelets, and 6 units of PRBCs. The second (and all subsequent even-numbered containers) had 3 units of plasma, one dose of platelets (6 units of platelets), and 6 units of PRBCs. Transfusion order of platelets first, followed by alternating 2 units of PRBC and 1 unit of plasma

- iii. No significant differences in 24-hour mortality (1:1:1 group of 12.7% vs. 1:1:2 group of 17.0%; OR 0.75; 95% CI, 0.52–1.08; $p=0.12$) or 30-day mortality (1:1:1 group of 22.4% vs. 1:1:2 group of 26.1%; OR 0.86; 95% CI, 0.65–1.12; $p=0.26$) were observed.
- iv. However, in the 1:1:1 arm, hemostasis was achieved in more patients (86.1% vs. 78.1%, $p=0.006$), possibly highlighting the importance of early platelet transfusion, and death from exsanguination at 24 hours was less (9.2% vs. 14.6%; $p=0.03$).
- v. Of note: Informed consent was waived for this study.
- c. Massive transfusion is defined as greater than 10 units of erythrocytes in a 24-hour period. Current recommendations for the initial management of expected massive hemorrhage include erythrocytes and plasma in a 2:1 or 1:1 ratio (grade 1B). Further resuscitation, including platelet transfusions, should be guided in a goal-directed fashion, using either standard laboratory coagulation assays or viscoelastic tests (grade 1C). An example of goal-directed resuscitation can be found in Box 1.
- d. In a prospective study of 111 patients, TEG-guided resuscitation was superior to standard laboratory coagulation-guided resuscitation with improved 6-hour mortality (7.1% vs. 21.8%; $p=0.049$) and total mortality (19.6% vs. 36.4%; $p=0.03$) and required less plasma and platelets in the first 2 hours of resuscitation. Notable limitations include that it was a single-center study and that TEG was available as point of care.

Box 1. Example of Goal-Directed Resuscitation

Conventional Coagulation Assay (CAA)	Thromboelastography (TEG)
INR $\geq 1.5 \rightarrow$ 2 units of FFP	Initial activated clotting time > 140 s $\rightarrow$ 2 units of FFP, 10 pack of cryoprecipitate, 1 apheresis platelet
Fibrinogen < 150 mg/dL $\rightarrow$ 10 pack of cryoprecipitate	Activated clotting time > 110 s $\rightarrow$ 2 units of FFP
Plt $< 100,000/\text{mm}^3 \rightarrow$ 1 apheresis platelet	Angle $< 63 \rightarrow$ 10 pack of cryoprecipitate
D-dimer > 0.5 mcg/mL $\rightarrow$ 1 g of tranexamic acid	MA < 55 mm $\rightarrow$ 1 apheresis platelet
	LY30a $> 3\% \rightarrow$ 1 g of tranexamic acid

FFP = fresh frozen plasma; LY30 = percentage decrease in amplitude after 30 minutes; MA = maximum amplitude.

aLY30 is a reflection of fibrinolysis, similar to estimated percent lysis.

Information from: Gonzalez E, Moore EE, Moore H, et al. Goal directed resuscitation of trauma induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assay. *Ann Surg* 2016;263:1051-9.

G. Antifibrinolytics

1. Tranexamic acid is an antifibrinolytic agent that binds plasminogen to prevent the dissolution of a fibrin clot. Tranexamic acid is a competitive inhibitor of plasmin and plasminogen.
 - a. Tranexamic acid (1 g over 10 minutes of bolus, followed by a 1-g infusion over 8 hours) reduced 28-day mortality for all-cause trauma compared with placebo (RR 0.91; 95% CI, 0.85–0.97; $p=0.0035$) in the CRASH-2 trial.
 - b. Number needed to treat is 67.
 - c. No difference between groups in risk of vascular occlusive events
 - d. Mortality caused by bleeding: Tranexamic acid, 489 (4.9%) vs. placebo, 574 (5.7%) (RR 0.85; 95% CI, 0.76–0.96; $p=0.0077$)
 - e. Greatest benefit for tranexamic acid observed with administration within 3 hours of injury (RR 0.79; 95% CI, 0.64–0.97; $p=0.03$), with an increased risk of death from bleeding after 3 hours from injury (RR 1.44; 1.12–1.8)

- f. In the MATTERs (Military Application of Tranexamic Acid in Trauma Emergency Resuscitation) study, tranexamic acid reduced the absolute mortality by 6.5% in all patients and by 13.7% in those requiring massive transfusion, suggesting a greater benefit in those with a higher injury severity.
- g. Tranexamic acid does not decrease the need for transfusion.
- h. Tranexamic acid should be administered as early as possible to a bleeding trauma patient or a patient at risk of significant hemorrhage within 3 hours of injury. Some hospital systems have begun giving the tranexamic acid loading dose prehospital to prevent full activation of fibrinolysis and have observed improved outcomes when it was given within 1 hour (grade 2C). This strategy requires validation in a clinical trial. The CRASH-3 trial is an ongoing randomized controlled trial evaluating the impact of tranexamic acid on outcomes in patients with traumatic brain injury.

H. Aminocaproic Acid

- 1. Aminocaproic acid is a lysine analog that is 10-fold weaker than tranexamic acid.
- 2. The recommended dose of aminocaproic acid is a 150-mg/kg bolus, followed by a 15-mg/kg/hour infusion.
- 3. Compared with tranexamic acid, aminocaproic acid may cause more adverse drug reactions, including hypotension and bradycardia with rapid administration and rhabdomyolysis.
- 4. Less high-level evidence exists for aminocaproic acid in the treatment of the acutely bleeding patient.

I. Recombinant Activated Factor VIIa (rFVIIa)

- 1. Activates hemostasis through the extrinsic pathway of the coagulation cascade by interacting with tissue factor to activate factor X to factor Xa and factor IX to factor IXa. Adequate levels of platelets and fibrinogen are needed to support activity.
- 2. Case series and case reports suggest that the administration of rFVIIa improves clinical outcomes.
- 3. A randomized controlled trial, terminated because of the futility for the primary end point of mortality, showed a reduction in PRBC transfusion.
- 4. There is no consensus on the use of rFVIIa for the treatment of acute bleeding. Institutional protocols vary with respect to appropriate indication, timing, dosing, and re-administration of rFVIIa.
- 5. Database reviews document an increased incidence of venous and arterial thromboembolic events associated with off-label rFVIIa use.
- 6. rFVIIa should only be considered if major bleeding and traumatic coagulopathy persist despite all other attempts to control bleeding (grade 2C).

J. Prothrombin Complex Concentrates (PCCs)

- 1. A combination of concentrated clotting factors II, VII, IX, and X and proteins C and S
 - a. Four different forms of PCC available in the United States. There is variability in the factor content of the PCCs, particularly for factor VII (Table 7).
 - b. FEIBA (factor eight inhibitor bypassing activity) is the only PCC composed of activated clotting factors, making it an activated prothrombin complex concentrate (aPCC). Although theoretically more efficacious, this may also lead to increased thrombotic events.
- 2. Kcentra, a nonactivated four-factor prothrombin complex concentrate (4PCC), has U.S. Food and Drug Administration (FDA)-approved labeling for use in the reversal of warfarin-related acute bleeding disorders (discussed further in the text that follows under Reversal of Oral Anticoagulant Agents) in life-threatening hemorrhage or for urgent surgery or invasive procedures. The other PCC products are approved for the treatment of hemophilia-related bleeding. The package insert warns of increased thromboembolic risk with Kcentra administration. Kcentra is contraindicated in patients with known heparin-induced thrombocytopenia because the product contains heparin. Few data support the off-label use of PCCs as a hemostatic agent in a bleeding patient who was not previously receiving an anticoagulant agent.

Table 7. Factor Content of PCCs Available in the United States

	Factor II^a (IU)	Factor VII^a (IU)	Factor IX^a (IU)	Factor X^a (IU)	Additives^b	Vial Dose (estimated factor IX IU)
Three-factor PCC^c						
Bebulin VH	100	< 5	100	100	Trace heparin	200–1200
Profilnine	150	35	100	100	N/A	500, 1000, 1500
Four-factor PCC^d						
Kcentra	106.9	55.1	100	141.4	Protein C, S, Z, anti-thrombin III, heparin	500, 1000
aPCC^e						
FEIBA	91.7–125	68.5–134.8	100	80–93.3	Protein C	500, 1000, 2500

^aExpressed as international units (IU) per 100 IU of factor IX; the individual factor contents vary depending on vial size and can be determined by multiplying the individual factor content of interest by vial dose and dividing by 100 IU of factor IX equivalent.

^bAnticoagulant factors in some PCC products are added to attenuate excessive thrombogenicity.

^cConsidered a three-factor PCC because of limited amounts of factor VII.

^dConsidered a four-factor PCC (4PCC) because of a significant concentration of factor VII.

^eFEIBA is an aPCC that contains mainly nonactivated factors II, IX, and X; factor VII is mainly in the activated form.

^fPCC = activated prothrombin complex concentrate; FEIBA = factor eight inhibitor bypassing activity; PCC = prothrombin complex concentrate.

Information from: Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Neurocrit Care* 2016;24:6-46.

K. Reversal of Oral Anticoagulant Agents (Table 8)

1. Warfarin

- Warfarin has a long physiologic half-life; thus, the reversal decision is usually based on the presence of an elevated INR in the setting of a life-threatening hemorrhage (e.g., central nervous system [CNS], retroperitoneal, pericardial, GI, and intramuscular with compartment syndrome) or need for urgent surgery or invasive procedure (within 24 hours).
- Phytonadione administration is the definitive reversal of warfarin, promoting hepatic production of vitamin K–dependent clotting factors depleted by warfarin.
 - In life-threatening hemorrhage, injectable phytonadione at a dose of 5–10 mg given intravenously is preferred.
 - Previous reports of anaphylaxis are related to solubilizing agents no longer included in the formulation.
 - Phytonadione has a delayed onset (6–12 hours); therefore, clotting factors are given concurrently to expedite reversal.

2. Clotting factors can be given as either plasma or PCC.

- Plasma has traditionally been used, but it requires large volumes, leads to incomplete correction of INR, requires compatibility testing, and requires extended time to achieve hemostasis.
- Compared with plasma in life-threatening hemorrhage, 4PCC is superior for laboratory reversal, is noninferior for clinical hemostasis, and has a similar rate of thromboembolic events. In an urgent surgical or invasive procedure, 4PCC is superior for rapid INR reversal and achievement of hemostasis. Integrated analysis from both trials suggests similar rates of thromboembolic events (4PCC 7.3% vs. fresh frozen plasma 7.1%), with fluid overload more common in the plasma group (4PCC 4.7% vs. 12.7%). Although nonactivated 4PCC has a black box warning for an increased risk of arterial and venous thromboembolic events, this risk appears to be similar to that for plasma. Although 4PCC is associated with a high direct acquisition cost, pharmacoeconomic analyses are currently investigating strategies for warfarin reversal to fully understand the cost implications.

3. rFVIIa is no longer recommended for warfarin reversal because of incomplete correction of factor levels inhibited by warfarin.
4. Recommendations: In a life-threatening hemorrhage, phytonadione 10 mg intravenously and a 4PCC (dose is determined by patient weight and pretreatment INR; see Table 9) are preferred for most patients. In patients with a contraindication to 4PCC (e.g., a history of heparin-induced thrombocytopenia), fresh frozen plasma 10–15 mL/kg may replace 4PCC for reversal. Although the goal INR is controversial, guidelines from the Neurocritical Care Society recommend trending an INR in patients with intracranial hemorrhage with repeat reversal strategies until the INR is less than 1.4. Randomized controlled trials of 4PCC included only patients with an INR of 2 or greater.
5. Target-specific oral anticoagulants (TSOACs) – Dabigatran/apixaban/rivaroxaban/edoxaban:
 - a. Proposed reversal with PCCs is theoretical, largely according to small clinical trials of healthy human volunteers evaluating laboratory reversal.
 - b. Coagulation assays that have direct, linear relationships to the TSOAC anticoagulation activity are not available for clinical use (Table 8). Therefore, the initial approach to reversal should be guided by clinical bleeding and the knowledge of preexisting TSOACs rather than coagulation assays.
 - c. Given the relatively short half-life of the TSOAC in patients with normal end-organ function and lack of drug-drug interactions, establishing the time from the last dose is critical in determining the likelihood that the drug is contributing to bleeding. In general, if it has been greater than 3–5 half-lives since the last dose, reversal is probably not indicated (Table 8).

Table 8. Summary of Oral Anticoagulants

	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Action	Vitamin K antagonist	Direct factor IIa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Peak action	4–5 days	~2 hr	~2 hr	~2 hr	1–2 hr
Half-life (hr)					
CrCl: > 80 mL/min/1.73 m ²	> 48 hr N/A	12–14	5–9	8–15	8.5
CrCl: 50–79 mL/min/1.73 m ²		17	9	15	9
CrCl: 30–49 mL/min/1.73 m ²		19	9	18	9
CrCl < 30 mL/min/1.73 m ²		28	10	17	9.5
Clinical coagulation monitoring	Protime/INR Quantitative	aPTT and TT Qualitative ECT and TT Quantitative	Protime Rivaroxaban: Qualitative Apixaban: Insensitive Edoxaban: Qualitative Chromogenic anti-factor Xa quantitative		

CrCl = creatinine clearance; ECT = ecarin clotting time; TT = thrombin time.

Information from: Dager WE. Developing a management plan for oral anticoagulation reversal. Am J Health Syst Pharm 2013;70:S21-31.

- d. Activated charcoal may be considered if the last dose was administered less than 2 hours previously. Given significant enterohepatic recirculation, charcoal can be given up to 6 hours after the last apixaban dose.

- e. Dabigatran reversal: Idarucizumab has recently been studied and approved for dabigatran reversal. Idarucizumab is a monoclonal antibody that directly binds both bound and unbound dabigatran with greater than 350 times the affinity of thrombin. In an interim analysis of 90 subjects, almost all patients who received idarucizumab 5 g intravenously had effective reversal of the anticoagulant effects of dabigatran immediately. However, given that dabigatran has a volume of distribution of greater than 50 L, about 20% of patients develop a redistribution of dabigatran and associated coagulopathy at 12–24 hours. The efficacy of repeat doses in this setting has not been established. If there is ongoing bleeding and suspicion for dabigatran activity, the package insert recommends obtaining an aPTT to rule out the presence of dabigatran before a repeat dose is given. Given the presence of idarucizumab, adjunctive reversal options such as dialysis should only be considered if there are concurrent indications based on renal function or if idarucizumab is ineffective.
- f. Factor Xa inhibitors: Andexanet alfa has also been studied for the reversal of factor Xa inhibitors, but it is not yet approved for clinical use at the time of writing this chapter. Andexanet is a modified factor Xa decoy protein, such that it directly binds to the factor Xa inhibitors to inactivate their anticoagulant response. It reverses the effects of both direct (TSOAC) and indirect (low-molecular-weight heparin) factor Xa inhibitors. Promising results of the effects of andexanet in healthy older adult volunteers have been published suggesting correction of the anti-factor Xa assay, and further studies are expected. Andexanet has a short half-life (1 hour); thus, redistribution and associated anticoagulant activity are also common after discontinuing andexanet, suggesting infusions are preferred to bolus dosing. Dosing for andexanet in phase III clinical trials is complex (Table 9) and individualized according to the anticoagulant used and the time from the last dose. For example, rivaroxaban achieves higher serum concentrations, so andexanet doses are higher for rivaroxaban with recent administration than for apixaban. Edoxaban is not included in the clinical trial, although andexanet would be expected to reverse its effects. Until andexanet is FDA label approved, several guidelines recommend 4PCC or aPCC administration at 50 units/kg.
- g. The novel antidotes for TSOAC reversal were reviewed by the FDA under fast track designation. Considering it is unethical to randomize a patient to placebo during antidote trials, the studies establishing efficacy and safety are single-arm trials. Therefore, it remains unknown whether the novel antidotes will affect morbidity or mortality associated with anticoagulants in life-threatening hemorrhage.

Table 9. Anticoagulant Reversal Agent Dosing in Life-Threatening Hemorrhage

Which Anticoagulant	Reversal Agent	Dose
Warfarin with elevated INR	Kcentra	INR 2–4: 25 unit/kg (max 2500 units) INR 4–6: 35 unit/kg (max 3500 units) INR > 6: 50 unit/kg (max 5000 units)
Dabigatran within 3–5 expected half-lives	Idarucizumab	5 g IV push
Enoxaparin or rivaroxaban within 7 hr or unknown time	Andexanet	IV bolus: 800 mg IV infusion: 8 mg/min for 120 min

IV = intravenous.

Information from: Sarode R, Milling TJ, Refaai MA, et al. Efficacy and safety of 4PCC in patients on vitamin K antagonists presenting with major hemorrhage. *Circulation* 2013;128:1234–43; Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med* 2015;373:511–20; and Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med* 2015;373:2413–24.

L. Reversal of Antiplatelet Agents (Table 10)

1. Clinical trials are controversial regarding the impact of antiplatelet agents on traumatic bleeding.
2. Recently, the first randomized controlled trial was published evaluating the impact of platelet transfusions in the setting of spontaneous intracranial hemorrhage in patients receiving antiplatelet therapy. In this

study, the odds of death were higher in the platelet transfusion group at 3 months than in placebo (OR 2.05; 1.18–3.56), suggesting platelet transfusions are inferior to standard of care. Study limitations include the lack of platelet function tests, inability to ensure compliance, and predominant use (greater than 90%) of aspirin as the antiplatelet agent. How this study translates to traumatic hemorrhage is unclear, but randomized controlled trials are clearly needed.

3. The European guidelines for the management of traumatic bleeding recommend platelet transfusions if clinically bleeding and platelet function assays show inhibition.
4. Desmopressin enhances platelet adherence and aggregation. Although its clinical efficacy is controversial, desmopressin 0.3–0.4 mcg/kg maybe considered to reverse platelet-inhibiting drugs but not routinely in bleeding trauma patients. There is a low risk of serious adverse effects, including hypervolemia, hyponatremia, facial flushing, and rare thrombosis.

Table 10. Antiplatelet Reversal in Life-Threatening Hemorrhage

Generic Drug (trade name) Mechanism of Action	Coagulation Assay Effects	Usual Half-life	Duration of Platelet Inhibition	Recommendations
Aspirin Inhibits platelet activation Irreversible inhibition of COX-1 and COX-2 enzymes	Optimal platelet function assay and thresholds controversial	3 hr	Lifetime of platelets 5–7 days	Use caution with antiplatelet reversal in patients with active or recent (within 3 mo) coronary artery disease <u>Reversal strategies:</u> Platelets Neurosurgical hemorrhage: 1 apheresis unit (moderate quality of evidence) Neurosurgery is not indicated: Platelet transfusions controversial and not recommended by the Society of Neurocritical Care (low quality of evidence) -and/or- Desmopressin (DDAVP) 0.4 mcg/kg once (low quality of evidence) *Transfused platelets with ticagrelor may become inhibited because of reversible activity at the P2Y ₁₂ receptor
Dipyridamole ± aspirin (Aggrenox, Persantine) Inhibits platelet activation Increases endogenous adenosine	Light transmission platelet aggregation is gold standard of platelet function	10–12 hr	2–3 days (dipyridamole) Lifetime of platelets 5–7 days for aspirin	
Clopidogrel (Plavix) Inhibits platelet activation Active metabolite irreversibly blocks ADP	testing but is not routinely available	6 hr	Lifetime of platelets 5–7 days	
Prasugrel (Effient) Inhibits platelet activation Active metabolite irreversibly blocks ADP	TEG with platelet mapping, VerifyNow, platelet	2–15 hr	Lifetime of platelets 5–7 days	
Ticagrelor (Brilinta) Inhibits platelet activation Reversibly blocks ADP	function analyzer, and bleeding time may be used	7–9 hr	3–5 days	

ADP = adenosine diphosphate; AA = arachidonic acid; COX = cyclooxygenase.

Information from: Levi M, Eerenberg E, Kamphuisen PW, et al. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. *J Thromb Haemost* 2011;9:1705-12; Mega J, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. *Lancet* 2015;386:281-91; and Rossant R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma, 4th ed. *Crit Care* 2016;20:R100. Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Neurocrit Care* 2016;24:6-46.

Patient Cases

6. A 54-year-old man with an unknown medical history presents after a helmeted motorcycle collision. On primary survey, his endotracheal tube is secured, respiratory rate is 32 breaths/minute, SBP is 84 mm Hg, and Glasgow Coma Scale score is 5T. The Focused Assessment with Sonography for Trauma (FAST) examination is positive, a massive transfusion protocol is initiated, and the patient is taken to the operating room for an emergency exploratory laparotomy. In the operating room, he is found to have grade 5 hepatic laceration, but ongoing coagulopathy and hypothermia necessitate a damage control surgery approach. After perihepatic packing, his abdomen is left open with a wound vacuum-assisted closure, and he is taken to the ICU for correction of his acidemia (pH 7.13), coagulopathy, and temperature 95°F (35°C). Five hours after admission, he has received 12 units of erythrocytes, 10 units of fresh frozen plasma, and 12 units of platelets. His laboratory values include aPTT 54 seconds, INR 1.4, fibrinogen 176 mg/dL, Plt 154,000/mm³, and ionized calcium 0.8 mmol/L. The TEG is normal other than LY30 15% (normal 0%–8%). His wife arrives at the hospital and clarifies that the patient was out for a Sunday afternoon ride. She also identifies that patient has a medical history of atrial fibrillation and takes dabigatran (last taken this morning). Which is the best pharmacologic treatment strategy for managing his ongoing hemorrhagic shock?
- A. Administer 4PCC 50 units/kg and calcium chloride 1 g over 10 minutes.
 - B. Administer tranexamic acid 1 g bolus with 1-g infusion over 8 hours and calcium chloride 1 g over 10 minutes.
 - C. Administer idarucizumab 5 g intravenous push and calcium chloride 1 g over 10 minutes.
 - D. Administer idarucizumab 5 g intravenous push, calcium chloride 1 g over 10 minutes, and tranexamic acid 1 g bolus, followed by 1 g infused over 8 hours.
7. A 67-year-old man is accidentally shot in the buttocks while deer hunting with his friends. He is brought to the ED immediately. While in transfer, the patient receives 500 mL of lactated Ringer solution. His vital signs on admission to the ED are as follows: blood pressure 97/58 mm Hg, heart rate 114 beats/minute, respiratory rate 25 breaths/minute, and temperature 95°F (35°C). On examination, he has 8/10 pain and appears anxious. Which is the best option for resuscitation strategies?
- A. Administer lactated Ringer solution at 1000 mL/hour to maintain a urine output greater than 30 mL/hour and an SBP greater than 100 mm Hg.
 - B. Transfuse 2 units of PRBCs, and administer a 1-L bolus of lactated Ringer solution to maintain a urine output greater than 1 mL/kg/hour.
 - C. Transfuse 2 units of PRBCs, 2 units of fresh frozen plasma, and a 1-L bolus of lactated Ringer solution to normal mentation.
 - D. Administer lactated Ringer solution at 1000 mL/hour to maintain a urine output greater than 30 mL/hour, an SBP greater than 90 mm Hg, and normal mentation.

Note: Cardiogenic shock will be discussed in the Cardiovascular Critical Care chapter.

VII. OBSTRUCTIVE SHOCK

A. Etiology and Epidemiology

1. Obstructive shock occurs as a result of extracardiac obstruction to flow in the cardiovascular system. The source of extracardiac obstruction may be either impaired diastolic filling (e.g., cardiac tamponade, tension pneumothorax, or constrictive pericarditis) or impaired systolic contraction (e.g., massive PE, acute or chronic PH or aortic dissection).
2. Obstructive shock is relatively rare, and only about 2% of patients requiring vasoactive medications have this type of shock.

B. Pathophysiology

1. The pathophysiologic hemodynamic hallmark of obstructive shock is decreased CO.
2. The specific pathophysiologic derangements depend on the underlying cause of the extracardiac obstruction but are generalized as follows.
 - a. In the setting of impaired diastolic filling, RV preload is significantly decreased because of the inhibition of venous return.
 - i. In cardiac tamponade, an accumulation of fluid in the pericardium leads to an increase in pericardial pressure.
 - ii. This results in an increase and equalization of diastolic pressures between the left and right heart (equalization of CVP, pulmonary artery diastolic pressure, and PCWP) and impaired ventricular filling. CVP and PCWP elevations should not be mistaken as representing an increase in ventricular volume (preload).
 - b. In the setting of impaired systolic function, ventricular afterload is acutely increased, leading to ventricular failure. This typically occurs in the setting of an acute RV afterload (PVR) increase caused by a massive PE or an acute PH. An acute increase in LV afterload does not typically lead to shock. An acute rise in RV afterload leads to reduced RV CO and a subsequent decrease in LV CO $\Rightarrow$ systemic hypotension $\Rightarrow$ reduced RV tissue perfusion (decreased right coronary artery perfusion) $\Rightarrow$ RV free wall ischemia $\Rightarrow$ reduced RV free wall contractility and further impairment of RV CO (a vicious cycle). In addition, acute RV pressure overload leads to a shift of the intraventricular septum toward the LV $\Rightarrow$ impaired LV diastolic filling (because of intraventricular dependence) $\Rightarrow$ further decrease in LV CO.

C. Resuscitation and Treatment

1. Fluid administration and vasoactive medications may be used as a temporizing measure to increase tissue perfusion.
 - a. Intravenous fluids (typically crystalloids) are usually recommended, but they may be ineffective at improving CO.
 - i. Cardiac tamponade: Patients with preexisting hypovolemia may respond to fluids, but in general, hemodynamics may not improve with fluid administration. Despite this finding, fluid administration is usually recommended in the setting of cardiac tamponade.
 - ii. Massive PE: Initial fluid administration improves CO, but care should be taken because excessive fluid administration can lead to further RV dilation and impaired LV CO from worsened septal shifting and decreased LV filling (because of intraventricular dependence).
 - iii. Optimization of fluids in patients with acute or chronic PH is challenging. Some patients (those with signs of intravascular volume depletion) may require fluids, whereas others may require diuretics to reduce RV dilation and improve LV filling (even in the setting of vasoactive medication administration).

- b. Vasopressors should be initiated to increase MAP and maintain an adequate perfusion pressure. This is particularly important in the setting of massive PE because adequate right coronary artery perfusion is of greatest importance to prevent/reduce RV free wall ischemia. Caution must be taken, though, because catecholamine vasopressors may increase PVR (which may worsen RV dysfunction).
 - c. Inotropes may increase RV CO in the setting of massive PE or acute or chronic PH but are likely ineffective in tamponade.
 - d. Inhaled nitric oxide or aerosolized prostacyclin therapy may be effective in decreasing RV afterload in the setting of acute or chronic PH, but neither therapy is likely effective for massive PE or cardiac tamponade.
2. Definitive treatment of the extracardiac obstruction is paramount.
 - a. Impaired diastolic filling
 - i. Cardiac tamponade: Pericardiocentesis or surgical evacuation and potential drain placement
 - ii. Tension pneumothorax: Needle decompression and potential chest tube thoracostomy
 - b. Impaired systolic function (massive PE): Embolism dissolution (thrombolytic therapy) or removal (surgical or catheter thrombectomy)
 - i. Thrombolytic agents (Table 11) bind the plasminogen/plasmin complex, which may be either circulating or bound to the clot surface. This binding hydrolyzes a peptide bond to form free plasmin. Circulating plasmin is quickly neutralized by α -antiplasmin, but fibrin-bound plasmin subsequently hydrolyzes bonds within the clot matrix, leading to clot lysis. As such, thrombolytic agents can lead to rapid PE dissolution and a subsequent decrease in RV afterload (PVR), but they may also cause bleeding.

Table 11. Thrombolytic Agents for Acute PE

Drug	Dose		Pearl
	Initial	Maintenance	
Alteplase ^a	10 mg over 10 min	90 mg over 2 hr	Fibrin selective Half-life: 5 min
Tenecteplase ^b	< 60 kg: 30 mg push 61–70 kg: 35 mg push 71–80 kg: 40 mg push 81–90 kg: 45 mg push > 91 kg: 50 mg push	N/A	Fibrin selective (14-fold) Half-life: 90–130 min Only need bolus dose Less expensive than alteplase
Streptokinase ^a	250,000 units over 30 min	100,000 units/hr over 24 hr	Nonselective Antigenic
Urokinase ^a	4400 units/kg over 10 min	4400 units/kg/hr over 12 hr	Nonselective Concentration too dilute

^aIndicates FDA approved for treatment of PE.

^bIdentifies drug is not FDA approved for the treatment of PE.

Information modified from: Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e419S-94S; and Daley MJ, Lat I. Clinical controversies in thrombolytic therapy for the management of acute pulmonary embolism. Pharmacotherapy 2012;32:158-72.

- ii. Thrombolytics do not decrease mortality in unselected patients with PE compared with heparin alone (6.7% vs. 9.6%; OR 0.67 [95% CI, 0.40–1.12]), but they may improve outcomes in patients with an increased risk of death. As such, early PE-related mortality risk stratification is necessary to guide thrombolytic therapy administration.
 - (a) High risk: Massive PE. Defined not by clot burden, but by acute PE causing hemodynamic changes: Hypotension (SBP less than 90 mm Hg for at least 15 minutes or requiring vasoactive support not from another cause), pulselessness, or bradycardia (heart rate less than 40 beats/minute with signs of shock)
 - (b) Intermediate risk: Submassive PE. Acute PE without systemic hypotension but with either (1) RV dysfunction (RV dilation or systolic dysfunction on echocardiogram, RV dilation on chest CT, brain natriuretic peptide greater than 90 pg/mL, N-terminal pro-brain natriuretic peptide greater than 500 pg/mL, or electrocardiographic changes [new complete or incomplete right bundle-branch block, anteroseptal ST-elevation or depression, or anteroseptal T-wave inversion]) or (2) myocardial necrosis (troponin I greater than 0.4 ng/mL or troponin T greater than 0.1 ng/mL)
 - (c) Intermediate risk may be further classified by the presence of both RV dysfunction and myocardial necrosis, termed *intermediate-high risk*. If only RV dysfunction or myocardial necrosis is present, it is classified as intermediate-low risk.
 - (d) Low risk: Acute PE not meeting the definition for massive or submassive PE
- iii. In cardiac arrest, guidelines recommend either an alteplase bolus of 50 mg (repeated if needed) or weight-based tenecteplase if PE is confirmed as the contributing cause of the arrest. If PE is suspected but not confirmed, the guidelines state that evidence is insufficient to either support or refute empiric systemic thrombolytics. These recommendations are based on possible improved outcomes with thrombolytics in peri-arrest settings, but prospective evaluations are conflicting.
- iv. Two practice guidelines recommend the administration of systemic thrombolytics for patients with massive PE and an acceptable risk of bleeding complications.
 - (a) These recommendations are supported by a meta-analysis, which found that in patients with massive PE, thrombolytics were associated with a lower rate of recurrent PE or death than heparin alone (9.4% vs. 19.0%; OR 0.45 [95% CI, 0.22–0.92]).
 - (b) In addition, a recent analysis of a Nationwide Inpatient Sample containing over 70,000 patients with unstable PE (defined as the presence of shock or a requirement for mechanical ventilation) suggested a mortality reduction attributable to PE with systemic thrombolytics (8.4% vs. 42%; $p < 0.01$).
 - (c) Systemic thrombolytics for massive PE are likely underused because about 70% of patients in this database were not treated.
- v. Clinical controversy exists regarding the risk-benefit profile of thrombolytic administration for submassive PE.
 - (a) In a study of patients with submassive PE, the addition of alteplase 100 mg infused over 2 hours to heparin compared with heparin plus placebo (heparin alone) was associated with a lower rate of death or clinical deterioration requiring an escalation in treatment (11.0% vs. 24.6%, $p = 0.006$). This result was driven by more patients in the heparin-alone arm who received secondary thrombolytics (23.2% vs. 7.6%, $p = 0.001$), which may have been influenced by the investigators' ability to break the blinding of treatment allocation in the study. Bleeding was no different between study arms.
 - (b) A recently published study of patients with submassive PE (fulfilling both RV dysfunction and myocardial necrosis criteria) randomized patients to weight-based tenecteplase plus heparin or placebo plus heparin (heparin alone). Between randomization and day 7, patients allocated to tenecteplase less commonly experienced death or hemodynamic

decompensation (2.6% vs. 5.6%, $p=0.02$; number needed to treat = 33 patients [95% CI, 18–162 patients]) but more commonly experienced major extracranial bleeding (6.3% vs. 1.2%, $p<0.001$; number needed to harm = 20 patients [95% CI, 13–35 patients]) and stroke (2.4% vs. 0.2%, $p=0.003$; number needed to harm = 47 patients [95% CI, 26–107 patients]). The difference in stroke incidence was driven by a higher incidence of hemorrhagic stroke in the tenecteplase arm (2.0% vs. 0.2%, $p=0.01$; number needed to harm = 57 patients [95% CI, 30–164 patients]). The overlapping 95% CIs for number needed to treat and number needed to harm for clinically important outcomes call into question the risk-benefit profile of tenecteplase for submassive PE.

- (c) Since publication of the trial of tenecteplase in intermediate-risk PE, two practice guidelines do not recommend routine systemic thrombolytics for most patients. However, in select patients with signs or risk of deterioration and a low bleeding risk, systemic thrombolytics may be considered.
- vi. The risks and benefits of thrombolytics are best determined on a case-by-case basis by the bedside clinician (Table 12).
- vii. In extreme circumstances (e.g., in the setting of massive PE with impending cardiac arrest), even the presence of strong risk factors for bleeding may not preclude some clinicians from administering thrombolytics because of the potential for benefit from the therapy. In these settings, even the “contraindications” noted in the product labeling, other than active internal bleeding, may be considered “relative contraindications” by some clinicians for thrombolytic administration.

Table 12. Risk Factors for Bleeding After Administration of Thrombolytic Therapy

Alteplase package insert contraindications	
Active internal bleeding	Recent intracranial or intraspinal surgery or trauma
History of cerebrovascular accident (intracranial hemorrhage or ischemic stroke)	Severe uncontrolled hypertension ^a
Malignant intracranial neoplasm, arteriovenous malformation, or aneurysm	Known bleeding diathesis ^b
Alteplase package insert warnings	
Recent major surgery	Significant closed-head or facial trauma with radiographic evidence of bony fracture or brain injury within 3 wk
Cerebrovascular disease	Recent GI or genitourinary bleeding
Hemostatic defects (including those secondary to severe hepatic or renal disease)	Hypertension (SBP $\geq$ 175 mm Hg and/or DBP $\geq$ 110 mm Hg)
Acute pericarditis	Subacute bacterial endocarditis
Recent trauma	Significant hepatic dysfunction
Age > 75 yr	Needle puncture at noncompressible site
Left heart thrombus	Pregnancy
Septic thrombophlebitis or occluded arteriovenous cannula at seriously infected site	Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions
Recent receipt of oral anticoagulants	

Table 12. Risk Factors for Bleeding After Administration of Thrombolytic Therapy (*continued*)

Bleeding risk factors reported in published literature	
Recent internal bleeding	Suspected aortic dissection
Poorly controlled hypertension at baseline	Acute pancreatitis
Acute myocardial infarction	Cardiopulmonary resuscitation > 10 min
Stool occult blood positive	Bilirubin concentration > 3 mg/dL
Presence of an intra-aortic balloon pump	Dementia
African American race	

^aUndefined for PE, but noted as > 185 mm Hg systolic or > 110 mm Hg diastolic for acute ischemic stroke.

^bUndefined for PE, but noted as INR > 1.7 or Plt < 100,000/mm³ for acute ischemic stroke.

Adapted, with permission, from: Curtis GC, Lam SW, Reddy AJ, et al. Risk factors associated with bleeding after alteplase administration for pulmonary embolism: a case-control study. *Pharmacotherapy* 2014;34:818-25; and Daley MJ, Lat I. Clinical controversies in thrombolytic therapy for the management of acute pulmonary embolism. *Pharmacotherapy* 2012;32:158-72.

- viii. Ultrasound-assisted catheter-directed thrombolysis provides the potential to administer thrombolytics locally, which may improve hemodynamics while significantly decreasing the risk of major bleeding. However, prospective comparative data with systemic thrombolytic therapy are lacking, and site experiences and resources are needed.
- ix. Patients with a massive or submassive PE should be considered for surgical embolectomy or catheter thrombectomy if they (1) have an unacceptably high risk of bleeding if administered thrombolytics, (2) remain unstable despite thrombolytic administration, or (3) have shock likely to cause death within hours (before the onset of systemic thrombolytics).
- x. Unless contraindicated, all patients should also receive a parenteral anticoagulant. Intravenous unfractionated heparin is recommended over alternative agents for patients in whom thrombolytic therapy is being considered or planned. The alteplase package insert recommends holding heparin during the alteplase infusion and reinstituting it when the aPTT returns to less than 2 times the upper limit of normal. However, in some clinical trials, heparin was continued during thrombolytic administration. Therefore, there is variability in concurrent heparin administration in practice, and this decision should be individualized according to risk assessment.
- xi. If anticoagulation is contraindicated, an IVC filter should be placed.

Patient Case

8. A 48-year-old woman (weight 75 kg) presented to the ED with shortness of breath. The patient's hypoxemia did not improve with supplemental oxygen, and her chest radiograph was not significant for any lung abnormalities. A contrasted chest CT scan revealed a PE in the subsegmental branch of the right pulmonary artery and no RV dilation. The patient's vital signs and significant laboratory values are as follows: heart rate 118 beats/minute, blood pressure 98/62 mm Hg, urine output 1 mL/kg/hour, troponin T 0.06 ng/mL, brain natriuretic peptide 60 pg/mL, lactate 0.9 mmol/L, and SCr 1.1 mg/dL. In addition to initiating a parenteral anticoagulant, which is best for the patient?
 - A. Tenecteplase 40-mg bolus.
 - B. Alteplase 100-mg infusion over 2 hours.
 - C. Alteplase 50-mg bolus.
 - D. No thrombolytic therapy.

VIII. VASODILATORY AND DISTRIBUTIVE SHOCK

A. Etiology and Epidemiology

1. *Vasodilatory shock* is a broad term that describes tissue hypoperfusion secondary to a decrease in SVR (or hypoperfusion despite a normal or elevated CO), whereas *distributive shock* is technically a subset of vasodilatory shock that describes maldistribution of blood flow at the level of microcirculation (shunting) or at the organ level. This differentiation is likely trivial, though, because distributive shock usually exists in vasodilatory shock, and the terms are often used interchangeably.
2. Septic shock is the most common cause of vasodilatory shock, but this shock type may also occur in the setting of several other conditions, including immune-mediated (“anaphylactic”) and nonimmunologic (“anaphylactoid”) reactions, neurogenic shock (classically secondary to spinal cord injury), intoxication, peridural or epidural infusion, adrenal insufficiency (Addisonian crisis), and thyroid insufficiency (myxedema coma) or as a component of ischemia-reperfusion injury (e.g., after cardiac arrest or cardiopulmonary bypass). Vasodilatory shock also occurs because of prolonged severe hypotension from any initial shock type (vasodilation is a final common pathway).
3. The three most commonly encountered causes of vasodilatory shock are septic shock (which will be covered in detail in section IX, Sepsis), immune-mediated (anaphylactic) shock, and neurogenic shock, which will be the focus of this section.
4. Vasodilatory shock is the most commonly encountered type of shock, with about 66% of patients requiring vasoactive medications having this shock type. Most cases (94%) of vasodilatory shock are caused by septic shock.

B. Pathophysiology

1. Vasodilatory shock occurs because of a failure of the vascular smooth muscle cells to constrict, whether from a failure of vasoconstriction methods or the inappropriate activation of vasodilatory mechanisms. In most cases (with the exception of neurogenic shock), this failure occurs despite high plasma concentrations of endogenous vasoconstrictors (e.g., norepinephrine, epinephrine, and angiotensin II).
2. Potential mechanisms of vasodilation
 - a. Activation of cellular ATP-dependent potassium channels leads to hyperpolarization of the vascular smooth muscle cell (through potassium efflux), which prevents extracellular calcium influx by voltage-gated calcium channels. As a result, cellular depolarization is prevented, high cytosolic calcium concentrations needed for vasoconstriction are not achieved, and vasodilation occurs.
 - b. Increased expression of inducible nitric oxide synthase leads to increased intracellular nitric oxide concentrations and resultant vasodilation by a cyclic guanosine monophosphate–mediated mechanism. Nitric oxide may also induce vasodilation by activating potassium channels in the plasma membrane, leading to cellular hyperpolarization, as described earlier.
 - c. Inappropriately low plasma vasopressin concentrations despite the level of shock (“relative vasopressin deficiency”) may contribute to the inability of the vascular smooth muscle cell to contract. Although initial plasma vasopressin concentrations may be high in the initial setting of shock, the concentrations of vasopressin may decrease to physiologic concentrations as quickly as 1 hour after the onset of hypotension.
3. The pathogenesis of vasodilation depends on the underlying cause.
 - a. Septic shock involves complex interactions between an infecting pathogen and the host inflammatory, immune, and coagulation response. The pattern-recognition (e.g., toll-like) receptors on innate immune system cells recognize specific molecules present in microorganisms and signal the release of nuclear factor- κ B, which leads to the transcription of both proinflammatory cytokines (e.g., interleukin-1 β , interleukin-6, tumor necrosis factor alpha) and anti-inflammatory cytokines (i.e.,

interleukin-10). These proinflammatory cytokines activate neutrophils and endothelial cells, leading to an increased expression of inducible nitric oxide synthase and subsequent vasodilation.

- b. Neurogenic shock involves a decrease in sympathetic outflow from the CNS with unopposed parasympathetic activity. As such, vascular tone is lost, resulting in a decrease in SVR and venous pooling of blood with a subsequent decrease in preload. Concomitant bradycardia is common, and decreased CO (even after fluid administration) may occur because of the interruption of cardiac sympathetic innervation, further contributing to hypotension. This shock type classically occurs as a complication of an acute spinal cord injury at the level of the thoracic or cervical vertebra, most commonly when the injury is above the fifth cervical vertebra.
 - c. Immune-mediated (anaphylactic) shock occurs because of reexposure to a sensitizing foreign pathogen that stimulates immunoglobulin E-mediated mast cell or basophil degranulation and resultant cytokine (e.g., histamine and tryptase) release. The mechanism of vasodilation is complex and multifaceted, but for example, the binding of histamine to the histamine-1 receptor can activate nitric oxide synthase with resultant increases in nitric oxide and vasodilation.
4. Profound vasodilation leads to ineffective circulating plasma volume (either from venodilation [“venous pooling”] or from fluid shifts because of increased vascular permeability) and resultant decreases in cardiac preload and CO.

C. Resuscitation and Treatment

1. Resuscitation and treatment of patients with sepsis and septic shock is covered later in the chapter.
2. The underlying cause of the shock state must quickly be addressed when resuscitation is initiated.
 - a. Septic shock requires rapid (within 1 hour of disease recognition) administration of antimicrobials with activity against all likely pathogens.
 - b. The potential offending agent should be discontinued (for medication-related reactions) and potentially removed (in the setting of envenomation) for patients with immune-mediated (anaphylactic) shock.
3. Treatment goals and end points of resuscitation are usually similar to those listed in section IX, Resuscitation Parameters and End Points. In the setting of acute spinal cord injury, a MAP goal of at least 85 mm Hg has been associated with improved outcomes in uncontrolled studies. As such, guidelines recommend an initial MAP goal of 85–90 mm Hg in patients with acute spinal cord injury (level III recommendation).
4. Initial resuscitation
 - a. The treatment of choice is intravenous fluids, which restore effective circulating volume.
 - i. Crystalloids (e.g., lactated Ringer solution or normal saline) are typically the initial fluid of choice.
 - ii. Fluid administration should be given until the patient is no longer fluid responsive.
 - b. Vasopressors should be initiated for hypotension unresponsive to fluid administration.
 - i. Norepinephrine is usually considered the first-line vasopressor because of its ability to increase SVR without decreasing CO.
 - ii. Epinephrine is typically used for patients with immune-mediated (anaphylactic) shock out of convention, but no compelling data support the use of epinephrine over alternative agents.
 - iii. In the setting of neurogenic shock, agents with combined vasoconstrictive and inotropic properties (e.g., norepinephrine, dopamine, epinephrine) are preferred. Phenylephrine may also be used, but a concomitant inotropic agent (e.g., dobutamine) is often administered.
 - (a) Atropine may also be given for symptomatic bradycardia.
 - (b) Adjunctive oral pseudoephedrine may also be used.

5. Additional therapies
 - a. Immune-mediated (anaphylactic) shock is also conventionally treated with concomitant histamine-1 and histamine-2 receptor antagonists and corticosteroids, though there are no strong data to support the use of these agents.
 - b. The most recent guidelines regarding the treatment of patients with acute cervical spine and spinal cord injuries recommend against administering methylprednisolone (level I recommendation).
 - c. Patients with vasodilatory shock secondary to adrenal insufficiency (Addisonian crisis) should receive intravenous corticosteroids (typically hydrocortisone 100 mg every 8 hours).
 - d. The management of vasodilatory shock secondary to thyroid insufficiency (myxedema coma) is outlined in the Hepatic Failure/GI/Endocrine Emergencies chapter.

IX. SEPSIS

- A. Introduction and Definitions
 1. Sepsis is caused by a dysregulated host response to infection.
 2. Traditionally, the diagnosis of sepsis has required a known or suspected source of infection with two or more criteria of the systemic inflammatory response syndrome. Sepsis was further classified as sepsis, severe sepsis (sepsis with organ dysfunction), or septic shock (sepsis with arterial hypotension unresponsive to fluid administration).
- B. The definition of sepsis was recently updated to reflect the contemporary understanding of this syndrome.
 1. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
 2. Organ dysfunction can be identified as an acute change in the total Sequential Organ Failure Assessment (SOFA) score of 2 points or higher consequent to the infection.
 3. A prompt identification tool (“qSOFA”) for bedside use outside the ICU was also proposed, which includes alteration in mental status, SBP of 100 mm Hg or less, and respiratory rate of 22 breaths/minute or greater. Fulfillment of two of these three criteria had predictive validity for mortality similar to the full SOFA score outside the ICU (technically, Glasgow Coma Scale score of 13 or less was used in the regression model but was simplified to any alteration in mental status for the qSOFA).
 - a. Of importance, qSOFA does not define sepsis, but two or more qSOFA criteria are a predictor of both increased mortality and ICU stays of more than 3 days in non-ICU patients. These criteria should also be used to investigate further for infection.
 - b. Use of the full SOFA score was superior to use of qSOFA for prediction of mortality in patients in the ICU.
 4. Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to increase mortality substantially.
 5. Patients with septic shock can be identified as those with sepsis with persistent hypotension requiring vasopressors to maintain a MAP of 65 mm Hg and greater and having a serum lactate concentration greater than 2 mmol/L.
 6. With this new definition, the systemic inflammatory response syndrome criteria are no longer used, and severe sepsis no longer exists as a clinical entity.
 7. The new sepsis definition better identifies patients at risk of in-hospital mortality secondary to sepsis (about 10% mortality) than the previous definition.

8. These definitions will likely shift patient identification and terminology in clinical practice, particularly for patient inclusion in studies.
9. The Surviving Sepsis Campaign (SSC), a joint collaboration between the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, has published three iterations of international guidelines for the treatment of patients with severe sepsis and septic shock. The 2012 SSC guidelines, published in early 2013, were sponsored or endorsed by 30 international organizations and inform many of the recommendations in this section.
10. An update to the SSC bundle was released online in 2015. The SSC website (www.survivingsepsis.org) contains updated recommendations, tools for implementation, and official statements from the campaign regarding ongoing events (e.g., the new sepsis definitions).

C. Epidemiology

1. Sepsis is common, with an annual incidence in the United States above 890,000, rising by about 13% per year, and has an associated cost exceeding \$24 billion.
2. In a European epidemiologic study, 37% of all ICU patients had sepsis.
3. Septic shock is the most commonly encountered shock type, accounting for 62% of all cases of shock syndromes requiring vasopressors.
4. In-hospital mortality associated with severe sepsis and septic shock (using previous definitions) is around 18%–25%, whereas mortality at 2 years is around 45%.
5. In-hospital mortality of patients with septic shock defined according to the new definition was 35%–54% in large retrospective data sets.

D. Pathophysiology

1. Sepsis and septic shock involve complex interactions between an infecting pathogen and the host inflammatory, immune, and coagulation response.
2. Hypotension develops through the inappropriate activation of vasodilatory mechanisms (increased nitric oxide synthesis) and the failure of vasoconstrictive pathways (activation of ATP-dependent potassium channels in vascular smooth muscle cells and vasopressin deficiency), resulting in a vasodilatory shock. In addition, blood flow is inappropriately dispersed at the organ level or in the microcirculation (shunting), leading to distributive shock.
3. Vascular endothelial cell injury leads to capillary fluid leak and a resultant decrease in preload. Venous dilation further exacerbates the decrease in cardiac preload.
4. Tissue DO_2 may be further impaired by a decrease in CO , inadequate CaO_2 (low hemoglobin concentration or saturation), or impaired oxygen unloading from hemoglobin. These multifactorial hemodynamic abnormalities lead to decreased effective tissue perfusion, in which VO_2 exceeds DO_2 and cellular injury results. This further compounds the proinflammatory and procoagulant state, precipitating multi-organ dysfunction and possibly death.

E. Diagnosis

1. There is no specific diagnostic test for sepsis or septic shock, and the diagnosis is typically based on the definitions noted earlier.
2. Although bacteremia has been suggested as a fundamental, pathophysiologic determinant of sepsis, positive blood cultures are infrequently established during sepsis. This may be because of delays in obtaining blood cultures, prior antibiotic treatment, or inadequate culturing techniques.
3. After a thorough history and physical examination, radiologic imaging should be performed in an effort to confirm a potential source of infection.

4. Recognizing that pneumonia is the most common site of infection (in about 45% of cases), followed by intra-abdominal infection (about 30%) and urinary tract infection (about 11%), microbial cultures should be sent from all suspected infectious sites as soon as possible.
5. All microbial cultures are negative in more than 25% of cases, and only 30% of patients have positive blood cultures. The most commonly isolated pathogens in ICU patients are gram-negative bacteria (62%), gram-positive bacteria (47%), and fungi (19%).
6. Cultures should be obtained before antimicrobial therapy is initiated unless doing so would result in a significant (greater than 45 minutes) delay in therapy.

F. Treatment of Sepsis and Septic Shock

1. The pharmacologic-related 2012 SSC recommendations (which use the previous definitions and terminology for sepsis) can be found in Box 2.

Box 2. Pharmacologic-Related Surviving Sepsis Campaign Recommendations for Patients with Sepsis and Septic Shock^{a,b}

Fluid Therapy
1. Crystalloids as the initial fluid of choice in the resuscitation of sepsis and septic shock (grade 1B) 2. Avoid the use of hydroxyethyl starch for fluid resuscitation of sepsis and septic shock (grade 1B) 3. Albumin in the fluid resuscitation of sepsis and septic shock when patients require a substantial amount of crystalloids (grade 2C)
Vasopressors and Inotropes
1. Vasopressor therapy initially to target a MAP of 65 mm Hg (grade 1C) 2. Norepinephrine as the first-choice vasopressor (grade 1B) 3. Epinephrine when an additional agent is needed to maintain adequate pressure (grade 2B) 4. AVP 0.03 unit/min can be added to NE with intent of either raising MAP or decreasing NE dosage (UG). AVP is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension, and AVP doses > 0.03–0.04 unit/min should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG) 5. Dopamine as an alternative vasopressor agent to NE only in highly selected patients (i.e., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C) 6. Phenylephrine is not recommended in the treatment of septic shock except (1) when NE is associated with serious arrhythmias, (2) when CO is known to be high and blood pressure persistently low, or (3) as salvage therapy when combined inotrope/vasopressor drugs and low-dose AVP have failed to achieve MAP targets (grade 1C) 7. A trial of dobutamine infusion (up to 20 mcg/kg/min) is to be administered or added to vasopressor (if in use) in the presence of (1) myocardial dysfunction as suggested by elevated cardiac filling pressures and low CO or (2) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C)
Antimicrobial Therapy
1. Administration of effective intravenous antimicrobials within the first hour of recognizing septic shock (grade 1B) and sepsis without septic shock (grade 1C) should be the goal of therapy 2a. Initial empiric anti-infective therapy should include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis (grade 1B) 2b. The antimicrobial regimen should be reassessed daily for potential de-escalation (grade 1B)

Box 2. Pharmacologic-Related Surviving Sepsis Campaign Recommendations for Patients with Sepsis and Septic Shock^{a,b} (continued)

Antimicrobial Therapy (continued)	
3.	Low procalcitonin concentrations or similar biomarkers should be used to assist the clinician in discontinuing empiric antibiotics in patients who appear to have sepsis but have no subsequent evidence of infection (grade 2C)
4a.	Combination empiric therapy for patients with neutropenia with sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as <i>Acinetobacter</i> and <i>Pseudomonas</i> spp. (grade 2B)
4b.	Combination therapy, when used empirically in patients with sepsis, should not be administered > 3–5 days. De-escalation to the most appropriate single-agent therapy should be performed as soon as the susceptibility profile of the pathogen(s) is known (grade 2B)
5.	Therapy duration should typically be 7–10 days, if clinically indicated. Longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with <i>Staphylococcus aureus</i> , some fungal and viral infections, or immunologic deficiencies, including neutropenia (grade 2C)
6.	Antiviral therapy should be initiated as early as possible in patients with sepsis and septic shock of viral origin (grade 2C)
7.	Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of a noninfectious cause (UG)
Corticosteroids	
1.	Avoid the use of intravenous hydrocortisone to treat adult patients with septic shock if adequate fluid resuscitation and vasopressor therapy can restore hemodynamic stability. If this is not achievable, intravenous hydrocortisone alone at a dose of 200 mg/day may be added (grade 2C)
2.	Avoid the use of the ACTH stimulation test to identify those who should receive hydrocortisone (grade 2B)

^aStrength and evidence level of recommendations listed in parentheses are according to the Grading of Recommendations Assessment, Development and Evaluation system. The system classifies strength of recommendations as strong (1) or weak (2) and quality of evidence as high (A), moderate (B), low (C), or very low (D). Recommendations not conducive for the grading process were regarded as ungraded (UG).

^bRecommendations pertaining to initial resuscitation were not included in this box because they were updated in 2015 and are included in Box 3.

ACTH = adrenocorticotropic hormone; AVP = arginine vasopressin; CO = cardiac output; MAP = mean arterial pressure; NE = norepinephrine.

Information from: Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.

2. Early recognition and treatment of patients with sepsis, particularly those with sepsis-induced end-organ hypoperfusion, is of utmost importance.
3. Initial resuscitation
 - a. The initial goals of therapy are to restore effective tissue perfusion (by administering intravenous fluids and vasoactive medications) while treating the underlying cause of the syndrome (through antimicrobial administration and infectious source control, as applicable).
 - b. Patients should first be administered a fluid challenge of 30 mL/kg of crystalloid solution as quickly as possible.
 - c. If the blood pressure reading does not improve after the fluid challenge, or if the initial serum lactate concentration is above 4 mmol/L, quantitative resuscitation should be initiated.
 - i. This strategy includes intensive monitoring (e.g., placement of a central venous [superior vena cava] catheter or echocardiography), setting goals for hemodynamic support, and using therapies to achieve those goals (e.g., use and optimization of fluids, vasopressors, and Do₂ methods).
 - ii. Priority should be placed on early, aggressive fluid administration to optimize cardiac preload and improvement/preservation of organ perfusion pressure.

- d. Quantitative resuscitation strategies
 - i. “Early goal-directed therapy”
 - (a) The landmark study of early goal-directed therapy evaluated 263 patients with severe sepsis and septic shock treated in the ED for the first 6 hours after presentation.
 - (b) Both study arms had treatment goals of a CVP greater than 8 mm Hg, MAP greater than 65 mm Hg, and urine output greater than 0.5 mL/kg/hour.
 - (c) Treatment of patients in the standard therapy group was at the clinician’s discretion, whereas treatment of those in the intervention arm uniformly incorporated a protocol to achieve the previously mentioned goals and incorporated ScvO₂ as a treatment goal (70% or greater).
 - (d) Early, aggressive, goal-directed resuscitation was associated with a 16% absolute risk reduction in hospital mortality versus standard therapy (30.5% vs. 46.5%, p<0.009).
 - (e) It is unclear whether the use of a goal-directed protocol or ScvO₂ as a treatment goal (or both) led to the study’s positive findings.
 - (f) There are several critiques of this study, including a higher-than-expected mortality rate in the standard therapy arm, the incorporation of CVP as a resuscitation goal, and the single-centered nature of the study.
 - (g) Several other observational studies have shown reductions in mortality with this approach compared with historical controls.
 - (h) Many centers faced logistical and financial barriers to implementing the early goal-directed therapy protocol. As such, alternative approaches to quantitative resuscitation were developed and studied.
 - ii. Protocolized Care for Early Septic Shock (ProCESS) study
 - (a) Randomized 1341 ED patients with septic shock in U.S. academic medical centers to three treatment arms:
 - (1) Early goal-directed therapy (with the same protocol noted previously)
 - (2) Protocol-based standard care that did not require the use of a central venous catheter but that used clinician judgment for fluid administration and hypoperfusion, together with a shock index (heart rate/SBP) less than 0.8 and an SBP greater than 100 mm Hg as resuscitation targets
 - (3) Usual care (treatment according to the bedside physician)
 - (b) There was no difference in 60-day mortality between the treatment arms (early goal-directed therapy 21.0% vs. protocol-based standard care 18.2% vs. usual care 18.9%, p=0.55, for the three-group comparison).
 - (c) Patients in the early goal-directed therapy arm more often were admitted to the ICU (91.3% vs. protocol-based standard care 85.4% vs. usual care 86.2%, p=0.01).
 - (d) Patients in the protocol-based standard care arm more commonly developed new renal failure in the first week (6.0% vs. early goal-directed therapy 3.1% vs. usual care 2.8%, p=0.04), despite having the highest volume of fluid administered during the first 6 hours after randomization (3.3 L vs. early goal-directed therapy 2.8 L vs. usual care 2.3 L, p<0.001).
 - (e) This study has several critiques, primarily a likely shift of usual care toward therapy that resembles quantitative resuscitation (both of which may have contributed to a type II error).
 - iii. Australasian Resuscitation in Sepsis Evaluation (ARISE) study
 - (a) Randomized ED patients in both academic and nonacademic centers mainly in Australia and New Zealand to either early goal-directed therapy (with the same protocol noted previously) or usual care (treatment according to the bedside physician)
 - (b) Patients were required to have been initiated on antimicrobials before study entry.

- (c) There was no difference in 90-day mortality between the treatment arms (early goal-directed therapy 18.6% vs. usual care 18.8%, $p=0.90$).
 - (d) In addition, there were no differences between treatment arms in prespecified subgroup analyses or mortality rates at different time points (including hospital mortality).
 - (e) Because the enrolled patients had lower severity of illness scores and lower mortality at 90 days, it could be suggested that the patients enrolled in this study were less acutely ill than patients enrolled in the ProCESS trial. However, about 70% of the patients in the ARISE study had septic shock at randomization (only 54% of patients in the ProCESS trial met this criterion), suggesting the patients in ARISE were critically ill and the intended population was studied.
- iv. Protocolised Management in Sepsis (ProMISe) study
- (a) Randomized 1260 ED patients in both academic and nonacademic centers in England to either early goal-directed therapy or usual care (identical to the ARISE study in design)
 - (b) Patients were required to have been initiated on antimicrobials before study entry.
 - (c) No difference in 90-day mortality was observed between those treated with early goal-directed therapy and those treated with usual care (29.5% vs. 29.2%, $p=0.90$).
 - (d) Patients in the early goal-directed therapy arm had higher SOFA scores at 6 hours (mean 6.4 ± 3.8 vs. 5.6 ± 3.8 , $p<0.001$), more commonly received advanced cardiovascular support (37.0% vs. 30.9%, $p=0.026$), and had a longer ICU length of stay (median [interquartile range] 2.6 [1.0–5.8] days vs. 2.2 [0.0–5.3] days, $p=0.005$).
 - (e) There was no difference between groups in health-related quality of life at 90 days.
 - (f) Although there was no difference in average cost between groups (early goal-directed therapy \$17,647 vs. usual care \$16,239; $p=0.26$), the probability that early goal-directed therapy was cost-effective was below 20%.
 - (g) There were no differences between treatment arms in prespecified subgroup analyses or mortality rates at different time points (including hospital mortality).
- v. Discussion of ProCESS, ARISE, and ProMISe studies
- (a) In a systematic review and meta-analysis that included the ProCESS, ARISE, and ProMISe studies, early goal-directed therapy was not associated with a difference in mortality compared with control (OR 1.01; 95% CI, 0.88–1.16; $p=0.9$), but it was associated with increased vasopressor use (OR 1.25; 95% CI, 1.10–1.41; $p<0.001$) and more frequent ICU admission (OR 2.19; 95% CI, 1.82–2.65; $p<0.001$).
 - (b) Patients in these studies received about 30 mL/kg of crystalloid solution before study enrollment. This is significantly different from the patients in the landmark early goal-directed therapy study, wherein patients were enrolled before resuscitation.
 - (c) The ARISE and ProMISe studies required antimicrobial administration before enrollment. In ProCESS, 76% of patients had antimicrobials administered before enrollment and 97% within 6 hours of enrollment. In the landmark early goal-directed therapy study, only 86% of patients had antimicrobials administered within 6 hours of enrollment.
 - (d) These studies highlight the benefits of timely administration of antibiotics and intravenous fluids, which should be a focus of the early care of patients with severe sepsis and septic shock.
 - (e) 51%–62% of patients in the usual care arms of these studies had a central venous catheter inserted, even though it was not required in the study protocol.
 - (f) The consistent findings of lower mortality rates in the contemporary studies suggest that care of patients with septic shock has evolved since the landmark early goal-directed therapy study.
 - (g) With ubiquitous early recognition and aggressive resuscitation, protocolized care may no longer be mandatory.

vi. Lactate clearance

- (a) In one study of patients with sepsis and septic shock, failure to achieve a lactate clearance of at least 10% was associated with a higher mortality rate than was failure to achieve an $ScvO_2$ above 70%.
- (b) A large, multicenter, noninferiority study randomized patients to a quantitative resuscitation protocol that incorporated $ScvO_2$ as a treatment goal or to a quantitative resuscitation protocol that incorporated a lactate clearance of 10% or greater as a treatment goal.
 - (1) The study aimed to address whether the use of $ScvO_2$ as a treatment goal was a necessary component of a quantitative resuscitation protocol.
 - (2) The lactate clearance strategy was determined to be noninferior to the $ScvO_2$ strategy (in-hospital mortality 17% vs. 23%, respectively; 95% CI for mortality difference -3% to 15% [above the -10% predefined noninferiority threshold]).
 - (3) Only 10% of the patients in each arm received a therapy specifically directed to improve either lactate clearance or $ScvO_2$, which biased the study toward finding no difference between treatment arms (and incorrect rejection of a true null hypothesis of the existence of a difference between groups in this noninferiority study; a type I error).
 - (4) Equally pertinent is that most patients with septic shock in this study (90%) achieved adequate Do_2 with only fluids and vasopressors.
- (c) Another multicenter, open-label study randomized ICU patients with a lactate concentration of 3 mmol/L or greater to the addition of lactate clearance of 20% or more (evaluated every 2 hours for the first 8 hours of therapy) or standard therapy (in which the treatment team was blinded for lactate concentrations).
 - (1) Both treatment arms had resuscitation targets of CVP 8–12 mm Hg, MAP 60 mm Hg or greater, and urine output above 0.5 mL/kg/hour. $ScvO_2$ monitoring was optional in the standard therapy group, but it was mandated as part of the lactate clearance group. In the lactate clearance group, if the $ScvO_2$ was 70% or greater but the lactate concentrations did not decrease by 20%, vasodilators (e.g., nitroglycerin) were initiated to improve microvascular perfusion.
 - (2) Adding lactate clearance as a treatment goal was not associated with a difference in hospital mortality on bivariate analysis (33.9% vs. 43.5%, $p=0.067$). After adjustment for baseline differences between groups with multivariable analysis, there was a significant difference favoring the lactate clearance group (HR 0.61; 95% CI, 0.43–0.87; $p=0.006$).
- (d) In light of these findings, in a low-level recommendation (grade 2C), the SSC has suggested targeting resuscitation to normalize lactate in patients with elevated lactate concentrations.

4. Blood pressure (MAP) goal

- a. As discussed previously, MAP is the true driving pressure for peripheral blood flow (and end-organ perfusion) and is preferred to SBP as a therapeutic target.
- b. A multicenter open-label study randomized patients with septic shock to resuscitation with a MAP goal of either 65–70 mm Hg (low-target group) or 80–85 mm Hg (high-target group). The higher MAP target was achieved through vasopressor administration; patients in the high-target group had a significantly higher infusion rate and duration of vasopressors than did those in the low-target group, but there was no difference between groups in total volume of fluid administration. There was no difference between treatment arms in 28-day mortality (34.0% in the low-target group vs. 36.6% in the high-target group, $p=0.57$). However, the incidence of atrial fibrillation was significantly higher in the high-target group (6.7% vs. 2.8%, $p=0.02$). In an a priori–defined subgroup analysis of patients with chronic hypertension (with randomization stratified according to this covariate), those

randomized to the high-target group had a lower incidence of a doubling of the SCr concentration (38.9% vs. 52.0%, $p=0.02$, stratum interaction $p=0.009$) and the need for renal replacement therapy (31.7% vs. 42.2%, $p=0.046$, stratum interaction $p=0.04$).

5. Summary and recommendations for initial resuscitation
 - a. After an initial fluid challenge, fluid therapy should be continued, using a fluid challenge technique, until the patient is no longer fluid responsive.
 - b. Vasopressors should be applied to initially target a MAP of 65–70 mm Hg, but the MAP goal may subsequently be adjusted if adequate organ perfusion is not attained (particularly in patients with chronic hypertension).
 - c. Adequate tissue DO_2 should be ensured. If a central venous catheter is not inserted, lactate clearance should be targeted. If a central venous catheter is inserted, a combination of markers is likely best (e.g., lactate clearance and Scvo_2 of 70% or greater).
6. Sepsis and septic shock care bundle
 - a. The SSC guidelines include a core set of process steps and treatment goals grouped into a care bundle for the treatment of patients with severe sepsis and septic shock.
 - b. The goal of the care bundle is to improve early recognition and treatment of severe sepsis and septic shock.
 - c. This care bundle from the SSC was updated in 2015 in response to new evidence from the three previously noted quantitative resuscitation studies (Box 3).
 - d. The updated bundle acknowledges the findings of the three studies and recommends using techniques in addition to CVP and Scvo_2 to reassess fluid responsiveness and tissue perfusion. These techniques include either use of a repeat focused examination by a licensed practitioner to evaluate for vital signs, cardiopulmonary findings, capillary refill, pulse, and skin findings or use of at least two of the following: CVP, Scvo_2 , bedside ultrasonography, or dynamic markers of fluid responsiveness (PLR or fluid challenge).
 - e. This care bundle has been adopted by the Centers for Medicare & Medicaid Services as a quality (core) measure (SEP-1).
 - f. The slight differences between the updated SSC bundle and the SEP-1 quality measure are noted in Box 3.
 - g. In July 2016, a letter to the editor from the SEP-1 measure stewards and a representative from the Centers for Medicare & Medicaid Services indicated that the SEP-1 measure would not be updated to correspond with the new sepsis definitions until further data are available (JAMA 2016;316:457-8).
 - h. The adjustment of the SSC bundle and implementation of sepsis as a quality measure will likely lead to a shift in resuscitation approaches for many clinicians.
 - i. To prepare for and implement this new quality measure, practitioners should systematically evaluate their institutional compliance and implement broad process steps to ensure compliance. These steps may include, but are not limited to, patient identification by clinical decision support tools in the electronic medical record and implementation of care paths and order sets for treatment.

Box 3. Sepsis and Septic Shock Management Bundle^a

Accomplished within 3 hr of presentation^b

1. Measure lactate concentration
2. Obtain blood cultures before administering antibiotics
3. Administer broad-spectrum antibiotics^c

If septic shock present,^d additional measures to be accomplished within 6 hr of presentation^b

4. Administer crystalloid 30 mL/kg for hypotension or lactate ≥ 4 mmol/L^e
5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain MAP ≥ 65 mm Hg
6. If persistent arterial hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial was lactate ≥ 4 mmol/L, reassess volume status and tissue perfusion, and document findings^f
7. Remeasure lactate if the initial lactate concentration was elevated^g

^aApplies to all patients presenting with severe sepsis and septic shock. Patients are excluded from the Centers for Medicare & Medicaid Services quality measure (SEP-1) if (1) they are transferred from another care facility (including an ED), (2) they have advanced directives for comfort care, (3) they have clinical conditions that preclude total measure completion (i.e., mortality within the first 6 hr of presentation), (4) they have a length of stay > 120 days, (5) they were administered intravenous antibiotics within 24 hours of presentation, (6) a central line is clinically contraindicated (must be documented), (7) a central line was attempted but could not be successfully inserted, or (8) a patient or surrogate decision-maker declined or is unwilling to consent to such therapies or central line placement. All components outlined must be fulfilled to satisfy the SEP-1 quality measure (it is an “all-or-none” measure).

^bTime of presentation is defined as the time of triage in the ED or, if the patient is located in another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock as ascertained through chart review.

^cSpecific antibiotics are outlined in the SEP-1 quality measure to qualify as “broad-spectrum.” The reader is referred to the measure documents for further details.

^dSeptic shock defined as hypotension (to SBP < 90 mm Hg, MAP < 70 mm Hg, or SBP decrease > 40 mm Hg from known baseline) or a lactate concentration ≥ 4 mmol/L.

^eTime of presentation is defined as the time of triage in the ED or, if the patient is located in another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock as ascertained through chart review.

^fTo meet the requirements, one of the following must be documented: (1) a focused examination by a licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings; or (2) any two of the following: measure CVP, measure ScvO₂, bedside cardiovascular ultrasonography, or dynamic assessment of fluid responsiveness with PLR or fluid challenge.

^gIn the SEP-1 quality measure, an initial lactate concentration ≥ 2 mmol/L is considered elevated.

Information from: Surviving Sepsis Campaign. Updated Bundles in Response to New Evidence [homepage on the Internet]. Available at www.survivingsepsis.org/SiteCollectionDocuments/SSC_Bundle.pdf. Accessed June 14, 2016; and The Joint Commission. Specifications Manual for National Hospital Inpatient Quality Measures. 2016. Available at https://www.jointcommission.org/specifications_manual_for_national_hospital_inpatient_quality_measures.aspx. Accessed June 14, 2016.

Patient Case

9. A 56-year-old woman with a medical history of hypertension presents to the ED with shortness of breath and cough productive of sputum. Her vital signs on admission are as follows: blood pressure 92/68 mm Hg, heart rate 104 beats/minute, respiratory rate 26 breaths/minute, and temperature 101.6°F (38.7°C). A chest radiograph reveals an opacity in the left lower lobe, but the radiograph is otherwise unremarkable. Her laboratory values of interest include Hgb 12.7 g/dL, WBC 16.4×10^3 cells/mm³, Plt 80,000/mm³, albumin 2.0 g/dL, lactate 3.2 mmol/L, and SCr 1.3 mg/dL. Her Glasgow Coma Scale score is 13. Which best describes the patient's condition?
 - A. Systemic inflammatory response syndrome.
 - B. Sepsis.
 - C. Severe sepsis.
 - D. Septic shock.

7. Antimicrobials

a. Timing of initiation

- i. Adequate empiric antibiotics should be initiated within 1 hour after recognizing severe sepsis or septic shock.
- ii. A multicenter, retrospective study of patients with septic shock found that within the first 6 hours after the onset of hypotension, each hour of delay beyond the first hour in the administration of appropriate antibiotics was associated with a 7.6% decrease in hospital survival.
- iii. Other studies have further shown the importance of empiric antimicrobials used together with a quantitative resuscitation protocol, associating antimicrobial administration either before shock or within the initial hour of shock with improved survival.

b. Initial empiric therapy should include one or more drugs with activity against all likely pathogens (bacterial and/or fungal and/or viral).

- i. In an observational study of more than 5700 patients with septic shock, those who received initial appropriate antimicrobials had a significantly higher hospital survival rate than did those who received initial inappropriate antimicrobials (52.0% vs. 10.3%, $p < 0.0001$).
- ii. The use of combination antibacterial therapy (at least two different classes of antibiotics) is likely indicated for patients with septic shock, but not for those with severe sepsis without shock.
 - (a) A randomized controlled trial of patients with severe sepsis that allocated patients to meropenem monotherapy or combination therapy with meropenem and moxifloxacin found no difference between groups in mean SOFA scores over 14 days (7.9 points vs. 8.3 points, $p = 0.36$) or mortality rates at 28 or 90 days. Important caveats to this study are that the patient population studied was at a low risk of resistant pathogens (half of the patients had a community-acquired infection) and that moxifloxacin inadequately covers pathogens with a high likelihood of multidrug resistance (e.g., *Pseudomonas aeruginosa* and *Acinetobacter* spp.).
 - (b) A meta-analysis that included 50 studies and more than 8500 patients with sepsis detected no overall mortality benefit of combination antibacterial therapy compared with monotherapy (pooled OR of death 0.86; 95% CI, 0.71–1.03, $p = 0.09$); however, a stratified analysis showed significantly lower mortality with combination therapy in more severely ill patients (monotherapy risk of death greater than 25%, pooled OR of death with combination therapy 0.54; 95% CI, 0.45–0.66, $p < 0.001$). The benefit of combination therapy was confined to patients with septic shock (with no benefit of combination therapy in patients without shock). In addition, a meta-regression analysis, which tried to elucidate the differences in the benefit seen with combination therapy according to baseline mortality risk, showed a significant benefit of combination therapy with a mortality risk greater than 25%. These data suggest that severely ill patients will benefit from combination antibacterial therapy.
 - (c) Combination therapy increases the likelihood that at least one drug is effective against the pathogen, particularly in the setting of known or suspected multidrug-resistant organisms such as *P. aeruginosa*.
 - (d) Empiric combination therapy is recommended for a maximum of 3–5 days.

c. As noted in the Pharmacokinetics/Pharmacodynamics (PK/PD) chapter, severe sepsis and septic shock can significantly affect the probability of attaining the antimicrobial PK/PD target.

- i. Most notably, the volume of distribution of hydrophilic antibiotics (e.g., β -lactams, aminoglycosides, and vancomycin) will be increased. Clearance may be either increased (in the setting of augmented renal clearance) or decreased (in the presence of end-organ dysfunction).

- ii. A PK/PD study of the first dose of β -lactams in patients with severe sepsis and septic shock suggested that the PK/PD target was attained in less than 50% of the patients given ceftazidime 2 g (28% target attainment), cefepime 2 g (16%), and piperacillin/tazobactam 4 g/0.5 g (44%). The PK/PD target was attained in 75% of patients receiving meropenem 1 g. For each antibiotic, the volume of distribution was higher and the clearance was lower than the values reported in healthy volunteers.
- iii. A multicenter cross-sectional study of β -lactam concentrations in critically ill patients found that the minimum PK/PD target of at least 50% of free drug time above the minimum inhibitory concentration (MIC) (50% fT>MIC) was not achieved in 16% of patients with an infection. Of importance, achievement of 50% fT>MIC or 100% fT>MIC was independently associated with a higher likelihood of a positive outcome on multivariable analysis (OR 1.02; 95% CI, 1.01–1.04 and OR 1.56; 95% CI, 1.15–2.13, respectively).
- iv. These data suggest that a loading dose approach for these antibiotics is necessary for patients with sepsis and septic shock. In addition, the impact of methods to improve the time the free drug concentration is above the MIC should be studied further.
- d. Antimicrobial therapy should be evaluated on a daily basis to determine whether opportunities for de-escalation or discontinuation exist.
 - i. Continued use of broad-spectrum antimicrobial therapy may cause untoward adverse effects and promote the development of resistance.
 - ii. De-escalation may be clear-cut in infections in which a contributive pathogen has been identified; in such cases, antimicrobial therapy should be reduced to the narrowest-spectrum agent with adequate activity. However, de-escalation may be more challenging in culture-negative sepsis.
 - iii. Antimicrobials are typically continued for 7–10 days, although longer courses may be indicated in patients with a poor clinical response, those with bacteremia, or those who are immunocompromised.
 - iv. Procalcitonin and other biomarkers may be used to limit the duration of antimicrobial therapy and are discussed in detail in the Infectious Diseases II chapter.
- 8. Source control measures (e.g., drainage of an abscess, debridement of infected necrotic tissue, or removal of a potentially infected device [including intravascular access devices]), as applicable, should be undertaken as soon as possible (within 12 hours after the diagnosis is made).
- 9. Fluid therapy
 - a. Crystalloids (i.e., 0.9% sodium chloride or lactated Ringer solution) are the initial fluid type of choice, particularly for an initial fluid challenge.
 - i. The SAFE study detailed previously detected no difference in mortality between 0.9% sodium chloride and 4% albumin. These data have informed the recommendation of crystalloids as the initial fluid type, particularly in light of their low cost.
 - ii. Crystalloid solutions that approximate the electrolyte composition of plasma (“balanced” solutions) are an attractive alternative to 0.9% sodium chloride (see section V, Agents Used to Treat Shock, for further discussion).
 - (a) A propensity-matched retrospective cohort study of medical ICU patients with sepsis found that receipt of a balanced solution compared with 0.9% sodium chloride was associated with a lower incidence of in-hospital mortality (19.6% vs. 22.8%, $p=0.001$). Contrary to analyses of general critical care patients, this study found no difference in the incidence of acute renal failure between groups, which leads to questions regarding the mechanism of the detected mortality difference between groups.
 - (b) A systematic review and network meta-analysis of patients with sepsis suggested a lower mortality rate in patients resuscitated with balanced solutions than in patients resuscitated with 0.9% sodium chloride (OR 0.78, credibility interval 0.58–1.05; low confidence in estimate of effect).

- b. Iso-oncotic (4%–5%) albumin may be used as a component of the resuscitation strategy.
 - i. A prospectively defined subgroup analysis of the SAFE study evaluated the effect of albumin 4% compared with 0.9% sodium chloride in patients with severe sepsis and septic shock. The unadjusted RR of death with albumin was 0.87 (95% CI, 0.74–1.02) in patients with severe sepsis and 1.05 (95% CI, 0.94–1.17) in patients without severe sepsis ($p=0.06$ for heterogeneity of treatment effect by subgroup). In a multivariable analysis that accounted for baseline factors, albumin administration was associated with a lower mortality risk (OR 0.71; 95% CI, 0.52–0.97; $p=0.03$).
 - ii. A systematic review and fixed-effect meta-analysis of albumin compared with alternative fluids for resuscitation in patients with sepsis found an association between albumin use and lower mortality (OR 0.82; 95% CI, 0.67–1.0; $p=0.047$). The benefit of albumin was retained when the analysis was restricted to crystalloids as the comparator (OR 0.78; 95% CI, 0.62–0.99; $p=0.04$). These data should be interpreted with caution, however, because many of the included studies had poor methodological quality, and when a random-effects model was used, the results for the overall analysis were not statistically significant (OR 0.84; 95% CI, 0.69–1.02, $p=0.08$).
 - iii. These data have renewed interest in 4%–5% albumin as a resuscitation fluid for patients with severe sepsis and septic shock. Indeed, the 2012 SSC guidelines suggest albumin as a component of the fluid resuscitation regimen when patients require a substantial amount of crystalloids.
 - c. Hydroxyethyl starch solutions should not be used for fluid resuscitation.
 - i. Compared with patients with severe sepsis allocated to lactated Ringer solution, those allocated to pentastarch (a hydroxyethyl starch formulation) had a significantly higher incidence of acute renal failure (34.9% vs. 22.8%, $p=0.002$) and need for renal replacement therapy (31.0% vs. 18.8%, $p=0.001$), with no difference in 28-day mortality (26.7% vs. 24.1%, $p=0.48$).
 - ii. Compared with patients with severe sepsis randomized to receive Ringer acetate solution, patients with severe sepsis randomized to receive hydroxyethyl starch had a significantly higher 90-day mortality (51% vs. 43%, $p=0.03$) and need for renal replacement therapy (22% vs. 16%, $p=0.04$).
 - iii. The increased need for renal replacement therapy and lack of mortality benefit in these studies led to the strong recommendation against the use of hydroxyethyl starch for fluid resuscitation in patients with severe sepsis and septic shock in the 2012 SSC guidelines.
 - d. Hyperoncotic (20%–25%) albumin replacement may be beneficial in patients with septic shock. An open-label study compared albumin replacement (with 20% albumin) to a goal serum albumin concentration of 3 g/dL plus crystalloid solution administration with crystalloid solution administration alone in patients with severe sepsis or septic shock. There was no difference between the albumin and crystalloid groups in the incidence of 28-day mortality (31.8% vs. 32.0%, $p=0.94$), but patients allocated to albumin had a shorter time to cessation of vasoactive agents (median 3 vs. 4 days, $p=0.007$). A post hoc subgroup analysis of patients with septic shock at enrollment showed that those randomized to albumin had a lower 90-day mortality rate (RR 0.87; 95% CI, 0.77–0.99); there was no difference in 90-day mortality in patients without septic shock (RR 1.13; 95% CI, 0.92–1.39; $p=0.03$ for heterogeneity). These data suggest that albumin replacement does not improve outcomes in patients with severe sepsis but that it may have hemodynamic (and potentially mortality) advantages in patients with septic shock. Hence, the role of albumin replacement in patients with septic shock warrants further study.
10. Vasoactive agents and inotropes
- a. Norepinephrine is the recommended first-line vasoactive medication. A meta-analysis of randomized trials that compared norepinephrine with dopamine for the treatment of septic shock found a higher risk of short-term mortality (RR 1.12; 95% CI, 1.01–1.20; $p=0.035$) and arrhythmias (RR 2.34; 95% CI, 1.46–3.77; $p=0.001$) in patients allocated to dopamine.

- b. The optimal approach to using vasoactive agents and inotropes beyond the choice of initial vasopressor is unclear, but the choice should be based on patient-specific clinical factors.
 - i. Potential interventions could include norepinephrine monotherapy (with appropriate dose escalation) or initiation of an additional therapy (i.e., a second catecholamine vasopressor, arginine vasopressin, corticosteroids, an inotrope, or a combination of these therapies).
 - ii. The optimal time or norepinephrine dose at which to consider additional therapies is unknown. A dose that constitutes the failure of norepinephrine is not well defined in the literature, and the maximal doses used by clinicians (or institutions) are variable and often subjective.
- c. The SSC guidelines recommend epinephrine (added to or potentially substituted for norepinephrine) when an additional vasoactive agent is needed.
 - i. A randomized trial of patients with septic shock compared epinephrine with norepinephrine with or without dobutamine. There was no difference between groups in 28-day mortality (40% vs. 34%, $p=0.31$), but patients allocated to epinephrine had significantly higher lactate concentrations on day 1 ($p=0.003$) and lower arterial pH values on each of the first 4 study days. Caution should be used in concluding that a difference in mortality between epinephrine and norepinephrine does not exist because the study was powered to detect a 20% absolute difference in mortality rates, and a smaller difference between agents cannot be ruled out.
 - ii. The benefit of adding epinephrine to norepinephrine (whether this approach has a norepinephrine-sparing effect or whether it is best used in norepinephrine failure) is unclear.
 - iii. Although norepinephrine may cause tachycardia or tachyarrhythmias (often the impetus to limit doses), adding catecholamine vasopressors with β_1 -adrenergic properties (e.g., epinephrine) to augment MAP in patients receiving norepinephrine is unlikely to prevent these tachyarrhythmias.
 - iv. In addition, epinephrine may preclude the use of lactate clearance as an initial resuscitation goal because it increases lactate concentrations through increased production by aerobic glycolysis (by stimulating skeletal muscle β_2 -adrenergic receptors), an effect that likely wanes with continued epinephrine administration.
 - v. It seems most prudent to use epinephrine in patients receiving norepinephrine with a low MAP and requiring CO augmentation.
- d. Phenylephrine should be reserved for the following patients: (1) those with a tachyarrhythmia on norepinephrine, (2) those with a confirmed high CO whose blood pressure is still low, or (3) those who have not achieved the goal MAP with other vasoactive agents, including low-dose vasopressin.
 - i. Because of its afterload augmentation effects (without β_1 -adrenergic properties), phenylephrine may theoretically decrease SV and CO. As such, it is not recommended as a first-line vasopressor in patients with septic shock who have decreased CO because of inadequate preload.
 - ii. A small study ($n=32$) that randomized patients with septic shock to phenylephrine or norepinephrine as first-line therapy found no difference in hemodynamic measures (including CO) between agents in the first 12 hours of therapy. These data are in contrast to the theoretical concerns with phenylephrine and warrant further study.
- e. Dopamine is best used in a select patient population, including those with a low risk of tachyarrhythmias (which is difficult to predict) or those with bradycardia-induced hypotension. Low-dose ("renal dose" 2 mcg/kg/minute) dopamine should not be used to improve renal blood flow and urine output (renal protection).
- f. Low-dose arginine vasopressin (up to 0.03 unit/minute) may be added to norepinephrine to improve MAP or decrease norepinephrine requirements.
 - i. Vasopressin constricts vascular smooth muscle directly (through actions on the V_1 receptor) and indirectly (by decreased nitric oxide-mediated vasodilation).

- ii. In patients with septic shock, a relative vasopressin deficiency may exist, and patients are sensitive to the vasoconstrictive effects of arginine vasopressin.
- iii. In light of these effects, arginine vasopressin has been used in patients with septic shock as both an endocrine replacement therapy (with a fixed-dose infusion) and a vasopressor (titrated to MAP).
- iv. A randomized trial compared the effects of adding arginine vasopressin (0.01–0.03 unit/minute) to norepinephrine with using norepinephrine monotherapy. Overall, the study found no difference in 28-day mortality between treatment arms (35.4% vs. 39.3%, $p=0.26$), but norepinephrine requirements were significantly lower during the first 4 study days in the patients allocated to receive arginine vasopressin ($p<0.001$). There was no difference in adverse effects between groups. In an a priori–defined subgroup analysis of patients based on shock severity (less severe shock defined as baseline norepinephrine dose 5–14 mcg/minute), with randomization stratified according to this covariate, 28-day mortality in the less severe shock stratum was lower in patients randomized to arginine vasopressin plus norepinephrine (26.5% vs. 35.7%, $p=0.05$) and no different between groups in the more severe shock stratum (44.0% vs. 42.5%, $p=0.76$, stratum interaction $p=0.10$).
- v. Conflicting findings regarding the effects of arginine vasopressin (and its analogs) on mortality have been observed in meta-analyses. One meta-analysis found a decreased mortality risk in patients with septic shock allocated to arginine vasopressin (RR 0.87; 95% CI, 0.75–1.0; $p=0.05$), whereas another found no significant benefit with arginine vasopressin (RR 0.91; 95% CI, 0.79–1.05; $p=0.21$). Both meta-analyses found a significant benefit of arginine vasopressin in decreasing norepinephrine doses.
- g. High-dose vasopressin (doses above 0.03–0.04 unit/minute) should be reserved for salvage therapy.
 - i. A study of patients with vasodilatory shock (about half with septic shock) requiring high-dose norepinephrine (greater than 0.6 mcg/kg/minute) randomized patients to arginine vasopressin 0.033 unit/minute versus arginine vasopressin 0.067 unit/minute. The study was designed to evaluate hemodynamic changes, not mortality. Patients randomized to the higher dose had a more pronounced reduction in norepinephrine requirements than those allocated to the lower dose ($p=0.006$). High-dose arginine vasopressin did not lead to a significantly lower cardiac index than low-dose arginine vasopressin (as might be expected with this pure vasoconstrictor), but this finding is difficult to interpret because most patients were receiving concomitant inotropes, and the study was likely underpowered to assess this outcome.
 - ii. High-dose vasopressin is best reserved for patients with septic shock requiring high norepinephrine doses (greater than 0.6 mcg/kg/minute) with a high CO.
- h. Despite the unclear benefits of arginine vasopressin on mortality, this agent offers an alternative mechanism to catecholamines for vasoconstriction, and low-dose arginine vasopressin is commonly used in practice (often as the second vasoactive medication).
 - i. Preliminary data suggest that midodrine is a useful agent to decrease vasopressor duration in patients in the convalescent stage of septic shock. Further studies are needed before implementing midodrine use in routine practice.
- j. Dobutamine may be indicated in patients with evidence or suggestion of myocardial dysfunction.
 - i. A low CO is common in early septic shock, but this is often corrected with fluid resuscitation alone.
 - ii. Myocardial dysfunction may persist despite fluid resuscitation, with 39% of patients having LV hypokinesia on ICU admission and an additional 21% of patients developing hypokinesia 24–48 hours after ICU admission in one series.
 - iii. If myocardial dysfunction leads to significant impairment in Do_2 , an inotrope such as dobutamine (up to 20 mcg/kg/minute) may be indicated to improve CO.
 - iv. Dobutamine should not be used to achieve a predetermined supranormal cardiac index or $Scvo_2$.

- k. The SSC guidelines do not include recommendations regarding the use of milrinone.
 - i. Few data exist for the use of milrinone in patients with septic shock.
 - ii. Milrinone is likely best avoided in patients with septic shock because it may increase vasodilation, and it is challenging to titrate because of its relatively long half-life.

Patient Case

10. A 55-year-old man presents to the medical ICU with presumed urosepsis. His medical history is significant for congestive heart failure with a baseline ejection fraction of 20%. In the medical ICU, the patient's vital signs are as follows: blood pressure 69/45 mm Hg, heart rate 84 beats/minute, respiratory rate 32 breaths/minute, and temperature 100.6°F (38.1°C). Blood cultures are obtained, and the patient is initiated on piperacillin/tazobactam. A central venous catheter is placed, which reveals a CVP of 18 mm Hg and an ScvO₂ of 70%. Which is the most appropriate initial vasopressor for this patient?
- A. Norepinephrine.
 - B. Vasopressin.
 - C. Dobutamine.
 - D. Epinephrine.
11. Corticosteroids should only be used in patients with septic shock who do not achieve resuscitation goals despite fluid administration and vasopressors.
- a. Corticosteroids are an attractive treatment option for patients with septic shock because of their anti-inflammatory effects (through inhibition of nuclear factor- κ B) and ability to improve blood pressure response to catecholamines (through up-regulation of adrenergic receptors and potentiation of vasoconstrictor actions).
 - b. The use of corticosteroids for patients with septic shock has been a source of controversy for years.
 - c. In studies of short courses of high-dose corticosteroids in patients with severe sepsis and septic shock, corticosteroids did not lead to improved patient outcomes.
 - d. In a French trial of patients with septic shock and vasopressor-unresponsive shock (i.e., inability to increase SBP above 90 mm Hg for 1 hour despite fluids and vasopressors), patients randomized to low-dose hydrocortisone and fludrocortisone had improved survival in a time-to-event analysis (HR 0.71; 95% CI, 0.53–0.97) and time-to-shock reversal. The mortality benefit with corticosteroids was limited to patients unable to increase their cortisol concentration by more than 9 mcg/dL in response to adrenocorticotrophic hormone (ACTH) administration (nonresponders).
 - e. In the larger, multicenter Corticosteroid Therapy of Septic Shock (CORTICUS) study, which had less-stringent inclusion criteria, hydrocortisone administration was not associated with improved survival in ACTH nonresponders (28-day mortality 39.2% vs. 36.1%, $p=0.69$).
 - f. In meta-analyses, corticosteroid administration has consistently been associated with improvements in shock reversal.
 - g. In a meta-analysis of only high-quality trials, corticosteroid administration was not associated with improved survival. When analyzed according to severity of illness, a systematic review of three randomized controlled trials found no mortality benefit with the use of corticosteroids in patients at a low risk of death (placebo mortality rate below 50%). In those with a high risk of death (placebo mortality rate above 60%), there was a numerical, although not statistically significant, mortality benefit with the use of corticosteroids (RR 0.77; 95% CI, 0.56–1.05).

- h. The SSC guidelines do not explicitly define poor response to initial therapy. If a clinician were considering adding corticosteroids to decrease the patient mortality risk, it would seem prudent to initiate corticosteroids in patients receiving norepinephrine doses above 40 mcg/minute (the mean maximal norepinephrine dose in the CORTICUS study was about this dose).
 - i. Because of immunoassay imprecision and the inconsistent benefit of identifying patient response, the ACTH test should not be used to identify patients for corticosteroid administration.
 - j. If hydrocortisone is indicated, a dose of 200 mg/day is recommended.
 - k. Unfortunately, the optimal dose, administration method, and therapy duration of hydrocortisone have not been fully elucidated. Emerging data suggest that even a 200-mg/day dose is too aggressive because of impaired hydrocortisone clearance in critically ill patients.
 - l. In low-level recommendations, the SSC guidelines suggest that hydrocortisone should be administered as a continuous infusion (rather than a bolus injection) to avoid glucose fluctuations and that it should tapered to avoid rebound hypotension or inflammation when patients no longer require vasopressors.
 - i. Clinicians must balance the potential benefit of decreased glucose variability with the need for dedicated intravenous access and drug y-site incompatibility with a hydrocortisone infusion.
 - ii. Tapered doses will likely lead to longer treatment courses; thus, adverse effects may occur more often with prolonged corticosteroid administration.
12. Supportive therapies
- a. Intravenous immunoglobulins should not be used for the treatment of patients with severe sepsis and septic shock. In a randomized study of patients with severe sepsis, 28-day mortality was no different between patients allocated to intravenous immunoglobulin G (IgG) and placebo (39.3% vs. 37.3%, $p=0.67$).
 - b. A transfusion threshold of 7 g/dL or less is appropriate for patients with septic shock.
 - i. A multicenter study compared two different transfusion thresholds in patients with septic shock. The study enrolled patients with septic shock and a hemoglobin concentration below 9 g/dL to receive PRBC transfusion if their hemoglobin was 7 g/dL or less (lower threshold) or 9 g/dL or less during their ICU stay.
 - ii. As expected, patients allocated to the lower-threshold group less commonly received PRBC transfusion and had lower hemoglobin concentrations.
 - iii. There was no difference between treatment arms in 90-day mortality (43.0% in the lower-threshold group vs. 36.6% in the higher-threshold group, $p=0.44$). Patients in the lower-threshold group had no higher incidence of ischemic events in the ICU (7.2% vs. 8.0%, $p=0.64$), and there was no difference in outcomes between groups in the subgroup of patients with chronic cardiovascular disease (RR 1.08 [95% CI, 0.75–1.40]; $p=0.25$ for heterogeneity of treatment effect by subgroup; only 14% of the overall population had chronic cardiovascular disease).
 - iv. Although the study did not specifically evaluate the practice of transfusing blood in patients with evidence of hypoperfusion (low $ScvO_2$ or elevated lactate concentrations) associated with a low hemoglobin concentration, the median $ScvO_2$ at baseline was below 70% and lactate concentrations were above 2 mmol/L in both groups, suggesting that most patients had evidence of hypoperfusion.
 - v. These data suggest that use of a hemoglobin transfusion threshold of 7 g/dL or lower is safe for most patients, including those with severe sepsis and septic shock.
13. Continued care of the patient with septic shock (resuscitation end points beyond first 6 hours). See section IV, Resuscitation Parameters and End Points, for additional discussion of this topic.
- a. Uncertainty persists regarding hemodynamic targets beyond the first 6 hours of presentation.
 - i. Therapy should be directed toward maintaining adequate end-organ perfusion and normalization of lactate concentrations, but the specific method(s) to achieve these goals will be patient-specific.
 - ii. A strategy of systematically increasing CO to predefined “supranormal” values was not associated with a mortality benefit; hence, it is not recommended.

- b. Care should be taken to avoid giving excessive fluids.
 - i. In a retrospective analysis of data from a randomized controlled trial of patients with septic shock, patients in the highest quartile of fluid balance had a significantly higher mortality rate than patients in the lowest two quartiles. This association was present when fluid balance was evaluated at both 12 hours and 4 days after study enrollment. In the same analysis, a CVP greater than 12 mm Hg conferred a higher risk of mortality than a lower CVP.
 - ii. Fluid administration can be limited by only giving fluid in patients who are proven or predicted to respond to fluid. This is best accomplished using dynamic markers of fluid responsiveness.
- c. Resuscitation targeted to improving microcirculatory perfusion is a potential new therapeutic frontier.
 - i. Studies have shown that the microcirculation is often altered in patients with sepsis, persistent microvascular alterations are associated with multisystem organ failure and death, alterations are more severe in non-survivors than in survivors, and improvements in microcirculatory blood flow correspond with improved patient outcomes.
 - ii. Impaired microcirculatory perfusion may at least partly explain why patients have elevated lactate concentrations despite achievement of (macrovascular) hemodynamic goals.
 - iii. Several strategies to improve microcirculatory perfusion have been investigated.
 - (a) In a nonrandomized trial, fluid resuscitation improved microvascular perfusion in early, but not late, sepsis. Another study found that microcirculatory perfusion improved with PLR or fluid administration in patients who were fluid responsive.
 - (b) Use of norepinephrine to increase MAP above 65 mm Hg has not been associated with correction of impaired microcirculatory perfusion.
 - (c) In a randomized trial of patients who underwent quantitative resuscitation, the addition of nitroglycerin was not associated with improved microcirculatory blood flow. In-hospital mortality was numerically higher in patients allocated to nitroglycerin than in placebo, but this difference was not statistically significant (34.3% vs. 14.2%, $p=0.09$).
 - (d) A prospective open-label study evaluated the effects of dobutamine 5 mcg/kg/minute initiated after quantitative resuscitation (but within the first 48 hours of presentation). Dobutamine significantly improved microcirculatory perfusion compared with baseline. Of interest, the beneficial effects of dobutamine were unrelated to changes in cardiac index or blood pressure.
 - (e) Initiation of inhaled nitric oxide after quantitative resuscitation did not improve microcirculatory flow or lactate clearance.
 - (f) In summary, fluid resuscitation and the initiation of dobutamine appear to improve microcirculatory perfusion. It is still unknown whether use of these therapies to improve microcirculatory perfusion can improve patient outcomes such as mortality.

Patient Case

11. A 62-year-old woman was admitted to the surgical ICU with presumed aspiration pneumonia. The patient has a history of insulin-dependent diabetes and hyperthyroidism. On admission, she was intubated and required aggressive resuscitation and vasopressor therapy. Currently, the patient is receiving norepinephrine 8 mcg/minute and has the following vital signs and laboratory values: blood pressure 100/60 mm Hg, heart rate 90 beats/minute, and CVP 14 mm Hg; her $ScvO_2$ is 55%. Which is the best choice regarding the patient's steroid therapy?
- A. Administer hydrocortisone 50 mg every 6 hours.
 - B. Administer hydrocortisone 8.3 mg/hour as a continuous infusion.
 - C. Perform the ACTH stimulation test.
 - D. No steroids are necessary right now.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

The patient has hypovolemic shock caused by his upper GI hemorrhage and has symptoms of compromised end-organ perfusion (i.e., confusion). Although his history of hypertension is relevant in relation to determining a resuscitation goal, it does not acutely affect DO_2 (Answer A is incorrect). Tachycardia is a symptom in response to his hypovolemia, and, in the absence of complicating factors (e.g., atrial fibrillation or LV diastolic dysfunction), tachycardia will increase (not decrease) DO_2 (Answer C is incorrect). Leukocytosis does not impede DO_2 until it reaches an exorbitant threshold (greater than 75 L/mm^3) (Answer D is incorrect). When examining the Fick equation for DO_2 , acute anemia is the determinant that is adversely affecting DO_2 (Answer B is correct).

2. Answer: C

The patient has evidence of vasodilatory shock, with relatively high CVP and PCWP values and a high CO (Answer C is correct). This is further confirmed by a calculated SVR of $541 \text{ dynes}\cdot\text{s}\cdot\text{cm}^{-5}$. The patient could be thought to have spontaneous bacterial peritonitis in the setting of cirrhosis and ascites complicated by upper GI hemorrhage. Even though his presentation suggests hypovolemic shock (from GI hemorrhage), his MAP did not respond to fluid and blood product administration. Furthermore, he does not have low preload or low CO (Answer A is incorrect). If the patient had a low CO together with a high SVR, cardiogenic shock or obstructive shock might be possible (with one differentiation based on CVP/right atrial pressure and PCWP), but this is untrue for the patient (Answers B and D are incorrect).

3. Answer: C

The patient's clinical scenario of refractory hypoxemia and hypotension with hypoperfusion suggests that an accurate prediction of fluid responsiveness is needed. Dynamic markers of fluid responsiveness (e.g., SVV) are superior to static markers of fluid responsiveness (e.g., CVP and PCWP) (Answer C is correct; Answers A and B are incorrect). A low MAP may be from either a low CO or a low SVR. Furthermore, a low preload is only one of many components that may contribute to a low CO. As such, a low MAP is not a good predictor of fluid responsiveness (Answer D is incorrect).

4. Answer: C

The patient has shock with hypoperfusion and a positive response to a PLR test, which suggests he is still fluid responsive (Answer D is incorrect). Data from a large randomized trial of patients with heterogeneous shock types showed no difference in efficacy and safety between albumin and 0.9% sodium chloride, but the cost of albumin is substantially higher. These data suggest that crystalloids such as 0.9% sodium chloride are preferred for fluid resuscitation in the ICU. In addition, the patient has not received a substantial volume of fluid (he has received less than 30 mL/kg ; Answer C is correct; Answer A is incorrect). Hydroxyethyl starch has been associated with an increased need for renal replacement therapy without a mortality benefit; it should be avoided for fluid resuscitation in the ICU (Answer B is incorrect).

5. Answer: D

The patient has evidence of ventricular dysfunction with a low Scvo_2 and poor ventricular contractility on echocardiogram. A vasoactive agent with strong inotropic properties is indicated. Epinephrine has strong β_1 -adrenergic properties and is the best selection in this case (Answer D is correct). Both phenylephrine and vasopressin are essentially pure vasoconstrictors that do not increase CO and could theoretically decrease CO (Answers A and B are incorrect). Although norepinephrine has β_1 -adrenergic properties, it primarily increases blood pressure through vasoconstriction secondary to its α_1 -adrenergic properties, with only minimal effects on CO. Increasing norepinephrine in this case is unlikely to improve the patient's CO (Answer C is incorrect).

6. Answer: C

At this point, ongoing resuscitation should be goal directed. Acute hypocalcaemia is a common complication of massive transfusion secondary to citrate added to stored blood and reduced metabolism in shock states. Calcium chloride is indicated to normalize ionized calcium concentrations (included in all the answers). Although the TEG reveals hyperfibrinolysis, tranexamic acid should only be administered within the first 3 hours from injury. This patient's injuries were greater than 5 hours prior (Answers B and D are incorrect). With the updated history that the patient was taking dabigatran pre-injury, it is likely that dabigatran is contributing to

the ongoing coagulopathy and hemorrhage. A normal TEG and elevated aPTT cannot rule out the presence of dabigatran. In addition, it seems the patient has taken the last dose of dabigatran within the previous 12 hours. Therefore, reversal of dabigatran is indicated. Idarucizumab is FDA approved for dabigatran reversal and recommended in various guidelines, whereas PCCs have weak supporting evidence and are recommended only if idarucizumab is unavailable (Answer C is correct; Answer A is incorrect).

7. Answer: D

It is important to recognize that this patient has class II hypovolemic shock after blood loss caused by penetrating trauma (heart rate greater than 100 beats/minute, respiratory rate 20–30 breaths/minute, and anxious on examination). In this case, the appropriate resuscitation strategy should focus on selecting the fluid, volume, and resuscitation goal. Recommended end points for resuscitation include SBP greater than 90 mm Hg, urine output greater than 30 mL/hour, and normal mentation. In this case, administering fluid to target an SBP greater than 90 mm Hg would be appropriate (Answer A is incorrect). Blood products for transfusion are indicated when the patient's estimated blood loss is greater than 30% (Answers B and C are incorrect because the patient has class II hypovolemic shock). Given his hemorrhagic shock class, the patient requires blood products and target resuscitation end points of urine output greater than 30 mL/hour, an SBP greater than 90 mm Hg, and normal mentation (Answer D is correct).

8. Answer: D

The patient has evidence of a PE, but she lacks features of increased risk of early mortality from it. She does not have shock or evidence of end-organ hypoperfusion and thus does not have a massive PE. In addition, she has no evidence of RV dysfunction (no RV dilation on chest CT, brain natriuretic peptide less than 90 pg/mL) or myocardial necrosis (troponin less than 0.1 mg/mL) and thus does not have submassive PE. The patient is best classified as having low-risk PE. A meta-analysis suggested that thrombolytics do not decrease mortality in unselected (and low risk) patients and may increase bleeding risk (Answer D is correct; Answers A–C are incorrect).

9. Answer: B

The patient has life-threatening organ dysfunction secondary to infection. Although not all criteria to calculate the score are available, her SOFA score is at least 4 points (2 points for Plt, 1 point for Glasgow Coma Scale score, and 1 point for SCr), indicating organ dysfunction. In addition, the patient fulfills all three qSOFA criteria (alteration in mental status, SBP of 100 mm Hg or less, and respiratory rate of 22 breaths/minute or greater). Therefore, she meets the criteria for sepsis according to the new definition (Answer B is correct). Although she has an elevated lactate concentration, she does not require vasopressors to maintain a MAP above 65 mm Hg and therefore does not meet the criteria for septic shock (Answer C is incorrect). In the new sepsis definition, severe sepsis and systemic inflammatory response syndrome are no longer clinical entities in the spectrum of sepsis severity and should not be used (Answers A and D are incorrect).

10. Answer: A

The patient currently has a MAP less than 65 mm Hg and signs of a global lack of perfusion with an increased lactate concentration. Vasopressor therapy is indicated to sustain perfusion. This patient has underlying severe congestive heart failure with an ejection fraction of 20%; however, the ScvO₂ shows that the patient's Do₂ is sufficient, which suggests he is in distributive septic shock as opposed to cardiogenic shock. The SSC guidelines recommend initiating vasopressor therapy to target a MAP of 65 mm Hg and norepinephrine as the first-choice vasopressor (Answer A is correct). Vasopressin is currently recommended only as a secondary vasopressor, as an addition to catecholamine therapy (Answer B is incorrect). In septic shock, dobutamine is recommended only when the ScvO₂ is less than 70% and the patient has an adequate hemoglobin concentration (Answer C is incorrect). Epinephrine is currently recommended as an alternative to norepinephrine. Although in a study that compared epinephrine with norepinephrine plus dobutamine, the two arms did not differ in mortality outcomes; epinephrine was associated with lower pH and higher lactate concentrations on day 1 (Answer D is incorrect).

11. Answer: D

According to the SSC guidelines, corticosteroids may be considered if patients are poorly responsive to fluid resuscitation and vasopressor therapy. In this case, the

patient is receiving relatively low doses of vasopressors with an adequate MAP; hence, no steroids are currently necessary (Answer D is correct). Because steroids are not indicated at this point, Answers A and B are incorrect. Hydrocortisone is recommended at a dose of 200 mg/day. Consideration may be given to administering it as a continuous infusion because this might lead to fewer variations in serum glucose. The ACTH stimulation test to determine which patients with sepsis should receive hydrocortisone is no longer recommended because the CORTICUS study showed that the results of the ACTH stimulation test did not predict response to hydrocortisone therapy (Answer C is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

This older adult patient presents with septic shock. Shock is a syndrome of impaired DO_2 , leading to tissue injury and end-organ failure. In this case, it is important to realize that fever is a symptom of an inflammatory syndrome, not a shock syndrome (Answers A, B, and D are incorrect). This patient's presentation with hypotension, confusion, and hyperlactatemia suggests the presence of a shock syndrome in the setting of impaired DO_2 (Answer C is correct).

2. Answer: B

Oxygen delivery is best shown by the Fick equation for DO_2 . According to this equation, DO_2 depends on CO and CaO_2 . Cardiac output depends on heart rate and SV. Typically, an elevated heart rate will lead to an increase in CO and DO_2 . If a patient has atrial fibrillation, though, ventricular filling is impaired, and the SV is decreased. This leads to a decrease in CO and DO_2 (Answer B is correct). Lactate does not impede DO_2 but is a by-product of impaired DO_2 (Answer A is incorrect). Similarly, DO_2 is not impaired by acute kidney injury (Answer C is incorrect). Finally, fever is an inflammatory response that increases VO_2 but does not impair DO_2 (Answer D is incorrect).

3. Answer: D

The patient's laboratory values and arterial pH are consistent with hyperchloremic metabolic acidosis, and chloride-rich fluids should be avoided. Lactated Ringer solution is considered a relatively chloride-poor solution (chloride content 111 mEq/L) and is the best choice in this case (Answer D is correct). With a chloride content of 154 mEq/L, 0.9% sodium chloride is considered a chloride-rich fluid. Liberal use of chloride-rich fluids such as 0.9% sodium chloride has been associated with an increased need for renal replacement therapy (Answer A is incorrect). Although albumin 5% is considered a chloride-poor solution, data from randomized controlled trials have not supported a mortality benefit with albumin over crystalloids, even in the setting of hypoalbuminemia. Moreover, the patient has not received a "substantial volume" of crystalloids (she has received less than 30 mL/kg of fluid) that would coincide with recommendations to give albumin (Answer B is incorrect). Hydroxyethyl starch solutions may also have a high

chloride content (depending on the formulation) and have been associated with an increased need for renal replacement therapy in the general critical care population, with no mortality benefit. Hydroxyethyl starch solutions should be avoided for fluid resuscitation in the ICU (Answer C is incorrect).

4. Answer: B

The patient has evidence of end-organ hypoperfusion (urine output less than 0.5 mL/kg/hour and elevated lactate concentration without significant clearance), despite a MAP greater than 65 mm Hg and quantitative resuscitation. The patient probably needs a higher perfusion pressure because of a right-shifted zone of autoregulation secondary to hypertension. The norepinephrine dose should be increased to target a higher MAP; the exact target will depend on the patient's response and should be selected as the threshold that improves end-organ perfusion (Answer B is correct). The patient has no evidence of impaired CO (his ScvO_2 is not low); therefore, fluids (to improve SV) and inotropes (e.g., dobutamine) are not indicated (Answers C and D are incorrect). Because the patient has continued evidence of hypoperfusion, action should be taken, and the current therapy should be modified (Answer A is incorrect).

5. Answer: B

The patient has hypotension and signs of hypoperfusion with an elevated lactate concentration; possible interventions such as fluid administration should be explored further. Because the patient requires a high FIO_2 , a reliable predictor of fluid responsiveness should be used to guide fluid therapy instead of administering fluid without respect to predicting responsiveness. In the setting of atrial fibrillation, an elevated PPV is not a reliable predictor of fluid responsiveness, and further evaluation should be done before fluids are administered (Answer A is incorrect). A PLR test can be used in both spontaneously breathing patients and those receiving mechanical ventilation to predict fluid responsiveness, and the patient has a method to assess the presence (or absence) of a CO response (Answer B is correct). Although the accuracy of the CO value from arterial pulse pressure waveform analysis may be somewhat limited by atrial fibrillation, this may be accounted for with the internal software of most devices and can be used to gauge a response to

the PLR test. The patient has a femoral central venous catheter, which cannot be used to assess hemodynamic markers such as CVP or ScvO₂ (Answers C and D are incorrect). Furthermore, CVP is an inadequate predictor of fluid responsiveness.

6. Answer: D

The patient has features of vasodilatory shock secondary to an immune-mediated (“anaphylactic”) reaction (low preload, a low ScvO₂ [suggestive of poor Do₂], and an elevated lactate concentration). The patient should receive aggressive fluid resuscitation and be initiated on a vasopressor such as norepinephrine with the primary effects of augmenting afterload (Answer D is correct). Although the patient has features of poor Do₂, this is likely because of inadequate preload, which will be augmented by fluid administration. Agents targeted toward improving Cao₂ (PRBCs) and CO (dobutamine and milrinone) should not be initiated unless the patient has inadequate Do₂ and is not fluid responsive (Answers A–C are incorrect).

7. Answer: C

It is important to realize that this patient presents with likely hemorrhagic shock after blunt trauma. The extent of injuries in highly vascularized areas suggests a hemorrhagic source. According to the extent of confusion, oliguria, tachycardia, and tachypnea, this patient has class III hemorrhage (Answer C is correct; Answers A, B, and D are incorrect).

8. Answer: A

The patient has a massive PE, as evidenced by pulslessness. Massive PE should be treated with thrombolytic therapy unless absolute contraindications to thrombolytics are present. Prolonged chest compressions may be considered a relative contraindication to thrombolytics, but this patient had a short duration of chest compressions (Answer A is correct). Troponin T and brain natriuretic concentrations may be helpful in classifying a patient as having a submassive PE, but the patient in this case has already fulfilled the criteria for massive PE, and these laboratory values will not change the patient’s treatment (Answers B and C are incorrect). Although a TTE can reveal the patient’s RV function, it is unlikely to change management in this patient’s case, and therapy with thrombolytic therapy should not be delayed while an echocardiogram is done (Answer D is incorrect).

9. Answer: A

The patient has received an initial fluid challenge of only 23 mL/kg of crystalloids and still has evidence of end-organ hypoperfusion (elevated lactate concentration and urine output less than 0.5 mL/kg/hour). An additional bolus of at least 500 mL of 0.9% sodium chloride is indicated to ensure an initial fluid challenge of at least 30 mL/kg of crystalloids and to improve end-organ perfusion (Answer A is correct). Because the patient has not received a complete initial fluid challenge (or even a substantial amount of crystalloids), albumin is not indicated (Answer B is incorrect). Vasopressors are not indicated right now because the patient’s MAP is above 65 mm Hg (the patient’s MAP is 67 mm Hg). In addition, if an initial vasopressor were to be selected, norepinephrine would be the preferred choice (Answer C is incorrect). The patient’s low ScvO₂ is likely caused by inadequate preload (resulting in inadequate SV and CO). Adequate preload should be ensured before giving PRBCs as part of improving Do₂ (Answer D is incorrect).

10. Answer: A

Despite an initial fluid challenge of greater than 30 mL/kg of crystalloids, the patient has continued evidence of hypotension (MAP 63 mm Hg) and hypoperfusion (an elevated lactate and a urine output less than 0.5 mL/kg/hour). A vasopressor should be initiated to improve blood pressure (MAP greater than 65 mm Hg) and organ perfusion. Norepinephrine is recommended by the SSC as the first-line vasopressor (Answer A is correct). Vasopressin is not recommended as the single initial vasopressor, but it may be added to norepinephrine (Answer B is incorrect). Phenylephrine is not recommended for the treatment of septic shock except when norepinephrine is associated with serious arrhythmias, when CO is known to be high despite the patient’s having persistently low blood pressure, or as a salvage therapy when combined inotrope, vasopressor, and vasopressin have failed to attain the patient’s MAP goal. Although this patient has a history of atrial fibrillation and a high heart rate, norepinephrine should still be tried, and the patient should be observed for signs of worsening tachyarrhythmias before phenylephrine is initiated (Answer C is incorrect). Dopamine is recommended as an alternative vasopressor to norepinephrine in select patients, such as those with bradycardia. In a meta-analysis of patients with septic shock, dopamine was associated with a higher mortality rate and a more frequent incidence of tachyarrhythmia (Answer D is incorrect).

11. Answer: B

Vasopressin can be added to norepinephrine to either increase MAP or lower norepinephrine requirements. In the VASST (Vasopressin and Septic Shock Trial) study comparing norepinephrine monotherapy with norepinephrine plus vasopressin, there was no difference in mortality between the two groups, but norepinephrine requirements were significantly lower in the patients allocated to receive arginine vasopressin. According to the SSC guidelines, vasopressin can be added to norepinephrine to either raise the MAP or decrease the norepinephrine dosage (Answer B is correct). Although a dynamic marker of fluid responsiveness is not presented, the patient's CO and cardiac preload are likely adequate, given that his $Scvo_2$ is 72%. Additional fluid loading is not indicated according to the information presented (Answer A is incorrect). Phenylephrine as a second-line vasopressor is recommended when a malignant tachyarrhythmia is associated with norepinephrine or as a salvage therapy when other catecholamines have failed. In this case, norepinephrine requirements are relatively low, and no signs of a malignant tachyarrhythmia are mentioned (sinus tachycardia is not considered a malignant tachyarrhythmia; Answer C is incorrect). Epinephrine is recommended when an additional agent (either added to or potentially substituted for norepinephrine) is needed to maintain blood pressure. Adding epinephrine to norepinephrine would only add inotropic support, but in this patient, there are no signs of low CO with an $Scvo_2$ of 72%, and the patient's inadequate blood pressure is the most likely reason for hypoperfusion (elevated lactate and low urine output). Adding epinephrine would also likely increase the patient's heart rate and potential for a tachyarrhythmia. As such, epinephrine is not indicated (Answer D is incorrect).

PULMONARY DISORDERS

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Learning Objectives

1. Synthesize a holistic treatment plan for a patient with acute respiratory distress syndrome that includes nonpharmacologic and pharmacologic therapies.
2. Recommend agents used for endotracheal intubation including premedications, induction agents, and neuromuscular blocking agents.
3. Recognize key parameters and commonly used modes for treatment with mechanical ventilation.
4. Identify pertinent therapies for the treatment of a cystic fibrosis exacerbation.
5. Formulate a treatment plan for a patient with pulmonary hypertension.
6. Describe a treatment plan for patients with asthma exacerbations and acute respiratory failure from chronic obstructive pulmonary disease exacerbation.

Abbreviations in This Chapter

AC/VC	Assist control/volume control
ARDS	Acute respiratory distress syndrome
CF	Cystic fibrosis
COPD	Chronic obstructive pulmonary disease
CVP	Central venous pressure
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
ICP	Intracranial pressure
ICU	Intensive care unit
MAP	Mean arterial pressure
MDI	Metered dose inhaler
mPAP	Mean pulmonary arterial pressure
MV	Mechanical ventilation
NMBA	Neuromuscular blocking agent
PAH	Pulmonary arterial hypertension
PEEP	Positive end-expiratory pressure
PH	Pulmonary hypertension
PS	Pressure support
PVR	Pulmonary vascular resistance
RSI	Rapid sequence intubation
RV	Right ventricular
SABA	Short-acting β -agonist
sGC	Soluble guanylate cyclase
SIMV	Synchronized intermittent mechanical ventilation
VAE	Ventilator-associated event

Self-Assessment Questions

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

1. A 65-year-old man presents to the emergency department (ED) with severe shortness of breath, tachypnea, altered mental status, and diaphoresis. A chest radiograph reveals diffuse, bilateral opacities. Vital signs are as follows: blood pressure 94/54 mm Hg, respiratory rate 26 breaths/minute, heart rate 120 beats/minute, pain score 2/10, and temperature 41.0°C. The patient's wife states that his symptoms began about 2 days ago and gradually worsened during the past day. The decision is made to transfer the patient to the intensive care unit (ICU), where he is intubated. An arterial blood gas shows pH 7.30, Paco_2 50 mm Hg, PaO_2 50 mm Hg, and Sao_2 85% while receiving fraction of inspired oxygen (Fio_2) 100%. Which is the best therapy plan for the next 24 hours?
 - A. Empiric antibiotic therapy, intravenous fluid resuscitation, and vasopressors for shock; low tidal volume (4–8 mL/kg) ventilation strategy; deep sedation to achieve a Richmond Agitation Sedation Scale (RASS) score of -4; and prone positioning.
 - B. Empiric antibiotic therapy, intravenous fluid resuscitation, and vasopressors for shock; low tidal volume (4–8 mL/kg) ventilation strategy; deep sedation to achieve a RASS score of -5 and cisatracurium administration to limit plateau pressures; and prone positioning.
 - C. Empiric antibiotic therapy, aggressive diuresis (goal central venous pressure [CVP] less than 4 mm Hg), and vasopressors for shock; low tidal volume (4–8 mL/kg) ventilation strategy; deep sedation to achieve a RASS score of -4; and prone positioning.
 - D. Empiric antibiotic therapy, intravenous fluid resuscitation, and vasopressors for shock; low tidal volume (4–8 mL/kg) ventilation strategy; deep sedation to achieve a RASS score of -4; and supine positioning.
2. Which best describes the category of acute respiratory distress syndrome (ARDS) that most benefits from prone positioning and cisatracurium administration?

- A. Acute lung injury.
B. Moderate to severe.
C. Mild to moderate
D. Mild.
3. Which order of medication administration would be most appropriate for a 34-year-old woman with no significant medical history receiving rapid sequence intubation (RSI)?
A. Rocuronium, etomidate, midazolam.
B. Fentanyl, succinylcholine, propofol.
C. Atropine, rocuronium, etomidate.
D. Fentanyl, etomidate, succinylcholine.
4. A 78-year-old man presents to the ICU after being intubated for a severe chronic obstructive pulmonary disease (COPD) exacerbation. His current ventilator settings are as follows: assist control/volume control (AC/VC) mode, tidal volume 700 mL (10 mL/kg), respiratory rate 20 breaths/minute, FiO_2 50%, positive end-expiratory pressure (PEEP) 5 cm H_2O , and pressure support (PS) 10 cm H_2O . The first arterial blood gas reveals pH 7.25, PaCO_2 65 mm Hg, bicarbonate (HCO_3^-) 15 mmol/L, PaO_2 65 mm Hg, and Sao_2 90%. Which is the most appropriate setting to adjust on the ventilator?
A. Reduce the tidal volume.
B. Increase the respiratory rate.
C. Increase the FiO_2 .
D. Increase the PEEP.
5. A 21-year-old woman (height 62 inches, weight 50 kg) with a medical history significant for cystic fibrosis (CF) is admitted to the ICU with acute respiratory failure requiring mechanical ventilation (MV). After intubation, her arterial blood gas results are as follows: pH 7.27, PaCO_2 45 mm Hg, HCO_3^- 22 mmol/L, PaO_2 55 mm Hg, and Sao_2 88%. Ventilator settings are as follows: AC/VC mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, FiO_2 60%, PS 5 cm H_2O , and PEEP 5 cm H_2O . Her blood pressure is 110/70 mm Hg and heart rate is 95 beats/minute. Which is the best option for a holistic therapy plan?
A. Initiate cefepime 2 g intravenously every 8 hours and tobramycin 150 mg intravenously every 8 hours; intravenous fluid resuscitation to maintain a CVP goal of 10–14 mm Hg; dornase alfa and hypertonic saline 7% nebulization.
B. Initiate cefepime 2 g intravenously every 8 hours and tobramycin 500 mg intravenously every 8 hours; intravenous fluid resuscitation to maintain a CVP goal of 10–14 mm Hg; dornase alfa and hypertonic saline 7% nebulization.
C. Initiate cefepime 2 g intravenously every 8 hours and tobramycin 150 mg intravenously every 8 hours; intravenous fluid resuscitation to maintain a CVP goal of 10–14 mm Hg.
D. Initiate cefepime 2 g intravenously every 8 hours and tobramycin 500 mg intravenously every 24 hours; diuresis to maintain a CVP goal less than 4 mm Hg while mean arterial pressure (MAP) is greater than 65 mm Hg; dornase alfa and hypertonic saline 7% nebulization.
6. A 55-year-old woman with pulmonary arterial hypertension (PAH) is admitted to the ICU for severe respiratory failure. She reports increased work of breathing for the past 5 days and full adherence to her PAH medication regimen, which includes macitentan 10 mg daily and sildenafil 40 mg three times daily. Current vital signs are as follows: blood pressure 76/60 mm Hg, heart rate 140 beats/minute, respiratory rate 30 breaths/minute, and 85% Sao_2 on 6 L nasal cannula. Right heart catheterization reveals the following: mean pulmonary arterial pressure (mPAP) 50 mm Hg, right arterial pressure 25 mm Hg, cardiac index 1.9 L/minute/ m^2 , and pulmonary capillary wedge pressure 16 mm Hg. A transthoracic echocardiogram (ECHO) reveals an ejection fraction of 60% with severe right ventricular (RV) dilatation. Which would be the most appropriate regimen to initiate for this patient?
A. Dopamine infusion.
B. Epoprostenol infusion.
C. Phenylephrine infusion.
D. Furosemide.

7. A 42-year-old man presents to the ED anxious and short of breath. Auscultation reveals audible wheezing. He has trouble speaking in full sentences. He has used his albuterol metered dose inhaler (MDI) at home for the past several hours without resolution of symptoms. His forced expiratory volume in 1 second (FEV₁) is 35% of predicted. Which is the best classification of this patient's asthma?
- A. Mild.
 - B. Moderate.
 - C. Severe.
 - D. Near-fatal.
8. A 66-year-old man presents to the ICU with acute respiratory failure from a COPD exacerbation. He has had no exacerbations in the past 2 years. His home medications include albuterol HFA (hydrofluoroalkane) 2 puffs four times daily as needed and tiotropium 1 puff once daily. The patient denies any recent sick contacts or changes in sputum production. He has no known drug allergies. The patient is placed on 3 L nasal cannula (SaO₂ 97%) and inhaled albuterol and ipratropium by nebulization. Which other therapy would be most appropriate for this patient?
- A. Azithromycin 500 mg intravenously daily.
 - B. Prednisone 40 mg orally daily.
 - C. Levofloxacin 500 mg orally daily.
 - D. Methylprednisolone 125 mg intravenously every 6 hours.

I. ACUTE RESPIRATORY DISTRESS SYNDROME

A. Definition and Epidemiology

1. First described in 1967; a consensus definition for ARDS was proposed in 1994 with the American-European Consensus Conference (AECC). Acute onset (not defined); $\text{PaO}_2/\text{FiO}_2$ of 200 mm Hg or less; bilateral infiltrates on chest radiography; absence of left atrial hypertension (pulmonary artery wedge pressure of 18 mm Hg or less). Acute lung injury fulfills the same criteria except for a milder pathology for hypoxemia ($\text{PaO}_2/\text{FiO}_2$ of 300 mm Hg or less).
2. AECC definition refined into the Berlin Definition of ARDS (Table 1). Notable differences in the revised definition (JAMA 2012;307:2526-33)

Table 1. Berlin Definition of ARDS

Variable	Definition
Timing	Onset within 1 wk of a known clinical insult or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (ECHO) to exclude hydrostatic edema if no risk factor present
Oxygenation	
Mild	$200 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mm Hg}$ with PEEP or CPAP $\geq 5 \text{ mm Hg}$
Moderate	$100 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mm Hg}$ with PEEP or CPAP $\geq 5 \text{ mm Hg}$
Severe	$\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mm Hg}$ with PEEP $\geq 5 \text{ mm Hg}$

CPAP = continuous positive airway pressure; ECHO = echocardiogram.

3. The reported incidence of ARDS in the United States is 59 per 100,000 person-years.
4. Estimated mortality ranges from 27% to 45% (Berlin Definition). Six variables are associated with increased mortality: age, immunocompromised state, multiorgan dysfunction score, acidemia, barotrauma, and presence of major organ dysfunction on admission (N Engl J Med 2005;353:1685-93).

B. Etiology and Pathophysiology

1. Direct and indirect causes of lung injury
 - a. Direct: Pneumonia, aspiration, and trauma
 - b. Indirect: Sepsis, transfusion injury, pancreatitis, burn injury, trauma
2. Hypoxemia develops because of the destruction of alveoli at the cellular level. Destruction of the alveolar epithelium and type I and type II cells causes impaired lymphatic drainage, disruption of the osmotic gradient, accumulation of cellular debris, reduced surfactant production, and microthrombi.
 - a. The pathophysiologic cellular changes manifest with pulmonary edema, impaired oxygenation, and organ failure.
 - b. Clinical hallmark of ARDS is hypoxemia.

C. Nonpharmacologic Therapy

1. The primary goals of nonpharmacologic therapy (e.g., MV, prone positioning) are to support oxygenation and minimize further organ dysfunction.

2. For patients with acute hypoxemic respiratory failure (non-hypercapnic), administering oxygen by high-flow nasal cannula (HFNC) resulted in greater ventilator-free days (24 ± 8 days vs. 22 ± 10 days in the standard oxygen therapy by face mask vs. 19 ± 12 days in the noninvasive positive-pressure ventilation arm). A reduction in 90-day mortality was also observed in favor of the HFNC group, hazard ratio (HR) 2.01 (95% CI, 1.01–3.99, $p=0.046$) with standard oxygen than with HFNC, and HR 2.50 (95% CI, 1.31–4.78, $p=0.006$) (N Engl J Med 2015;372:2185-96).
3. Lung-protective ventilation in the form of a low tidal volume strategy (6 mL/kg of ideal body weight) was shown to improve survival in a multicenter study by the Acute Respiratory Distress Syndrome Network (ARDSNet); it is now the standard of care (N Engl J Med 2000;342:1301-8).
 - a. Targeting a plateau pressure of 30 cm H₂O or less is recommended.
 - b. Permissive hypercapnia (Pco₂ 50–55 mm Hg) is acceptable to optimize tidal volume strategy.
4. In a multicenter, randomized trial of 767 patients, a ventilation strategy of moderate PEEP compared with a PEEP level set to a target plateau pressure (28–30 cm H₂O) showed no difference in 28-day mortality, but it did show improved ventilator-free days and organ failure-free days (JAMA 2008;299:646-655).
5. A separate multicenter, randomized study evaluated using PEEP as a recruitment strategy to improve ventilation in 983 patients and found no difference in hospital mortality (JAMA 2008;299:637-45).
6. Prone positioning for the treatment of early ARDS (less than 36 hours) in moderate to severe ARDS (Pao₂/Fio₂ of 150 mm Hg or less) reduces 28-day mortality compared with supine positioning (16% vs. 32.8%, $p<0.0001$; HR 0.44; 95% confidence interval [CI], 0.29–0.67) (N Engl J Med 2013;368:2159-68).
7. Extracorporeal membrane oxygenation (ECMO)
 - a. CESAR trial showed that treatment at an ECMO referral center resulted in improved 6-month survival (Lancet 2009;374:1351-63).
 - i. ARDS with a Murray score of 3 or greater or a pH less than 7.20
 - ii. Not all patients randomized to ECMO referral center received ECMO treatment (68 of 90 patients in the experimental group received ECMO).
 - iii. Potential for confounding because of experiential bias – Clinicians at ECMO treatment center may have more experience in treating ARDS.
 - b. The Respiratory ECMO Survival Prediction (RESP) score was developed from a registry of ECMO-treated patients (Am J Respir Crit Care Med 2014;189:1374-82).
 - i. The RESP score predicts patient survival after ECHO initiation.
 - ii. Does not help quantify the decision of whether to initiate ECMO and whether ECMO treatment will improve survival in a specific patient
 - c. A global consortium of experts recommended that ECMO be provided in regional centers of excellence with adequate access to clinical support services, staffing, and infrastructure for quality assurance.

D. Pharmacologic Therapy

1. In a randomized trial comparing optimal fluid management strategies, a conservative fluid management strategy (CVP less than 4 mm Hg) compared with a liberal fluid management strategy (CVP 10–14 mm Hg) in patients with ARDS and hemodynamic stability (not requiring vasopressors or MAP greater than 60 mm Hg) increased ventilator-free days (14.6 ± 0.5 vs. 12.1 ± 0.5 , $p<0.001$) (N Engl J Med 2006;354:2564-75). Patients with concomitant shock were enrolled in the study and randomized to both treatment arms. If shock was present for patients randomized to the fluid-conservative strategy, diuretics were withheld and administered once the patient had established hemodynamic stability (discontinuation of vasopressors or MAP greater than 60 mm Hg).
2. Early administration of cisatracurium (less than 48 hours) reduced mortality in a cohort of patients with moderate to severe ARDS (Pao₂/Fio₂ less than 150 mm Hg) compared with placebo (HR 0.68; 95% CI, 0.48–0.98; $p=0.04$) (N Engl J Med 2010;363:1107-16).

3. Corticosteroids are presupposed to mediate the inflammatory cytokines and mitigate fibrotic alveolar changes during ARDS.
 - a. Several studies tested the effects of administering corticosteroids during early ARDS and found no benefit.
 - b. A multicenter study of 24 patients with ARDS for more than 7 days reported mortality benefit. Limitations of this study include unbalanced groups (treatment = 16 patients vs. placebo = 8 patients). In addition, four patients were crossed over from the placebo arm to the corticosteroid arm.
 - c. ARDSNet tested corticosteroid administration in late ARDS (ARDS for 7 days or more) and reported no survival benefit (n=180).
 - i. Increased mortality in the subgroup of patients receiving corticosteroids after day 14
 - ii. However, corticosteroid treatment was associated with improved ventilator- and shock-free days during the first 28 days of treatment.
4. Statins
 - a. Presumed to be beneficial by modulating inflammatory response of lung parenchyma. Statins reduced inflammatory response in murine models of ARDS. In addition, observational studies and small randomized controlled trials suggest a clinical benefit to statins for sepsis and ARDS.
 - b. Simvastatin vs. placebo (N Engl J Med 2014;371:1695-703)
 - i. Patients recruited from 40 sites in the United Kingdom and Ireland, accruing 540 patients with ARDS (259 patients randomized to simvastatin compared with 281 patients randomized to placebo)
 - ii. Simvastatin 80 mg daily compared with placebo
 - iii. Outcomes: Ventilator-free days (of 28) (primary), change in Sequential Organ Failure Assessment score (secondary), number of nonpulmonary organ failure days (secondary), mortality (secondary)
 - iv. Ventilator-free days: No difference between groups, 12.6 ± 9.9 days (simvastatin) versus 11.5 ± 10.4 days (placebo); $p=0.21$ (primary) or with secondary end points
 - v. Study does not provide support for administering statins for the treatment of sepsis-associated ARDS.
 - c. Rosuvastatin vs. placebo (N Engl J Med 2014;371:2191-200)
 - i. National Heart, Lung, and Blood Institute., ARDSNet study of 44 sites. Patients with ARDS (P_{aO_2}/F_{iO_2} less than 300 mm Hg) caused by sepsis. Ventilator management according to lung-protective, low tidal volume strategy for ARDS. Fluid management according to a simplified version of FACTT (Fluid and Catheter Treatment Trial)
 - ii. Rosuvastatin 40 mg (loading dose) followed by 20 mg daily (dose reduction for serum creatinine (SCr) greater than 2.8 mg/dL: 10 mg daily) compared with placebo
 - iii. Outcomes: Hospital mortality (primary), ventilator-free days (secondary), organ failure-free days (secondary), and ICU-free days (secondary). Powered to detect an absolute difference of 9% (27% to 18%)
 - iv. Terminated for futility in primary end point after enrollment of 745 patients (in-hospital mortality: 28.5% vs. 24.9%; $p=0.21$)
 - v. Study did not support administering statins for the treatment of sepsis-associated ARDS.

Patient Cases

1. A 56-year-old man is admitted to the ICU with ARDS after experiencing increasing dyspnea during the past 24 hours, culminating in cardiopulmonary arrest. His medical history is significant for alcoholism and hypertension. Results of the initial arterial blood gas are as follows: pH 7.24, PaCO_2 58 mm Hg, HCO_3^- 24 mmol/L, PaO_2 50 mm Hg, and SaO_2 84% while receiving MV AC mode with FIO_2 100%. Chest radiography reveals diffuse bilateral infiltrates. The patient has blood pressure 120/40 mm Hg (MAP 67 mm Hg), heart rate 142 beats/minute, and CVP 8 mm Hg while receiving a norepinephrine (10 mcg/minute) infusion after intravenous fluid resuscitation. Ceftriaxone 1 g intravenously every 24 hours and levofloxacin 750 mg intravenously every 24 hours have been initiated for the treatment of community-acquired pneumonia. Which is the best therapeutic plan for the management of ARDS and septic shock?
 - A. Continue fluid resuscitation to maintain a CVP of 10–14 mm Hg; low tidal volume strategy of 4–8 mL/kg of ideal body weight; prone positioning; and sedative administration to target deep sedation and cisatracurium infusion.
 - B. Diuresis to target a CVP less than 4 mm Hg; low tidal volume strategy of 4–8 mL/kg of ideal body weight; supine positioning; and sedative administration to target deep sedation and cisatracurium infusion.
 - C. Diuresis to target a CVP less than 4 mm Hg; low tidal volume strategy of 4–8 mL/kg of ideal body weight; supine positioning; and sedative administration to target deep sedation.
 - D. Discontinue fluid resuscitation and norepinephrine infusion, and begin diuresis to target a CVP less than 4 mm Hg while maintaining a MAP greater than 65 mm Hg; low tidal volume strategy of 4–8 mL/kg of ideal body weight; prone positioning; and sedative administration to target deep sedation and cisatracurium infusion.
2. A 70-year-old woman (height 63 inches, weight 65 kg) is transferred to your ICU from an outside hospital after outside hospital admission for hypoxic respiratory failure. She had been treated at the outside hospital for ARDS for 3 days before her son requested hospital transfer. On admission, the patient is receiving MV with the following settings: synchronized intermittent mechanical ventilation (SIMV) mode, tidal volume 600 mL (12 mL/kg), respiratory rate 12 breaths/minute, PS 10 mm Hg, and PEEP 10 mm Hg. Which option represents the best therapy plan for the treatment of her ARDS?
 - A. AC/VC mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, PS 10 mm Hg, PEEP 5 mm Hg; supine positioning.
 - B. AC/VC mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, PS 10 mm Hg, PEEP 5 mm Hg; prone positioning; cisatracurium administration.
 - C. SIMV mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, PS 10 mm Hg, PEEP 5 mm Hg; supine positioning; cisatracurium administration.
 - D. AC/VC mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, PS 10 mm Hg, PEEP 5 mm Hg; prone positioning.

II. INTUBATION

A. Endotracheal Intubation

1. Provides access for suctioning of tracheobronchial secretions, maintains a patent airway, and allows administration of medications
2. Indications include airway protection, facilitation of ventilation and oxygenation, assurance of airway patency, and anesthesia and surgery.
3. Orotracheal intubation is preferred for elective and emergency cases.
4. Nasotracheal intubation is beneficial for patients undergoing maxillofacial surgery or dental procedures and for patients with limited mouth opening. May be associated with increased risk of bleeding and sinusitis and should be avoided in patients with severe nasal or midface trauma
5. Complications include insertion trauma, gastric aspiration, hypoxemia, laryngospasm, esophageal intubation, right main bronchus intubation, cardiac arrhythmias, and hemodynamic impairment.

B. Rapid Sequence Intubation (RSI)

1. Rapid and simultaneous administration of a rapid-acting induction agent and a neuromuscular blocking agent (NMBA) to facilitate intubation and decrease the risk of aspiration
2. Series of seven distinct steps: preparation, preoxygenation, pretreatment, paralysis with induction, protection and positioning, placement of the tube in the trachea, and postintubation management

C. Pretreatment

1. Occurs 3 minutes before any induction agent or NMBA is administered
2. The purpose of pretreatment is to attenuate the sympathetic and parasympathetic response (catecholamine release, hypertension, tachycardia, potentially increased intracranial pressure (ICP) in patients with impaired cerebral autoregulation) to laryngoscopy.
3. Fentanyl or lidocaine is recommended for pretreatment (Table 2).
4. Atropine and defasciculating doses of non-depolarizing NMBA are not recommended for routine use in RSI for adult patients.

Table 2. Pretreatment Agents

Agent	Dose	Onset	Duration	Advantages	Disadvantages
Fentanyl (Sublimaze)	IV: 1–3 mcg/kg	< 30 s	0.5–1 hr	• Blunts hypertensive response from intubation • Recommended over other opioids because of its rapid onset and short duration of action	• Chest wall rigidity (doses > 100 mcg/kg) • Hypotension, bradycardia, and respiratory depression
Lidocaine (Xylocaine)	IV: 1.5 mg/kg	45–90 s	10–20 min	• Prevents rise in ICP through blunting of cough reflex; lack of evidence of improved outcomes in patients at risk • May reduce bronchospasm in patients with reactive airway disease	• Contraindicated in patients with an amide anesthetic allergy, bradycardia, or severe heart block

ICP = intracranial pressure; IV = intravenous(ly).

D. Induction Agents

1. Given as rapid intravenous push immediately before paralyzing agent to help achieve optimal conditions for intubation
2. Agents should provide rapid loss of consciousness, analgesia, amnesia, and stable hemodynamics.
3. Agents used for induction during RSI include barbiturates, benzodiazepines (midazolam), etomidate, ketamine, and propofol (Table 3).
4. Barbiturates
 - a. Thiopental is no longer available in the United States.
 - b. Methohexital is rarely used because of its adverse effect profile, which includes respiratory depression, hypotension, and histamine release.
5. Etomidate
 - a. Etomidate is a nonbarbiturate, imidazole derivative with a rapid onset of action and a very short elimination half-life.
 - b. Enhances the effects of γ -aminobutyric acid, thereby blocking neuroexcitation and inducing unconsciousness (does not provide analgesia)
 - c. Etomidate transiently inhibits the conversion of cholesterol to cortisol by inhibiting 11 β -hydroxylase, leading to transient adrenal suppression.
 - i. There is no convincing or consistent evidence to suggest that etomidate is associated with an increased risk of death (Intensive Care Med 2011;37:901-10; Chest 2015;147:335-46).
 - ii. Large randomized, prospective, adequately powered studies are needed to clarify the clinical significance of etomidate in patients at risk of adrenal insufficiency.

Table 3. Induction Agents

Agent	Dose	Onset	Duration	Advantages	Disadvantages
Etomidate (Amidate)	IV: 0.2–0.6 mg/kg	10–20 s	4–10 min	- Minimal cardiovascular effects - Decreased ICP with minimal effects on cerebral perfusion	- Myoclonic jerks - Transient decrease in cortisol production
Ketamine (Ketalar)	IV: 1–2 mg/kg IM: 4–10 mg/kg	IV: 10–15 s IM: 3–4 min	IV: 5–15 min IM: 12–25 min	- Catecholamine reuptake inhibition (transient rise in blood pressure and heart rate) - Respiration and airway reflexes maintained - Does not increase ICP - Relieves bronchospasm - Has both amnestic and analgesic effects	- Negative inotropic/chronotropic effects (in catecholamine-depleted patients) - Emergence delirium, nightmares, and hallucinations (premedication with a benzodiazepine does not reduce the incidence)
Midazolam (Versed)	IV or IM: 0.2–0.3 mg/kg	60–90 s	1–4 hr	Recommended over other benzodiazepines because of its relatively faster onset of action	- Compared with other induction agents, slow onset and longer duration - Dose-dependent respiratory depression and hypotension

Table 3. Induction Agents (*continued*)

Agent	Dose	Onset	Duration	Advantages	Disadvantages
Propofol (Diprivan)	IV: 1.5–2.5 mg/kg	15–45 s	3–10 min	- Decreases ICP; however, may also decrease CPP - Mild bronchodilating effects - Drug of choice in pregnancy	- Hypotension and bradycardia - Negative inotropic effects

IM = intramuscular(ly); CPP = cerebral perfusion pressure

E. Neuromuscular Blocking Agents

- Quaternary ammonium compounds that mimic the structure of acetylcholine
- Block impulse transmission at the neuromuscular junction, resulting in skeletal muscle paralysis
- Used immediately after induction to help achieve optimal conditions for intubation
- Have no sedative, analgesic, or amnestic properties
- Problematic in patients with a difficult or failed airway
- Depolarizing NMBAs
 - Succinylcholine: Noncompetitively binds to acetylcholine receptors, leading to sustained depolarization of the neuromuscular junction and prevention of muscle contraction
 - Best agent for RSI
- Nondepolarizing NMBAs (Table 4)
 - Rocuronium and vecuronium: Competitive antagonists of acetylcholine at the neuromuscular junction, leading to the prevention of muscle contraction
 - Intermediate-acting non-depolarizing agents are alternatives when succinylcholine is contraindicated.
 - Usually have a slower onset of action and a longer duration of action

Table 4. Common Neuromuscular Blocking Agents

Agent	Dose	Onset	Duration	Cautions
Succinylcholine (Anectine)	IV: 1–2 mg/kg IM: 3–4 mg/kg (max 150 mg)	IV: 1 min IM: 2–3 min	IV: 3–5 min IM: 10–30 min	- Prolonged effects in pseudocholinesterase deficiency - Hyperkalemia or patients at risk of hyperkalemia (prolonged immobilization, crush injuries, myopathies, burns, muscular dystrophy, stroke, and spinal cord injuries) - Malignant hyperthermia - Bradycardia/hypotension with repeated doses - Mild increase in ICP
Rocuronium (Zemuron)	IV: 0.6–1.2 mg/kg	1–2 min	30–60 min	Moderate increase in duration with liver dysfunction, minimal increase in duration with renal dysfunction
Vecuronium (Norcuron)	IV: 0.08–0.1 mg/kg	2–3 min	20–60 min	Prolonged duration in renal and liver dysfunction

F. Postintubation Management

- Provide continued sedation/analgesia as needed to assist in adequate oxygenation and ventilation
- Minimize long-term use of analgesics and sedatives
- Maintain head-of-bed elevation 30–45 degrees

4. Mouth and eye care
5. Bowel regimen
6. Stress ulcer and deep venous thrombosis prophylaxis

Patient Cases

3. A 55-year-old man (weight 75 kg) is admitted to the burn ICU after sustaining a 65% total body surface area burn to the abdomen, back, and lower extremities from a house fire. He is unconscious and unable to protect his airway. His medical history is significant for hypertension and hyperlipidemia. He is currently receiving high-dose norepinephrine and vasopressin to maintain a MAP of 65 mm Hg. His current laboratory data show the following: sodium 130 mEq/L, potassium 5.9 mEq/L, chloride 122 mEq/L, carbon dioxide 15 mg/dL, blood urea nitrogen (BUN) 10 mg/dL, and SCr 1.3 mg/dL. Which medications would be most appropriate to use for RSI?
 - A. Propofol, fentanyl, rocuronium.
 - B. Ketamine, fentanyl, succinylcholine.
 - C. Etomidate, fentanyl, rocuronium.
 - D. Propofol, fentanyl, succinylcholine.
4. A 39-year-old homeless man (weight 70 kg) was admitted to the neurosciences ICU with a traumatic head injury after falling off a 3-ft ladder while intoxicated. Imaging reveals a subdural hematoma. The team decides to intubate this patient. His current laboratory values are as follows: sodium 133 mEq/L, potassium 4.5 mEq/L, chloride 97 mEq/L, carbon dioxide 28 mg/dL, BUN 13 mg/dL, SCr 0.7 mg/dL, and glucose 140 mg/dL. Which induction medication would be most appropriate to use for RSI?
 - A. Propofol 90 mg intravenous push.
 - B. Ketamine 100 mg intravenous push.
 - C. Midazolam 15 mg intravenous push.
 - D. Etomidate 150 mg intravenous push.

III. MECHANICAL VENTILATION

- A. Critical to Understanding How MV Works: A fundamental knowledge of acid-base disorders and normal respiratory physiology
- B. Two Essential Categories of Respiratory Failure: Hypercapnic and hypoxic. Derangements in P_{aO_2} or P_{aCO_2} will help determine the etiology of respiratory failure. (Table 2 provides the context for normal oxygenation and ventilation values.)
- C. Modes
 1. AC ventilation
 - a. Volume control
 - i. The patient receives a predetermined respiratory rate and tidal volume, with additional patient-initiated breaths provided at the preset tidal volume. Patient-initiated respiration generates a negative pressure within the ventilator circuit, which is sensed by the ventilator, and a full tidal volume breath is provided.

- ii. Potential for ventilator dyssynchrony, “double-stacking,” and respiratory alkalosis
 - iii. Mode used in the ARDSNet study of tidal volume strategy to limit spontaneous tidal volumes (N Engl J Med 2000;342:1301-8)
 - b. Pressure control
 - i. The patient will receive a breath at a fixed rate until a predetermined peak pressure limit is reached. The tidal volume is variable and limited by the peak pressure limit.
 - ii. Not ideal for patients with low minute ventilation and may lead to hypoventilation and further hypoxia
 - 2. SIMV: The patient will receive a predetermined respiratory rate and tidal volume plus additional spontaneous, self-generated breaths at whatever tidal volume the patient can generate. Not ideal for the treatment of ARDS, given the ability of patients to exceed the present tidal volume for spontaneous breaths in excess of 6 mL/kg
 - 3. PS ventilation
 - a. Usually used as a weaning mode of MV from a more intensive mode of MV (i.e., AC ventilation)
 - b. The patient initiates each breath with assistance from the ventilator in the form of a preset pressure value. The ventilator is set to provide a correct amount of pressure to assist each inspiratory effort. The tidal volume and respiratory rate depend on the patient.
- D. Ventilator Parameters
- 1. FiO_2
 - a. The amount of oxygen that is delivered with each breath, from 21% to 100%
 - b. FiO_2 is generally titrated to a PaO_2 greater than 55 mm Hg. Amount of FiO_2 delivered is limited by concerns for oxygen toxicity.
 - 2. Tidal volume
 - a. The volume of air inspired in a breath (delivered by MV or spontaneous)
 - b. Tidal volume is set according to oxygenation and ventilation needs. Patients with ARDS will be treated with a low tidal volume strategy, whereas most other patients will have the tidal volume titrated to PaCO_2 and pH.
 - 3. Respiratory rate
 - a. The respiratory rate is set to provide a minimal number of breaths from the ventilator at the set tidal volume.
 - b. The respiratory rate is titrated minute ventilation, PaCO_2 , and pH. Minute ventilation (liters per minute) = tidal volume (liters) x respiratory rate (breaths/minute). $6.0 \text{ L/minute} = 0.5 \text{ (L)} \times 12 \text{ (breaths/minute)}$
 - 4. Flow rate: Describes the velocity of air delivered. The velocity is greatest initially on inspiration and decelerates toward the end of the inspiratory effort.
 - 5. PEEP
 - a. Positive pressure in the alveoli during expiration
 - b. Provides greater surface area at the alveolar epithelial surface to promote diffusion of oxygen and improve ventilation/perfusion matching
 - c. Titrated to meet oxygenation needs
- E. Quality Improvement – Ventilator-associated events (VAEs) (Am J Respir Crit Care Med 2015;192:1420-30)
- 1. In 2013, the Centers for Disease Control and Prevention released a model for evaluating complications from MV, VAEs. VAE definition: At least 2 days of increasing ventilator settings (increase in PEEP of 3 cm H_2O or greater or increase by 20% or more of FiO_2) after at least 2 days of stable or decreasing ventilator settings. VAE can further be subclassified into infection-related ventilator-associated complications (Table 5).
 - 2. A VAE model was developed to enable a population-based method of assessment and tool for quality improvement.

3. VAEs are attributed to one of four common clinical conditions: pneumonia, fluid overload, atelectasis, or ARDS.
4. Six potential strategies have been identified to minimize VAEs, according to the accumulation of data from literature:
 - a. Minimize sedation
 - b. Paired spontaneous awakening trials and spontaneous breathing trials
 - c. Early mobility
 - d. Low tidal volume ventilation
 - e. Conservative fluid management
 - f. Conservative transfusion thresholds

Table 5. Normal Respiratory Physiology Values

Value	Normal Range
Tidal volume (mL/kg)	5–10
Respiratory rate (breaths/minute)	12–20
Minute ventilation (L/minute)	5–10
Paco ₂ (mm Hg)	35–45
Pao ₂ (mm Hg)	80–100
Sao ₂ (%)	95–100

Patient Case

5. A 74-year-old woman (height 63 inches, weight 65 kg) is transferred to your ICU from an outside hospital after admission for hypoxic respiratory failure. She had been treated at the outside hospital for ARDS for 3 days before her son requested transfer. On receiving the patient in your ICU, she is receiving MV with the following settings: SIMV mode, tidal volume 600 mL/kg (12 mL/kg), respiratory rate 12 breaths/minute, PS 10 mm Hg, and PEEP 10 mm Hg. Which option represents the best ventilator plan for treatment of her ARDS?
 - A. AC/VC mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, PS 10 mm Hg, PEEP 5 mm Hg.
 - B. SIMV mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, PS 10 mm Hg, PEEP 5 mm Hg.
 - C. PS mode, PS 10 mm Hg, PEEP 5 mm Hg.
 - D. SIMV mode, tidal volume 300 mL (6 mL/kg), respiratory rate 10 breaths/minute, PS 10 mm Hg, PEEP 5 mm Hg.

IV. CYSTIC FIBROSIS

- A. Cystic Fibrosis – A chronic disease process affecting many organs, including the pancreas, liver, and intestine, but primarily the lung (Chest 2004;125:1-39)
 1. CF is a recessive disorder that is caused by a mutation of the CFTR (cystic fibrosis transmembrane conductance regulator).

2. Acute exacerbations include symptoms of increased cough, sputum production, shortness of breath, weight loss, and a decline in lung function.
3. The lungs become colonized with bacteria, and chronic infections become common. Gradually, the formation of a thick mucus (“mucoid”) harboring *Pseudomonas aeruginosa* becomes common.

B. Antibiotic Therapy

1. Because of the high incidence of resistance, initial treatment with two antipseudomonal agents is recommended (Am J Respir Crit Care Med 2009;180:802-8). Aggressive dosing of β -lactam antibiotics is recommended to optimize time above the minimum inhibitory concentration.
2. Antibiotic dosing is challenging because of the altered pharmacokinetics in patients with CF. Patients with CF can be distinguished by their large volume of distribution and increased renal clearance.
3. Evidence is currently lacking for the simultaneous administration of inhaled and intravenous antibiotics for acute CF exacerbations (Am J Respir Crit Care Med 2009;180:802-8).
4. Once-daily dosing of tobramycin (10 mg/kg) to target a peak concentration of 20–30 mg/L and a trough concentration of less than 1 mg/L was as effective as conventional dosing (Lancet 2005;365:573-8).

C. Adjunctive Therapies for CF Exacerbations

1. Adjunctive therapies for CF exacerbations are key to improving outcomes and mucous clearance.
 - a. Aggressive chest physical therapy
 - b. Dornase alfa administered as a nebulized therapy
 - c. Hypertonic saline (7%)
2. Nutrition
 - a. Providing nutrition during acute exacerbations is key to maintaining metabolic function and promoting optimal outcomes for lung transplantation, should the situation arise.
 - b. Administer pancreatic enzymes to assist with digestion.
3. Corticosteroids: Insufficient evidence for administering corticosteroids (Am J Respir Crit Care Med 2009;180:802-8)

Patient Case

6. A 20-year-old woman is admitted to the ICU for an acute exacerbation of her CF. Before admission, the patient was doing well. The patient had maintained her ideal body weight and had just completed a home regimen of suppressive antibiotics. The patient requires MV for management of hypoxic respiratory failure. She is initiated on AC/VC mode with a lung-protective strategy (4–8 mL/kg tidal volume). Which represents the best option for managing her acute CF exacerbation?
 - A. Tobramycin nebulization; hypertonic saline 7% nebulization; and tube feedings to target a hypocaloric goal during her acute illness (15 kcal/kg/day).
 - B. Ceftriaxone 2 g intravenously every 24 hours; tobramycin nebulization; normal saline 0.9% nebulization; and tube feedings to target her goal caloric intake (25 kcal/kg/day).
 - C. Piperacillin/tazobactam 4.5 g intravenously every 6 hours; tobramycin 10 mg/kg intravenously once daily; hypertonic saline 7% nebulization; and tube feedings to target her goal caloric intake (25 kcal/kg/day).
 - D. Piperacillin/tazobactam 3.375 g intravenously every 6 hours; tobramycin 10 mg/kg intravenously every 8 hours; hypertonic saline 7% nebulization; and tube feedings to target her goal caloric intake (25 kcal/kg/day).

V. PULMONARY HYPERTENSION

A. Definition

1. Pulmonary hypertension (PH) is a chronic, life-threatening disease defined as an mPAP of 25 mm Hg or greater at rest measured by right heart catheterization. No definition of PH is currently accepted during exercise.
2. PAH is defined as an mPAP of 25 mm Hg or greater at rest, pulmonary capillary wedge pressure of 15 mm Hg or less, and elevated pulmonary vascular resistance (PVR) of greater than 3 Wood units measured by right heart catheterization.

B. Clinical Classification of PH by the World Health Organization: Updated at the 2013 World Conference on Pulmonary Hypertension (J Am Coll Cardiol 2013;62:D34-41):

1. Group 1: PAH
2. Group 1: Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
3. Group 2: PH caused by left heart disease
4. Group 3: PH caused by chronic lung disease and/or hypoxia
5. Group 4: Chronic thromboembolic PH
6. Group 5: Unclear multifactorial mechanisms

C. Functional Classification

1. Developed in 2004 by the World Health Organization (Table 6)
2. Used to determine the baseline functional status of the patient and throughout the disease

Table 6. World Health Organization of Functional Class Assessment

Class	Definition
I	No symptoms (dyspnea, fatigue, syncope, chest pain) with normal activities
II	Symptoms with strenuous normal daily activities that slightly limit functional status and activity level
III	Symptoms of dyspnea, fatigue, syncope, and chest pain with normal daily activities that severely limit functional status and activity level
IV	Symptoms at rest; cannot perform normal daily activities without symptoms

D. Pathophysiology

1. In PH, vascular changes occur, including vasoconstriction, cellular proliferation, and thrombosis.
2. Thromboxane A₂ (potent vasoconstrictor) concentrations are increased.
3. Prostacyclin (potent vasodilator, inhibitor of platelet aggregation, and antiproliferative properties) concentrations are decreased.
4. Endothelin-1 (potent vasoconstrictor, mitogenic properties on pulmonary artery smooth muscle cells) concentrations are increased.
5. Nitric oxide concentrations (vasodilator, inhibitor of platelet activation, and inhibitor of vascular smooth muscle cell proliferation) are decreased.

E. Treatment Goals for PH

1. Achieve and maintain World Health Organization functional class assessment (WHO-FC) I or II.
2. Preserve 6-minute walk distance to 380 m or more.
3. Preserve RV size and function (right arterial pressure less than 8 mm Hg and cardiac index greater than 2.5–3.0 L/minute/m²).
4. Normalize B-type natriuretic peptide.

5. Sustain cardiopulmonary exercise testing, including peak oxygen consumption greater than 15 mL/minute/kg and ventilator equivalent for carbon dioxide less than 45 L/minute.

F. Management of PAH

1. Supportive therapy
 - a. Oxygen: Maintain Sao_2 of 90% or greater and Pao_2 of 60 mm Hg or greater.
 - b. Diuretics should be used for the symptomatic management of RV dysfunction and signs of fluid overload; choice of diuretic is variable.
 - c. Digoxin will increase cardiac output; consider in patients who develop atrial tachyarrhythmias.
 - d. Anticoagulation should be considered in idiopathic PAH, heritable PAH, and PAH secondary to anorexigenic use (goal INR 1.5–2.5).
2. Vasodilator therapy with calcium channel blockers (diltiazem, amlodipine, nifedipine)
 - a. Considered first line for the treatment of PAH, WHO-FC I–III, in patients who have a positive response to acute vasoreactivity testing (reduction in mPAP of 10 mm Hg or more to an mPAP of 40 mm Hg or less with unchanged cardiac output) (N Engl J Med 1992;327:76–81)
 - b. Around 15% of patients with PAH will have a positive response to the vasoreactivity test (Circulation 2005;111:3105–11).
 - c. Calcium channel blockers improve mPAP, PVR, WHO-FC, and survival in patients with PAH and a positive vasoreactivity test (Circulation 1987;76:135–41; N Engl J Med 1992;327:76–81).
 - d. Patients should not be considered candidates for calcium channel blocker therapy if they have RV dysfunction, depressed cardiac output, or WHO-FC IV symptoms.
3. Targeted therapies include prostacyclin derivatives, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, soluble guanylate cyclase (sGC) stimulators, and selective prostacyclin receptor (IP receptor) agonists.

G. Prostacyclins

1. Parenteral prostacyclins
 - a. Recommended in patients with PAH with WHO-FC III or IV symptoms
 - b. Continuous-infusion epoprostenol is the most thoroughly studied of the medications approved for the treatment of PAH and prolongs survival.
 - i. 100% survival with intravenous epoprostenol compared with 80% survival with conventional therapies at 12 weeks (N Engl J Med 1996;334:296–301)
 - ii. 88% survival with intravenous epoprostenol compared with 80% survival in historical controls at 1 year (Circulation 2002;106:1477–82)
 - iii. 55% survival with intravenous epoprostenol compared with 34% survival in historical controls at 5 years (J Am Coll Cardiol 2002;40:780–8)
 - c. Complications related to delivery include the need for a dedicated intravenous line, local catheter infections/bloodstream infections, and catheter-related thrombosis.
2. Inhaled prostacyclins (Table 7)
 - a. Recommended for use in patients with WHO-FC III symptoms – Advantages over intravenous route: selective pulmonary vasodilation with minimal systemic effects
 - b. 11 studies evaluated the use of inhaled epoprostenol (not FDA approved) in critically ill patients with PH (Pharmacotherapy 2010;30:728–40).
 - i. Studies included patients undergoing cardiac surgery or lung or heart transplantation, as well as non-specific ICU patients.
 - ii. Most studies showed a significant decrease in pulmonary pressures; however, significance with improving outcomes is unknown.
 - iii. Minimal adverse effects reported

- c. Inhaled iloprost
- Small studies of critically ill patients with PH
 - Not diluted in glycine buffer and no need for continuous administration

Table 7. Available Prostacyclins

Agent	Epoprostenol IV		Treprostinil IV	Treprostinil SC	Treprostinil Inhaled	Iloprost Inhaled	Treprostinil Oral
	Flolan	Velettri	Remodulin	Remodulin	Tyvaso	Ventavis	Orenitram
WHO-FC	III–IV		II–IV		III	III–IV	II–III
Initial dose	1–4 ng/kg/min IV; based on dry dosing weight		1.25 ng/kg/min IV or SC; based on dry dosing weight; dose adjustments in hepatic impairment		18 mcg four times daily	2.5–5 mcg six to nine times daily	0.25 mg every 12 hr or 0.125 mg every 8 hr; caution with strong CYP2C8 inhibitors and severe hepatic dysfunction
Elimination half-life	6 min		4 hr			25 min	4 hr
Stability	Protect from light		48 hr at room temp	72 hr at room temp	—		—
	8 hr at room temp; 24 hr with cold packs	48 hr at room temp					
Adverse effects	Flushing, headache, diarrhea nausea/vomiting, jaw pain, thrombocytopenia				Cough, throat irritation, bronchospasm, hypotension		Headache, diarrhea, nausea, flushing, jaw pain, and abdominal discomfort
Cautions	Rebound PH with abrupt discontinuation						

CYP = cytochrome P450; PH = pulmonary hypertension; SC = subcutaneously; WHO-FC = World Health Organization of Functional Class.

H. Endothelin Receptor Antagonists (Table 8)

- Minimal place in therapy for critically ill ICU patients
- Macitentan is the only drug in this class with long-term data on morbidity and mortality; pooled primary end point (worsening PAH to mortality) occurred in 31% of patients receiving macitentan compared with 46% of patients receiving placebo ($p < 0.001$) (N Engl J Med 2013;369:809-18).

Table 8. ET Receptor Antagonists

	Bosentan (Tracleer) – Oral	Ambrisentan (Letairis) – Oral	Macitentan (Opsumit) – Oral
WHO-FC	II–IV	II–III	II–IV
Receptor affinity	Blocks ETA & ETB	Blocks ETA	Blocks ETA & ETB
Elimination half-life	5 hr	15 hr	16 hr
Approved dose	62.5–125 mg BID	5–10 mg daily	10 mg daily
Outcomes	Improved hemodynamics and functional capacity		
Adverse effects	Hepatotoxicity, peripheral edema, anemia		
Drug interactions	Glyburide (increased LFTs) and cyclosporine (decreased effects of both cyclosporine and bosentan), CYP2C8/9 and CYP3A4 inhibitors and inducers	Caution with cyclosporine (maximum ambrisentan dose is 5 mg daily)	CYP2C19 and CYP3A4 inhibitors and inducers

BID = twice daily; ET = endothelin; LFT = liver function test.

I. Phosphodiesterase Type 5 Inhibitors (Table 9)

1. Intravenous formulation available for patients who temporarily cannot ingest tablets; however, limited by hemodynamic effects
2. Improvement in RV contractility by increasing cyclic guanosine monophosphate inhibiting downstream phosphodiesterase type 3, exerting an inotropic effect (Br J Clin Pharmacol 2011;71:289-92)

Table 9. Phosphodiesterase Type 5 Inhibitors

	Sildenafil (Revatio) – Oral	Sildenafil (Revatio) – IV	Tadalafil (Adcirca) – Oral
WHO-FC	II–III	II–III	II–III
Elimination half-life	4 hr		35 hr
Approved dose	20 mg three times daily	10 mg three times daily	40 mg daily; dose adjustment necessary for renal impairment
Outcomes	Improved hemodynamics and functional capacity		
Adverse effects	Headache, epistaxis, flushing, dyspepsia, hypotension visual alterations (nonischemic arteritic optic neuropathy)		
Drug interactions	Contraindicated in patients receiving nitrates; avoid with strong CYP3A4 inhibitors and inducers		

J. sGC Stimulators

1. Riociguat (Adempas) sensitizes sGC to endogenous nitric oxide by stabilizing the nitric oxide–sGC binding. It also stimulates sGC independent of the nitric oxide pathway.
2. Approved for group 1 PH to improve exercise capacity and WHO-FC and delay clinical worsening

3. Currently, riociguat is the only medication approved for patients with group 4 PH having residual chronic thromboembolic pulmonary hypertension (CTEPH) after surgical treatment or inoperable CTEPH to improve exercise capacity (N Engl J Med 2013;369:319-29).
 4. Elimination half-life is 12 hours.
 5. Approved dose is 1–2.5 mg three times daily (higher doses for smokers).
 6. Adverse effects include hypotension, hemoptysis, headache, dizziness, dyspepsia, nausea, diarrhea, vomiting, and anemia.
 7. Contraindicated in patients receiving nitrates and phosphodiesterase inhibitors; avoid with strong CYP3A4/2C8 inhibitors and inducers and with P-glycoprotein/breast cancer resistance protein inhibitors
- K. Selective Prostacyclin Receptor (IP Receptor) Agonist
1. Selexipag (Uptravi) is a non-prostanoid that targets the prostacyclin pathway. Indicated for the treatment of PAH to delay disease progression and reduce the risk of hospitalization (N Engl J Med 2015;373:2522-33)
 2. Elimination half-life is 0.8–3 hours and for the active metabolite, 6–14 hours.
 3. Approved dose is 200 mcg twice daily; increase at weekly intervals to the highest tolerated dose (maximum dose: 1600 mcg twice daily); adjustment necessary for moderate hepatic impairment
 4. Adverse effects similar to those of other prostacyclins
- L. Managing Decompensated PH
1. Control contributing factors such as infections, arrhythmias, rebound PH (nonadherence or ineffective dosing), hypoxemia, acidosis, and metabolic abnormalities.
 2. Supportive therapies include optimizing RV preload, maintaining aortic root pressure, improving RV contractility, and reducing RV afterload.
 3. Hemodynamic support (Table 10)
 - a. Maintaining aortic root pressure and minimizing RV ischemia can be accomplished using vasopressors, which increase the systemic vascular resistance and ultimately improve RV perfusion (Crit Care Med 2007;35:2037-50).
 - b. Direct effects on the pulmonary circulation from vasopressors may increase the PVR, potentially leading to further clinical decompensation.
 - c. Few studies published to help guide the optimal vasopressor in patients with PH; recommendations are extrapolations from other patient populations
 - d. Inotropes are used to further augment the cardiac output of the RV and may improve PVR; because of systemic vasodilatory properties from inotropes, expect possible systemic hypotension and need for vasopressors.
 4. Unloading the RV with pulmonary vasodilators is essential to controlling decompensated PH and RV failure.

Table 10. Agents Used for Hemodynamic Support for Decompensated PH

Drug	Actions	Effects on PVR	Effects on CO	Comments
Dopamine	Dose-dependent dopaminergic effects; β_1 - and α_1 -agonists	$\leftrightarrow$	$\uparrow$	May not improve RV ejection fraction; arrhythmias
Norepinephrine	α_1 >> β_1 -adrenergic receptors	$\uparrow$	$\uparrow$ or $\leftrightarrow$	Decreased mortality in subgroup of cardiogenic shock and decreased rate of arrhythmias compared with dopamine in a randomized trial ^a
Phenylephrine	α_1 -Adrenergic receptors	$\uparrow$	$\uparrow$ or $\leftrightarrow$	Reflex bradycardia may have detrimental effects in the setting of RV failure
Epinephrine	- α and β -adrenergic receptors	$\uparrow$ or $\leftrightarrow$	$\uparrow$	Arrhythmias, hyperglycemia, increased lactate concentrations
Vasopressin	V_1 receptors	$\uparrow$ or $\leftrightarrow$	$\leftrightarrow$ or $\downarrow$	Use low dose (≤ 0.03 unit/min); favorable effects on urine output
Dobutamine	β_1 >> β_2	$\downarrow$	$\uparrow$	Combine with peripheral vasoconstrictor to attenuate systemic vasodilation
Milrinone	PDE-3 inhibitor	$\downarrow$	$\uparrow$	Combine with peripheral vasoconstrictor to attenuate systemic vasodilation

^aN Engl J Med 2010;362:779-89.

CO = cardiac output; PDE = phosphodiesterase; PVR = pulmonary vascular resistance; RV = right ventricular.

M. Limitations of Targeted Therapies

1. Indicated only for patients with PAH
2. May result in worsening fluid retention, pulmonary edema, and gas exchange in other PH groups
3. Limited data describing efficacy and safety in other PH groups
4. Small population size, primarily surrogate markers as outcomes measures, limited data in hospitalized and critically ill patients, and sparse long-term data
5. Outcomes from combination therapy remain elusive.

Patient Case

7. A 44-year-old man is transferred to the medical ICU for treatment of his worsening PAH. He currently receives no treatment for PAH. The patient reports having increased dyspnea on exertion for the past 6 months with exercise, but for the past 3 days, he has had severe shortness of breath at rest. His physical examination is remarkable for blood pressure 105/64 mm Hg and heart rate 85 beats/minute. Lung examination is clear, and extremities are notable for trace edema. An ECHO reveals an elevated pulmonary systolic pressure and a normal ejection fraction. The patient has an unfavorable response to vasodilator challenge. Pertinent laboratory data are BUN 10 mg/dL, SCr 0.6 mg/dL, AST 160 IU/L, and ALT 100 IU/L. Which would be the most appropriate regimen to initiate for this patient?
 - A. Epoprostenol infusion at 2 ng/kg/minute.
 - B. Diltiazem 180 mg orally daily.
 - C. Macitentan 10 mg orally daily.
 - D. Sildenafil 10 mg intravenously three times daily.

VI. ASTHMA EXACERBATION

- A. Classification of Asthma Exacerbations in the Urgent or Emergency Care Setting (Table 11)
1. Asthma is a chronic inflammatory disorder of the airways causing recurrent episodes of wheezing, cough, chest tightness, or breathlessness that is often reversible spontaneously or with treatment (NAEPP Guidelines 2007).
 2. Severe refractory asthma is defined as one major and two minor criteria (Am J Respir Crit Care Med 2000;162:2341-51):
 - a. Major criteria: Treatment with high-dose inhaled corticosteroids or treatment with oral corticosteroids for 50% or more of the year
 - b. Minor criteria: (1) requirement for additional daily controller treatments (long-acting β_2 -agonists, theophylline, omalizumab, leukotriene receptor antagonists); (2) asthma symptoms requiring albuterol on a daily basis; (3) persistent airway obstruction (FEV_1 of 80% or less, peak expiratory flow rate of 20% or less); (4) one or more urgent care visits per year; (5) three or more oral corticosteroid bursts per year; and (6) near-fatal asthma event in the past (requiring noninvasive or invasive ventilator support)
 3. Asthma exacerbations are characterized by decreases in expiratory airflow that can be quantified by measuring lung function such as spirometry or peak expiratory flow.
 4. Objective measures more reliably denote the severity of an exacerbation than the severity of symptoms.
 5. Status asthmaticus is an acute, severe asthma exacerbation that does not respond to initial intensive therapy.
 6. Near-fatal asthma is status asthmaticus that progresses to respiratory failure.
 7. Patterns of near-fatal asthma:
 - a. Type 1: Subacute worsening (up to 85% of cases)
 - i. Slow onset of symptoms in days to weeks
 - ii. Poor response to inhaled bronchodilators
 - iii. Copious mucous, eosinophilic infiltration
 - b. Type 2: Acute deterioration (up to 20% of cases)
 - i. Onset over minutes to hours
 - ii. Marked response to bronchodilators
 - iii. Absence of secretions, neutrophilic infiltration

Table 11. Classification of Asthma Exacerbations in the Urgent or Emergency Care Setting

	Symptoms	Initial PEF (or FEV_1)	Clinical Course
Mild	Dyspnea only with activity	$\geq 70\%$ of predicted or personal best	• Usually cared for at home • Prompt relief with inhaled SABA • Possible short course of oral CS
Moderate	Dyspnea interferes with or limits usual activity	40%–69% of predicted or personal best	• Usually requires office or ED visit • Relief from frequent inhaled SABA • Oral CS; some symptoms last 1–2 days after treatment is initiated
Severe	Dyspnea at rest; interferes with conversation	$< 40\%$ of predicted or personal best	• Usually requires ED visit and likely hospitalization • Partial relief from frequent inhaled SABA • Oral CS; some symptoms last > 3 days after treatment is initiated • Adjunctive therapies are helpful (see below)

Table 11. Classification of Asthma Exacerbations in the Urgent or Emergency Care Setting (*continued*)

	Symptoms	Initial PEF (or FEV ₁)	Clinical Course
Near-fatal	Too dyspneic to speak; perspiring	< 25% of predicted or personal best	• Requires ED/hospitalization; possible ICU • Minimal or no relief from frequent inhaled SABA • IV CS • Adjunctive therapies are helpful (see text that follows)

CS = corticosteroid(s); FEV₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow; SABA = short-acting β -agonist.

Adapted from: National Institutes of Health National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program Guidelines (NAEPP) 2007. NAEPP Expert Panel Report 3. Available at www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/index.htm. Accessed June 4, 2016.

B. Mortality Risk Factors

1. Prior episode of near-fatal asthma
2. Two or more hospitalizations in the previous year
3. Three or more ED visits in the previous year
4. Hospitalization or ED visit for asthma in the past month
5. Use of more than 2 canisters of short-acting β -agonists (SABAs) in the past month
6. Social history that includes major psychosocial problems, illicit drug use, low socioeconomic status
7. Concomitant illnesses including cardiovascular diseases, psychiatric illness, or other chronic lung diseases

C. Alternative Causes (mimic severe asthma exacerbation)

1. Upper airway: Vocal cord dysfunction, anaphylaxis, laryngeal stenosis
2. Central airway: Tracheomalacia, tracheal stenosis mucus plugging
3. Lower airway: Bronchiolitis, COPD, valvular heart disease, diastolic heart dysfunction

D. Arterial Blood Gas Assessment

1. Acute, severe asthma typically presents as a respiratory alkalosis.
2. As respiratory status worsens, arterial carbon dioxide increases (patient exhaustion, inadequate alveolar ventilation and/or an increase in physiologic dead space), leading to respiratory acidosis.
3. Metabolic (lactic) acidosis may coexist. Lactate production presumably stems from the use of high-dose β -agonists, increased work of breathing resulting in anaerobic metabolism of the ventilatory muscles, and tissue hypoxia.

E. Oxygen

1. Oxygen therapy is an important component in the management of acute, severe asthma.
2. Oxygen by nasal cannula or mask should be administered to patients experiencing severe exacerbations with hypoxemia to achieve Sao_2 values greater than 90% (pregnant women and patients with cardiac history may require higher goals) (NAEPP 2007).

F. Noninvasive Ventilation: Data are insufficient for use in severe exacerbations.

G. Mechanical Ventilation

1. Indications
 - a. Worsening hypoxemia or hypercarbia
 - b. Drowsiness or altered mental status
 - c. Hemodynamic instability
 - d. Increased work of breathing

2. Low minute ventilation (by reduced tidal volume and/or respiratory rate), high inspiratory flow rate, and minimal PEEP on the ventilator will help minimize dynamic hyperinflation.

H. β -Agonists

1. SABAs stimulate the β_2 -receptors on smooth muscle cells, leading to relaxation of respiratory smooth muscle and causing bronchodilation and a decrease in airway obstruction.
2. SABAs are the cornerstone in the management of acute, severe asthma; whereas long-acting β_2 -agonists and anticholinergic agents are not recommended in the acute treatment of a severe asthma exacerbation.
3. Patients with an asthma exacerbation should receive a SABA repeatedly with either an MDI or nebulization at presentation, and the SABA should be continued until resolution of acute symptoms (NAEPP 2007).
4. Patients with severe acute exacerbations may benefit from continuous versus intermittent nebulization of SABAs (Cochrane Database Syst Rev 2003;4:CD001115).
 - a. Intermittent dosing of albuterol: 2.5–5 mg every 20 minutes for three doses; then 2.5–10 mg every 1–4 hours as needed
 - b. Continuous nebulization of albuterol: 10–15 mg/hour
5. If albuterol administered by MDI, the following must be considered:
 - a. Dose: 4–8 puffs every 20 minutes up to 4 hours; then every 1–4 hours as needed
 - b. The canister must be removed from the actuator and connected to the inspiratory limb of the ventilator circuit with spacer.
 - c. The actuation of an MDI must be synchronized with the onset of inspiratory airflow from the ventilator.
 - d. A longer inspiratory time and slower inspiratory flow improve aerosol delivery in ventilated patients.
 - e. Wait 15 seconds between actuations.
6. Systemic β -agonists (intravenous or subcutaneous epinephrine or terbutaline) may be considered if the patient does not respond to inhaled therapy after several hours; however, they have no proven advantage over inhaled agents.
7. Adverse effects include tremor, tachyarrhythmias, hypokalemia, tachyphylaxis, hyperglycemia, and type B lactic acidosis.

I. Anticholinergic Agents

1. Inhaled anticholinergic agents (ipratropium bromide) selectively bind to the muscarinic receptors on smooth muscle cells in the airways and thereby reduce bronchoconstriction.
2. Should be given in combination with a SABA to promote additional bronchodilation through a different pathway
3. Adding ipratropium to inhaled albuterol compared with using albuterol alone in patients with severe asthma resulted in improved response; however, outcomes with this combination in status asthmaticus or near-fatal asthma remain elusive (Am J Respir Crit Care Med 2000;161:1862-8).
4. See above (albuterol MDI) for administration technique on the ventilator.
5. Adverse effects include headache, flushed skin, blurred vision, tachycardia, palpitations, and urinary retention.

J. Corticosteroid Therapy

1. Corticosteroids decrease airway obstruction during an asthma exacerbation by decreasing inflammation, increasing the number of β_2 -receptors and increasing their responsiveness to β -agonists, reducing airway edema, and suppressing certain proinflammatory cytokines (Respir Med 2004;98:275-84).
2. Systemic corticosteroids should be administered to patients who have moderate or severe exacerbations or to patients who do not respond promptly and completely to SABA treatment (Am J Med 1983;74:845-51).

3. Typically, there is a 6- to 8-hour delay in the response to corticosteroids in status asthmaticus or near-fatal asthma; therefore, administration should be considered early in the course (within 1 hour of presentation) (Cochrane Database Syst Rev 2001;1:CD002178).
4. Oral prednisone is as effective as parenteral corticosteroids; however, it may not be beneficial in the critically ill patient with impaired gastric absorption.
5. Methylprednisolone 40–80 mg per day (or equivalent) in one or two divided doses until peak expiratory flow reaches 70% of predicted or personal best
6. The duration of systemic corticosteroids for a severe asthma exacerbation requiring hospitalization may be 3–10 days.
 - a. For corticosteroid courses less than 1 week, tapering is not necessary.
 - b. For longer courses (up to 10 days), there is probably no need to taper, especially if patients are concurrently using an inhaled corticosteroid.
7. Inhaled corticosteroids can be initiated any time in the treatment of an asthma exacerbation.

K. Adjunctive Therapies

1. Ketamine is a phencyclidine derivative that has bronchodilatory properties through reducing airway resistance and preventing the reuptake of norepinephrine, which may stimulate β_2 -receptors (Iran J Allergy Asthma Immunol 2003;2:175-80).
2. Helium-oxygen (heliox) is a blended gas (mixture of about 70%–80% helium and 20%–30% oxygen) that decreases airway resistance, which leads to improved airflow and ventilation. May delay the need for intubation by allowing other therapies to work
3. Magnesium sulfate infusions may be considered in patients who have life-threatening exacerbations and are unresponsive to conventional therapies after 1 hour.
 - a. Magnesium is thought to cause bronchodilation by inhibiting calcium channels on smooth muscle, leading to relaxation.
 - b. In addition, magnesium may have anti-inflammatory properties that interfere with the activation and release of neutrophils in patients with asthma.

L. Treatments Not Recommended

1. Methylxanthines (theophylline and aminophylline) do not improve lung function or other outcomes in hospitalized adults.
2. Antimicrobials are not generally recommended for the treatment of acute asthma exacerbations; however, consider using them if there is evidence of concurrent infection.
3. Mucolytics may worsen cough or airflow obstruction.

Patient Cases

8. A 30-year-old woman (weight 115 kg) with status asthmaticus is admitted to the ICU. She has a history of severe refractory asthma that has required endotracheal intubation on three occasions in the past 6 months. Her medical history includes hypertension, diabetes mellitus, obesity, and bipolar disease. She reports that she has used at least 3 canisters of albuterol per month for the past 2 months to manage her symptoms. Which best represents the patient's risk factors that place her at risk of a higher mortality?
 - A. Three hospitalizations in the past 6 months and bipolar disorder.
 - B. Use of more than 2 canisters of SABAs in the past month and obesity.
 - C. Hospitalization for asthma in the past month and diabetes mellitus.
 - D. Prior episode of near-fatal asthma and hypertension.
9. The patient is endotracheally intubated and placed on MV. Which would be the most appropriate initial therapy for this patient with near-fatal asthma?
 - A. Inhaled albuterol by nebulization 2.5 mg every 4 hours.
 - B. Inhaled albuterol by nebulization 2.5 mg every 4 hours and inhaled ipratropium by nebulization 0.5 mg every 6 hours.
 - C. Inhaled albuterol by nebulization 2.5 mg every 4 hours, inhaled ipratropium by nebulization 0.5 mg every 6 hours, and methylprednisolone 40 mg intravenously twice daily.
 - D. Inhaled albuterol by nebulization 2.5 mg every 4 hours, inhaled ipratropium by nebulization 0.5 mg every 6 hours, and methylprednisolone 125 mg intravenously every 6 hours.

VII. ACUTE CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION**A. Definitions (Table 12)**

1. COPD is characterized by a chronic limitation in expiratory airflow that is not fully reversible. Chronic airflow limitation results from a combination of small-airway disease (emphysema) and parenchymal destruction caused by inflammation (chronic bronchitis).
2. A COPD exacerbation can be defined as an acute worsening in the patient's baseline status (increase in dyspnea, cough, and/or sputum production), necessitating a change in medications.
3. General criteria for diagnosing an acute exacerbation are based on clinical presentation, including an acute change of symptoms that is beyond normal day-to-day variation.
 - a. Arterial blood gas should be measured.
 - b. Pulse oximetry can be used to determine the need for supplemental oxygen.
 - c. Spirometry is not accurate during an exacerbation and is not recommended.

Table 12. Classification of COPD Severity

Stage	Spirometric GOLD Classification	Characteristics
GOLD 1: Mild	$FEV_1 \geq 80\%$ predicted	0 or 1 exacerbation per year AND no hospitalizations for exacerbation
GOLD 2: Moderate	$50\% \leq FEV_1 < 80\%$ predicted	

Table 12. Classification of COPD Severity (*continued*)

Stage	Spirometric GOLD Classification	Characteristics
GOLD 3: Severe	$30\% \leq FEV_1 < 50\%$ predicted	≥ 2 exacerbations per year OR ≥ 1 hospitalization for exacerbation (patients in GOLD classifications 3 and 4 are at increased risk of hospital admission and death)
GOLD 4: Very severe	$FEV_1 < 30\%$ predicted	

COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

Adapted from: Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014 Update. Available at www.goldcopd.org/uploads/users/files/GOLD_Report_2014_Jun11.pdf. Accessed June 4, 2016.

B. Causes of Acute COPD Exacerbation

1. Respiratory tract infection (representing 40%–50% of COPD exacerbations)
 - a. Bacterial
 - i. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the most common organisms.
 - ii. *P. aeruginosa* is common in patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) 3 and 4 severities.
 - b. Viral (influenza, rhinovirus, parainfluenza, respiratory syncytial virus)
2. Pulmonary embolism
3. Pneumothorax
4. Respiratory depression (may be a result of the injudicious use of sedative and/or analgesic medications)
5. Surgery (especially of chest and upper abdomen)
6. Medication nonadherence
7. Temperature change
8. Air pollution

C. Oxygen

1. Oxygen therapy is an important component in the management of COPD exacerbations (GOLD 2014 Update).
2. Oxygen by nasal cannula or mask should be administered to patients experiencing severe exacerbations to achieve an SaO₂ of 88%–92% (BMJ 2010;341:c5462).
3. Caution is advised with oxygen supplementation in patients with COPD:
 - a. A slight level of hypoxemia may serve as a trigger for their respiratory drive secondary to chronic hypercapnia.
 - b. May increase ventilation/perfusion mismatch and decrease respiratory rate centrally and perpetuate the Haldane effect

D. Noninvasive MV

1. Should be considered in patients with respiratory acidosis and severe dyspnea with increased work of breathing or clinical signs of respiratory muscle fatigue (GOLD 2014 Update)
2. Improves mortality and respiratory acidosis and decreases the need for intubation and treatment failures. Decreases complications associated with invasive mechanical ventilation such as ventilator-associated pneumonia and hospital length of stay (N Engl J Med 1995;333:817-22)

E. Mechanical Ventilation

1. Indications
 - a. Failure of noninvasive ventilation
 - b. Severe dyspnea, acidosis, hypercapnia, or hypoxemia
 - c. Respiratory rate greater than 35 breaths/minute
 - d. Inability to clear respiratory secretions
 - e. Hemodynamic instability

F. Bronchodilators

1. Inhaled SABAs (nebulized or MDI) with or without a short-acting anticholinergic are the preferred agents for bronchodilation in COPD exacerbation (GOLD 2014 Update).
2. The role of long-acting β -agonists and anticholinergic agents remains unclear in acute exacerbations in the critically ill patient.

G. Corticosteroid Therapy

1. The dose recommended by the guidelines is 40 mg of prednisone equivalent daily (preferably oral) for 5 days. If oral administration is not an option (altered bioavailability of corticosteroids secondary to hypoxemia or fluid overload), equivalent doses of intravenous hydrocortisone or methylprednisolone or nebulized budesonide may be administered (GOLD 2014 Update).
2. Systemic corticosteroids in non-critically ill patients reduce the risk of early relapse rate, treatment failure, and hospital length of stay and improve FEV₁ (N Engl J Med 1999;340:1941-7; Chest 2001;119:726-30).
3. REDUCE (Reduction in the Use of Corticosteroids in Exacerbated COPD) was a randomized, noninferiority trial. Patients were randomized to prednisone 40 mg daily for either 5 or 14 days (inhaled bronchodilators and antimicrobials in both groups). COPD exacerbations occurred in 35.9% of patients in the 5-day group and in 36.8% of patients in the 14-day group; $p=0.006$ (JAMA 2013;309:2223-31). This study did not include critically ill patients requiring MV.
4. Studies including ICU patients:
 - a. A randomized, double-blind trial including 83 adult patients with a COPD exacerbation requiring hospitalization and ventilatory support (invasive or noninvasive) compared methylprednisolone 0.5 mg/kg intravenously every 6 hours for 72 hours, 0.5 mg/kg every 12 hours on days 4–6, and 0.5 mg/kg daily on days 7–10 with placebo. Patients receiving corticosteroids had a shorter duration of MV ($p=0.04$), shorter length of ICU stay ($p=0.09$), less noninvasive ventilation failures ($p=0.004$), and more hyperglycemia ($p=0.04$). This study was not powered to detect differences in length of stay or mortality (Arch Intern Med 2011;171:1939-46).
 - b. An open-label, randomized trial included 217 critically ill patients 40 years and older with COPD exacerbation requiring MV to receive oral prednisone 1 mg/kg daily for a maximum of 10 days or usual care. No significant differences in ICU mortality, noninvasive ventilation failure, duration of MV, or ICU length of stay were observed, although the study did not meet power. Hyperglycemia significantly increased in the steroid group (Eur Respir J 2014;43:717-24).
 - c. A cohort study compared high-dose (240 mg/day or greater) with low-dose (240 mg/day or less) methylprednisolone in over 17,000 patients with a COPD exacerbation admitted to an ICU. Patients in the high-dose group had longer ICU and hospital lengths of stay, higher hospital costs, longer duration of MV, and more hyperglycemia and fungal infections. No differences in mortality were observed between the two groups (Am J Respir Crit Care Med 2014;189:1052-64).
5. Antimicrobials (Cochrane Database Syst Rev 2012;12:CD010257)
 - a. Should be administered if one of the following is met:
 - i. All three cardinal symptoms of a COPD exacerbation (increased dyspnea, sputum production, and sputum purulence) are present (supported by clinical trials, but limited literature)

- ii. Two of the three cardinal signs are present, with increased sputum purulence as one of the symptoms (supported by nonrandomized and observational trials)
 - iii. Require noninvasive or invasive ventilation (supported by clinical trials, but limited literature)
 - b. Recommended duration of antimicrobials is 5–10 days.
 - c. Optimal antimicrobial therapy is not established; however, should be based on local resistance patterns
- H. Heliox: Effect may be minimal in a COPD exacerbation because small airways in the lungs are largely affected when flow is laminar rather than turbulent.
- I. Treatments Not Recommended: Doxapram or other respiratory stimulants

Patient Case

10. A 79-year-old woman (weight 70 kg) is admitted to the ICU for the management of hypercapnic respiratory failure related to a COPD exacerbation. The patient presents with profound dyspnea, increased sputum production (thick and purulent), and confusion. She has a history of anaphylaxis to penicillin. Her blood pressure is currently 190/100 mm Hg, heart rate is 110 beats/minute, and respiratory rate is 22 breaths/minute. Her chest is hyperinflated and has poor entry bilaterally. Her blood gas is as follows: pH 7.20, P_{CO_2} 85 mm Hg, and P_{aO_2} 44 mm Hg on 6 L nasal cannula. The patient is intubated and placed on MV. Which would be the most appropriate medications to treat this patient's severe COPD exacerbation?
- A. Methylprednisolone 1 mg/kg intravenously administered as two divided doses, inhaled albuterol by nebulization, ampicillin/sulbactam 3 g intravenously every 6 hours for 7 days, and azithromycin 500 mg intravenously daily for 5 days.
 - B. Prednisone 40 mg by nasogastric tube (NGT) daily x 5 days, inhaled albuterol and ipratropium by nebulization, ampicillin/sulbactam 3 g intravenously every 6 hours for 10 days, and azithromycin 500 mg daily intravenously for 5 days.
 - C. Methylprednisolone 1 mg/kg intravenously administered as two divided doses, inhaled albuterol and ipratropium by nebulization, and levofloxacin 500 mg by NGT daily for 7 days.
 - D. Prednisone 40 mg by NGT daily x 5 days, inhaled albuterol and ipratropium by nebulization, and levofloxacin 500 mg intravenously daily for 10 days.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D

The patient has early, severe ARDS (for less than 48 hours and $\text{PaO}_2/\text{FiO}_2$ less than 150 mm Hg) and hemodynamic stability (post-resuscitation MAP greater than 65 mm Hg). According to the findings of a multicenter trial sponsored by ARDSNet, this patient would qualify for a conservative fluid management strategy (CVP less than 4 mm Hg). In addition, vasopressors should be discontinued and diuresis initiated to achieve a target CVP of less than 4 mm Hg (Answer A is incorrect). Given the timing and the severity of the patient's ARDS, he should be placed in the prone position (Answers B and C are incorrect). In addition, this patient would qualify for receiving a cisatracurium infusion. In light of the timing and severity of this patient's ARDS, he qualifies to receive a lung-protective ventilation strategy (tidal volume 4–6 mL/kg of ideal body weight) and diuresis to a CVP less than 4 mm Hg (hemodynamically stable if weaned off vasopressors) while placed in the prone position and administered a cisatracurium infusion (Answer D is correct).

2. Answer: A

The patient presents to your ICU after 3 days of care. Therefore, she does not currently meet the criteria for being administered cisatracurium or being placed in the prone position (Answers B–D are incorrect). Currently, the applicable therapy to apply is a lung-protective ventilation strategy (tidal volume 4–6 mL/kg of ideal body weight) (Answer A is correct).

3. Answer: C

Propofol, ketamine, and etomidate may all be used for induction. Propofol may worsen hypotension because this patient is already receiving vasoactive medications to maintain his blood pressure (Answer A is incorrect). Succinylcholine causes the up-regulation of acetylcholine receptors, predisposing the muscle fibers to release excess potassium because they are depolarized, which leads to significant dysrhythmias or cardiac arrest (Answers B and D are incorrect). Appropriate induction and neuromuscular blockade in this patient would be to administer etomidate (indicated for hemodynamically unstable patients), fentanyl (providing adequate analgesia), and rocuronium (does not increase serum potassium) (Answer C is correct).

4. Answer: B

Although propofol may promptly lower ICP, it may also induce hypotension and thus decrease cerebral perfusion pressure (Answer A is incorrect). Midazolam could be used as an induction agent; however, it is not the best agent for RSI because of its delayed onset of action (Answer C is incorrect). Etomidate may be considered in the setting of increased ICP; however, the dose in this case is too high (Answer D is incorrect). Ketamine not only decreases ICP, but also prevents fluctuations in ICP (Answer B is correct).

5. Answer: A

After recognizing that the patient has ARDS, it is important to implement a lung-protective ventilation strategy (tidal volume 4–6 mL/kg). Choosing a PS or SIMV mode would allow the patient to initiate spontaneous breaths in excess of the goal tidal volume (Answers B–D are incorrect). In the ARDSNet study of tidal volume strategy, the AC mode was most commonly used to promote the application of low tidal volumes (Answer A is correct).

6. Answer: C

The patient presents with an exacerbation of CF, probably caused by an infection. The most likely causative organism of her infection is *P. aeruginosa*; therefore, therapy directed to treat *P. aeruginosa* is imperative (Answer B is incorrect). In addition, antibiotic treatment should include the empiric selection of two antibacterial agents, ideally a β -lactam and an aminoglycoside, dosed to effectively treat the infection (Answers A and D are incorrect). The ideal regimen should include a β -lactam dosed to treat *P. aeruginosa*—in this case, piperacillin/tazobactam at the recommended dose—and an aminoglycoside dosed once daily (Answer C is correct).

7. Answer: A

The patient's symptoms and physical findings place him in WHO-FC IV. His unfavorable response to the vasodilator challenge makes calcium channel blockers an undesirable class of medications for him (Answer B is incorrect). Epoprostenol continuous infusion is indicated for patients with PAH WHO-FC IV to improve symptoms, exercise capacity, and hemodynamics. In addition, it is the only treatment shown to reduce mortality in PAH (Answer A is correct). Macitentan and sildenafil could

be considered in this patient; however, his elevated liver enzymes do not make macitentan an ideal agent (Answer C is incorrect). Intravenous sildenafil is also not an ideal agent because of the hypotension associated with the intravenous formulation (Answer D is incorrect).

8. Answer: A

Risk factors for increased mortality in patients with asthma include (1) prior episode of near-fatal asthma; (2) two or more hospitalizations in the previous year; (3) three or more ED visits in the previous year; (4) hospitalization or ED visit for asthma in the past month; (5) use of more than 2 canisters of SABAs in the past month; (6) social history that includes major psychosocial problems, illicit drug use, and low socioeconomic status; (7) prior episode of near-fatal asthma; and (8) concomitant illnesses, including cardiovascular diseases, psychiatric illness, and other chronic lung diseases (Answer A is correct). The patient's history of obesity, hypertension, and diabetes mellitus are not risk factors (Answers B–D are incorrect).

9. Answer: C

For near-fatal asthma exacerbations, SABAs and intravenous corticosteroids are recommended (Answers A and B are incorrect). The recommended dose for intravenous corticosteroids is methylprednisolone 40–80 mg intravenously per day administered early in the course of the exacerbation (Answer C is correct; Answer D is incorrect).

10. Answer: D

The latest GOLD guidelines recommend systemic corticosteroids to shorten recovery time, improve FEV₁, and improve hypoxemia. The recommended dose is prednisone 40 mg orally once daily (or equivalent) for 5 days. No evidence suggests that higher doses of corticosteroids are beneficial, and higher doses may in fact be associated with more adverse effects (Answers A and C are incorrect). Adding inhaled SABAs (nebulized or MDI) with or without a short-acting anticholinergic is the preferred treatment in a COPD exacerbation. Antibiotic treatment for 5–10 days is also indicated because the patient has all three cardinal symptoms of infection. This patient has a history of anaphylactic reaction to penicillin (Answers A and B are incorrect); therefore, levofloxacin would be the best recommendation (Answer D is correct).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B

It is important to recognize that this patient has both ARDS and septic shock. In addition, the patient has likely had ARDS less than 48 hours; therefore, the time-to-initiation of several treatments is essential. The patient is actively in shock (as evidenced by his blood pressure), thus making a fluid-conservative strategy (CVP less than 4 mm Hg) impossible (Answer C is incorrect). Because the time to presentation is less than 48 hours and the patient has severe ARDS, he meets the criteria for cisatracurium administration and prone positioning, and a treatment plan should include these two therapies (Answers A and D are incorrect). A therapy plan should include shock resuscitation (fluid-liberal strategy, CVP 10–14 mm Hg), lung-protective ventilation (tidal volume 4–8 mL/kg of ideal body weight), prone positioning, and cisatracurium administration (Answer B is correct).

2. Answer: B

According to the Berlin Definition for ARDS, the category of acute lung injury was removed in favor of categorizing the severity of ARDS (P_{aO_2}/F_{iO_2} less than 200 mm Hg) (Answer A is incorrect). Because of the relative difference in mortality rates, mild and moderate ARDS are less likely to benefit from therapeutic interventions, given the number needed to treat to show an effective intervention (Answers C and D are incorrect). In the trials evaluating prone positioning and cisatracurium, patients with severe ARDS were most likely to benefit. Although the criteria used for severe ARDS in these studies differed from the Berlin Definition (both studies were initiated before publication of the Berlin Definition), a post hoc analysis shows a survival benefit in favor of the group with the highest mortality rate (Answer B is correct).

3. Answer: D

Neuromuscular blocking agents should always be administered after induction agents (Answers A–C are incorrect). In addition, atropine is not routinely recommended (Answer C is incorrect) in adult patients for RSI. Atropine should be kept nearby for patients who are at an increased risk of bradycardia during RSI (use of β -blockers, calcium channel blockers, digoxin, or amiodarone). Induction agents (and pretreatment medications) should be administered before NMBAs (Answer D is correct).

4. Answer: B

The patient has hypercarbic respiratory failure, for which the primary treatment goals are to restore normalized ventilation parameters and acid-base status (Answer B is correct). A reduction in tidal volume will only exacerbate the problem of hypercarbia (Answer A is incorrect). Increasing the F_{iO_2} and PEEP will improve oxygenation; however, this will not help improve ventilation (Answers C and D are incorrect).

5. Answer: D

It is imperative to recognize that this patient has ARDS caused by a CF exacerbation. Therefore, an inclusive therapy plan will include appropriate treatments for ARDS and CF. Regarding the treatment of ARDS, a lung-protective ventilation strategy (tidal volume 4–6 mL/kg) and a fluid-conservative strategy (CVP less than 4 mm Hg if not in shock) are of utmost importance (Answers A and C are incorrect because of the CVP goal). Appropriate treatment of the CF exacerbation includes empiric therapy for *P. aeruginosa* in the form of optimal doses of β -lactam and aminoglycoside (Answer B is incorrect because of the inappropriate tobramycin dose and CVP goal of 10–14 mm Hg).

6. Answer: D

This patient presents with severe right heart failure. The primary goal is to optimize RV preload by maintaining a net negative fluid balance using gentle diuresis and blood pressure monitoring (Answer D is correct). Dopamine would increase blood pressure; however, it might worsen the patient's tachycardia, thereby worsening the patient's already tenuous clinical status (Answer A is incorrect). Epoprostenol would help decrease pulmonary pressures; however, epoprostenol would potentially worsen the patient's blood pressure because of its peripheral vasodilating effects (Answer B is incorrect). Phenylephrine would not be optimal because this vasopressor might worsen RV function, further elevate pulmonary artery pressure by α_1 -receptors in the pulmonary vasculature, and potentially induce a reflex bradycardia (Answer C is incorrect).

7. Answer: C

This patient is experiencing shortness of breath at rest that is interfering with his conversational ability, and his FEV_1 is less than 40% of predicted; therefore, the

patient's asthma would be classified as severe (Answer C is correct). In near-fatal asthma, the FEV₁ would have been less than 25% of predicted (Answer D is incorrect). In mild asthma, patients experience dyspnea with activity and an FEV₁ of 70% or greater of predicted (Answer A is incorrect). In moderate asthma, dyspnea interferes with or limits usual activity, and patients have an FEV₁ of 40%–60% of predicted (Answer B is incorrect).

8. Answer: B

The recommended corticosteroid dose for a COPD exacerbation is prednisone 40 mg orally once daily (Answer D is incorrect; Answer B is correct). Antimicrobial treatment should be initiated if (1) all three cardinal symptoms of a COPD exacerbation (increased dyspnea, increased sputum production, and increased sputum purulence) are present; (2) two of the three cardinal signs are present, with increased sputum purulence as one of the symptoms; or (3) the patient needs noninvasive or invasive ventilation. This patient has no indication for antimicrobials (Answers A and C are incorrect).

HEPATIC FAILURE/GI/ENDOCRINE EMERGENCIES

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Learning Objectives

1. Define acute liver failure (ALF), and describe the most common causes for its occurrence.
2. Develop a treatment strategy to help manage and reduce the complications associated with ALF.
3. Evaluate the severity of an episode of acute pancreatitis, and construct a plan for pharmacologic, nutritional, and surgical management.
4. Identify patients at high risk of developing fistulas postoperatively, and assess the need for pharmacologic versus surgical treatment.
5. Identify risk factors and treatment options for postoperative ileus and postoperative nausea and vomiting.
6. Design a treatment plan for patients who present with an acute upper gastrointestinal bleed.
7. Differentiate between the main endocrine emergencies in the intensive care unit, and be able to design a therapeutic regimen for a patient presenting with each condition.

Abbreviations in This Chapter

ALF	Acute liver failure
AP	Acute pancreatitis
BG	Blood glucose
CIRCI	Critical illness–related corticosteroid insufficiency
CPP	Cerebral perfusion pressure
CT	Computed tomography
DILI	Drug-induced liver injury
DKA	Diabetic ketoacidosis
ED	Emergency department
ERCP	Endoscopic retrograde cholangiopancreatography
HHS	Hyperosmolar hyperglycemic state
ICP	Intracranial pressure
ICU	Intensive care unit
INR	International normalized ratio
MRI	Magnetic resonance imaging
NAI-ALF	Non–acetaminophen-induced acute liver failure
NG	Nasogastric
NJ	Nasojejunal
NSAID	Nonsteroidal anti-inflammatory drug
POI	Postoperative ileus
PONV	Postoperative nausea and vomiting

PPI	Proton pump inhibitor
SIRS	Systemic inflammatory response syndrome
T ₃	Triiodothyronine
T ₄	Thyroxine
TPN	Total parenteral nutrition
TSH	Thyroid-stimulating hormone
UGIB	Upper gastrointestinal bleeding

Self-Assessment Questions

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

Questions 1 and 2 pertain to the following case.

A 25-year-old woman is brought to the emergency department (ED) after a suspected overdose of acetaminophen. The time of ingestion is unknown. On presentation, her acetaminophen concentration is undetectable, but her alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations are 3500 IU/L and 2500 IU/L, respectively. The patient is markedly confused with incoherent speech, but arousable. Other pertinent laboratory values include bilirubin 3.0 mg/dL and alkaline phosphatase 500 IU/L. White blood cell count is 12×10^3 cells/mm³, platelet count is 90,000/mm³, and international normalized ratio (INR) is 2.6.

1. Which option best represents the two signs or symptoms that would qualify this patient for a diagnosis of acetaminophen-induced acute liver failure (ALF)?
 - A. Jaundice and encephalopathy.
 - B. Thrombocytopenia and encephalopathy.
 - C. Coagulopathy and encephalopathy.
 - D. Leukocytosis and encephalopathy.
2. Which is the most appropriate treatment for her suspected acetaminophen-induced ALF?
 - A. Give intravenous acetylcysteine 21-hour regimen, continuing if necessary until signs and symptoms of ALF have resolved.
 - B. Acetylcysteine therapy is not indicated at this time because her acetaminophen concentration is undetectable.
 - C. Give oral acetylcysteine 72-hour regimen.
 - D. Oral acetylcysteine or intravenous acetylcysteine may be used because the two routes are similarly efficacious.

3. A 46-year-old man presents with alcohol-induced severe acute pancreatitis (AP). Pertinent medical history includes alcoholic cirrhosis and several admissions for aspiration pneumonia secondary to hepatic encephalopathy. He is given intravenous fluids for initial volume resuscitation with lactated Ringer solution. Which action would be best for the patient's nutrition?
- A. Give nothing by mouth (i.e., kept NPO) to rest the pancreas until AP is resolved.
 - B. Initiate total parenteral nutrition (TPN).
 - C. Give enteral feeding by the nasogastric (NG) route.
 - D. Give enteral feeding by the nasojejunal (NJ) route.
4. A 37-year-old woman presents after a Roux-en-Y gastric bypass for morbid obesity. Her postoperative course was complicated by the formation of an enterocutaneous fistula, fevers, and leukocytosis. She was initiated on broad-spectrum antibiotics, and a wound vacuum-assisted closure was placed on her fistula site to help with drainage and healing. Her fistula output was 570 mL/day yesterday, and today, it was 250 mL/day. Which statement is most accurate regarding her fistula output between the two recordings?
- A. Her output would be defined as a low output on both days.
 - B. Her output would be defined as a high output that has converted to a low output.
 - C. Her output would be defined as a high output that has converted to a moderate output.
 - D. Her output would be considered moderate on both days.
5. A 68-year-old man presents for a large bowel resection. Given the high incidence of postoperative ileus (POI) with this procedure, he is initiated on alvimopan before surgery. To reduce the cardiovascular risk associated with alvimopan, the U.S. Food and Drug Administration (FDA) placed a restriction on alvimopan use that has been implemented through the EASE (ENTEREG Access Support & Education) program. Which best represents that restriction?
- A. Start continuous electrocardiogram (ECG) monitoring on initiation to monitor for corrected QT (QTc) prolongation.
 - B. Use is restricted to short term with a limit of 15 doses.
 - C. Decrease alvimopan dose to 6 mg twice daily.
 - D. Use is contraindicated in patients with previous myocardial infarction.
6. A 40-year-old woman presents for elective abdominal surgery to remove a malignancy from her liver. Given the extensiveness of the surgery, the expected use of volatile anesthetics, and the use of perioperative opioids, a multimodal plan is developed to avoid postoperative nausea and vomiting (PONV). Which best describes the timing of prophylactic administration with respect to surgery?
- A. Dexamethasone 4 mg intravenously given at the end of surgery.
 - B. Ondansetron 4 mg intravenously given when inducing anesthesia.
 - C. Neurokinin-1 receptor antagonist (aprepitant 40–125 mg) given at the end of surgery.
 - D. Droperidol 0.625–1.25 mg intravenously given at the end of surgery.
7. A 69-year-old woman presents to the surgical intensive care unit (ICU) at your institution with upper gastrointestinal bleeding (UGIB) caused by a gastric ulcer. She has lost a significant amount of blood because of the bleed and currently requires blood transfusions. As part of her diagnostic workup to determine the etiology of her ulcer, she tests positive for a *Helicobacter pylori* infection. Which best reflects an inappropriate treatment option for her?
- A. Octreotide 50-mcg bolus, followed by 50 mg/hour for 72 hours.
 - B. Treatment with a proton pump inhibitor (PPI)/antibiotic combination for 14 days.
 - C. A therapeutic endoscopy within 24 hours.
 - D. Blood transfusions to maintain hemoglobin greater than 7 g/dL.
8. Which set of laboratory abnormalities best reflects those that patients in thyroid storm typically present with?
- A. High thyroid-stimulating hormone (TSH), triiodothyronine (T_3), and thyroxine (T_4) concentrations.
 - B. Low TSH, high T_3 , and high T_4 concentrations.
 - C. Low TSH, high T_3 , and low T_4 concentrations.
 - D. Low TSH, low T_3 , and low T_4 concentrations.

I. ACUTE LIVER FAILURE**A. Epidemiology**

1. Incidence of ALF is less than 10 cases per 1 million individuals per year (2000 cases per year in the United States), though morbidity and mortality are exceedingly high with ALF. Multiorgan failure and death occur in as many as 50% of patients.
2. ALF accounts for less than 10% of liver transplants annually in the United States.
3. ALF can occur in any age and demographic group, though the etiology of ALF is sometimes geographically dependent. Viral hepatitis cases are more common in developing countries, whereas toxin-related cases (e.g., those related to acetaminophen) occur more often in developed countries.
4. The most common causes in the United States are drug induced, viral, autoimmune, and shock. Drug-induced causes, primarily acetaminophen, account for about 50% of the ALF cases in the United States. About 15% have no identifiable cause.
5. The mortality rate has decreased significantly during the past few decades because of advances in medical care and early consideration for liver transplantation. Survival rates for ALF now exceed 65%, whereas before early transplantation, survival rates were less than 15%.

B. Definitions

1. ALF is defined by the U.S. Acute Liver Failure Study Group and the American Association for the Study of Liver Diseases as evidence of coagulopathy, usually considered an INR of 1.5 or greater, and any degree of mental alteration (encephalopathy) in a patient without preexisting liver failure and with an illness duration less than 26 weeks.
2. ALF may be further differentiated according to the time to encephalopathy after the onset of jaundice. These intervals typically provide clues regarding the cause of the ALF; however, the differentiation itself generally has no prognostic implications distinct from the causes themselves.
 - a. Hyperacute ALF: Encephalopathy occurs less than 7 days after the onset of jaundice. This subclass of ALF is typically caused by acetaminophen toxicity and ischemic hepatitis and is associated with higher rates of transplant-free survival. Patients tend to have high-degree encephalopathy at presentation and a higher incidence of cerebral edema, albeit a better prognosis overall.
 - b. Acute ALF: Encephalopathy occurs 7–21 days after the onset of jaundice. Common causes of acute ALF include viral hepatitis. These patients have a high incidence of cerebral edema but, unlike in hyperacute ALF, lower rates of transplant-free survival.
 - c. Subacute ALF: Encephalopathy occurs more than 21 days and less than 26 weeks after the onset of jaundice. Typical causes are drug induced or indeterminate, and this subclass is associated with lower transplant-free survival, though patients have less marked coagulopathy and encephalopathy at presentation.

C. Diagnosis

1. An unexplained elevated INR in a patient presenting with encephalopathy requires further evaluation for ALF because the combination of these two symptoms is very specific to ALF.
2. In ALF, certain markers of chronic liver disease (e.g., jaundice, ascites, right upper quadrant pain, portal hypertension) may not be present.
3. Additional physical examination, laboratory analysis, and imaging necessary for the diagnosis and workup of ALF are shown in Table 1.
4. Patients with any degree of encephalopathy should be transferred to an ICU, ideally with contact to a transplant center, because rapid progression can occur.

Table 1. Diagnostic Approach to a Patient with Suspected ALF

History	Assess for exposure history to viruses, drugs (acetaminophen), or toxins (mushrooms)
	Assess substance abuse history
Physical examination	Normal signs of chronic liver disease (ascites, jaundice, right upper quadrant pain) may not be present
	Assess encephalopathy grade
Laboratory analysis	Basic metabolic panel, CBC, liver function tests, coagulation tests, arterial blood gas, acetaminophen concentrations, ammonia, toxicology screen, blood typing
	Viral serologies
	Liver biopsy useful for determining autoimmune hepatitis or ALF associated with HSV
Imaging	Hepatic imaging studies (computed tomography [CT], ultrasonography) may be used to detect a thrombus of the hepatic vein

ALF = acute liver failure; CBC = complete blood cell count; HSV = herpes simplex virus.

Adapted from: Lee WM. Acute liver failure. Semin Respir Crit Care Med 2012;33:36-45.

Table 2. Causes of ALF in the United States

Acetaminophen	46%
Indeterminate	13%
Non-acetaminophen drug induced	12%
Hepatitis B	7%
Autoimmune	6%
Ischemic	5%
Hepatitis A	2%
Wilson disease	1.2%
Budd-Chiari	0.94%
Pregnancy	0.94%
Other	4.6%

Adapted from: Ostapowicz GA, Fontana RJ, Schiodt FV, et al. U.S. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137:947-54.

D. Causes (Table 2)

1. Acetaminophen

- Acetaminophen overdose is responsible for almost 50% of ALF cases in the United States. Acetaminophen overdose is considered the primary cause of ALF in the United States and Europe, and it was responsible for 70,000 health care encounters and 300 deaths in the United States in 2005.
- Unlike most other types of drug-induced liver injury (DILI), acetaminophen-induced liver failure is dose-dependent and predictable, and it is typically associated with doses above 10 g/day (or 150 mg/kg) in adults.
- Rates of ALF caused by acetaminophen have increased during the previous 2 decades.
- If not treated in the early stages (i.e., before the development of encephalopathy), the mortality rate is around 20%–40%.

- e. Acetaminophen-induced ALF typically presents as hyperacute liver failure and is defined by four stages of progression.
 - i. Preclinical: Occurs within the first 24 hours of ingestion. Typically associated with minimal or no signs or symptoms of hepatotoxicity
 - ii. Injury: Occurs 24–48 hours after ingestion. Associated with marked elevation in liver transaminases
 - iii. Failure: Occurs 72–96 hours after ingestion. Associated with peak liver injury including encephalopathy, coagulopathies, and jaundice
 - iv. Recovery: Occurs 1 week after ingestion if patient survives through failure stage
 - f. Additional information on background, pathophysiology, and treatment of acetaminophen overdose can be found in the Toxicology review chapter.
2. Non-acetaminophen-induced acute liver failure (NAI-ALF)
- a. DILI
 - i. When DILI is caused by drugs other than acetaminophen, the incidence is rare, causing about 12% of ALF cases per year.
 - ii. Unlike acetaminophen-induced liver failure, DILI rarely causes dose-related toxicity, and most cases are idiosyncratic.
 - iii. DILI typically presents as a subacute ALF, with most cases occurring within the first 6 months after drug initiation. However, some drugs (e.g., nitrofurantoin, minocycline, statins) have the potential to cause DILI 6 months or more after initiation.
 - iv. Transplant-free survival is low for these patients (about 30%), and most patients will require transplantation.
 - v. DILI is ultimately a diagnosis of exclusion. The American College of Gastroenterology guidelines for the management of DILI recommend a specific workup for viral hepatitis, autoimmune hepatitis, Wilson disease, and Budd-Chiari syndrome before diagnosis of DILI.
 - vi. To identify potential culprit medications, a detailed patient medication history should be obtained, including herbal medications. Classes of drugs commonly associated with DILI include antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants, which together account for greater than 60% of DILI.
 - vii. Scoring systems such as the RUCAM (Roussel Uclaf Causality Assessment Method) have been developed to assess the causality attribution for suspected DILI. These scoring systems give points on the basis of timing of exposure and liver function tests, risk factors for DILI, competing medications and diagnoses, and rechallenge information. Higher scores indicate a higher likelihood of drug cause.
 - viii. See Appendix 1 for a list of medications linked to DILI.
 - b. Viral
 - i. Infection with hepatitis A, B, or E is the primary etiology of ALF in the developing world and has become a relatively infrequent cause of ALF in the United States (about 12%).
 - ii. Hepatitis A
 - (a) Accounts for about 4% of ALF cases in the United States
 - (b) Transmission is usually by the fecal-oral route.
 - iii. Hepatitis B
 - (a) Rates of hepatitis B-induced ALF have fallen significantly in the past few decades; however, hepatitis B is still the cause of about 8% of ALF cases per year.

- (b) ALF secondary to hepatitis B is often caused by reactivation of chronic or inactive hepatitis B during times of immunosuppression (e.g., chemotherapy, high-dose steroids). To prevent reactivation, patients who are positive for HBsAg (hepatitis B antigen) and who are to begin immunosuppressive regimens require antiviral prophylaxis with a nucleos(t)ide analog, typically lamivudine. Treatment, which is usually initiated before immunosuppression, continues during immunosuppressive therapy and for 6 months thereafter.
- iv. Hepatitis E
 - (a) Rare cause of ALF in the United States; however, hepatitis E–induced ALF is a significant cause of ALF in countries where it is endemic, such as Russia, Pakistan, Mexico, and India
 - (b) Hepatitis E–induced ALF tends to be more severe in pregnant women, and hepatitis E can be transmitted to neonates during acute infections in pregnant women.
- v. Herpes simplex virus (HSV)
 - (a) HSV is rarely a cause of ALF; however, cases have been reported, particularly in immunocompromised and pregnant patients.
 - (b) Patients with HSV ALF can be treated with acyclovir 5–10 mg/kg every 8 hours for at least 7 days.
- vi. Viral hepatitis–induced ALF generally presents as acute or subacute liver failure with an onset of symptoms greater than 1 week after onset of jaundice.
- vii. Globally, mortality rates are greater than 50% because of ALF from hepatitis A and E in the developing world; however, mass vaccination and better public health standards have helped reduce the incidence of viral infections in the developed world.
- c. Acute ischemic injury
 - i. Often called “shock liver,” acute ischemic injury may lead to ALF after cardiac arrest, any period of significant hypovolemia or hypotension, or during severe congestive heart failure.
 - ii. Documented hypotension is not always evident with acute ischemic injury. Drug-induced hypotension or hypoperfusion may also cause acute ischemic injury, such as with cocaine and methamphetamine.
 - iii. Typical laboratory presentation includes markedly elevated aminotransferase concentrations. In addition, simultaneous renal dysfunction and other markers of hypoperfusion may be present.
 - iv. Acute ischemic injury is classified as a hyperacute ALF, which generally resolves with resolution of the circulatory problem.
- d. Mushroom poisoning
 - i. Typically caused by the *Amanita phalloides* spp. of mushrooms
 - ii. Mushroom poisoning is classified as a hyperacute ALF with an onset of symptoms within 24 hours after ingestion. In addition to hepatotoxicity, patients with mushroom poisoning present with severe gastrointestinal (GI) symptoms including nausea, vomiting, diarrhea, and abdominal cramping.
- e. Wilson disease
 - i. Rare cause of ALF; implicated in about 2%–3% of cases per year, mostly affecting young people
 - ii. Wilson disease is a rare disorder that causes too much copper to accumulate in the body. Diagnosis is characterized by an abrupt onset of Coombs-negative hemolytic anemia with serum bilirubin greater than 20 mg/dL. Other diagnostic laboratory findings include low serum ceruloplasmin, presence of Kayser-Fleischer rings, and high urinary and hepatic copper concentrations.
 - iii. Patients who present with fulminant liver failure secondary to Wilson disease have exceedingly high mortality rates without transplantation.

- f. Autoimmune hepatitis
 - i. Autoimmune hepatitis is considered a chronic inflammatory disease; however, patients can still be considered to have ALF if they had rapid deterioration of symptoms. About 20% of patients with stable disease will have ALF, which is typically instigated by an environmental trigger.
 - ii. Initiation of corticosteroid therapy may be considered for some patients with early-stage ALF without multiorgan failure; however, patients with progressive disease will require liver transplantation.
 - g. Budd-Chiari syndrome
 - i. Budd-Chiari syndrome is caused by an acute hepatic vein thrombosis. Presenting symptoms include abdominal pain, ascites, and frank hepatomegaly.
 - ii. Prognosis is poor if patients present with ALF, and commonly, transplantation may be required instead of venous decompression.
 - h. Acute fatty liver of pregnancy/hemolysis, elevated liver enzymes, low platelets (HELLP)
 - i. Toward the end of pregnancy, a small percentage of women will develop rapidly progressive hepatic failure that is generally associated with three hallmark systems: jaundice, coagulopathy, and low platelets, also known as HELLP.
 - ii. HELLP is associated with increased mortality for both the fetus and the mother.
 - iii. Requires emergency delivery of fetus, after which symptoms should resolve
- E. Complications
- 1. ALF affects almost every organ system in the body:
 - a. Neurologic
 - i. Cerebral edema and elevated intracranial pressures (ICPs) are the most serious complications of ALF. Uncontrolled edema and elevated ICPs can lead to uncal herniation and are usually fatal. Cerebral edema may also lead to tissue hypoxia, which may result in long-term neurologic deficits.
 - (a) Elevated ICPs can be caused by several factors, but osmotic shifts in the brain, inflammation, and neurotoxins are thought to be the primary causes.
 - (b) Because ammonia is converted to osmotically active glutamine, concentrations have been correlated with both encephalopathy and cerebral edema. Concentrations greater than 200 mcg/dL are associated with cerebral herniation, whereas concentrations less than 75 mcg/dL are rarely associated with hepatic encephalopathy. In ALF, either because of impaired hepatocyte activity or the abnormal shunting of venous flow away from the liver, normal mechanisms to detoxify and clear ammonia are no longer effective.
 - ii. Encephalopathy is considered an indicator for the clinical presentation of cerebral edema. Encephalopathy can be difficult to identify and may present initially as agitation and confusion; however, it may progress rapidly to unresponsiveness. Table 3 gives useful guidelines for measuring the severity of encephalopathy.
 - iii. Occurrence of cerebral edema and elevated ICPs is generally related to the severity of hepatic encephalopathy. Patients with grade I and grade II encephalopathy rarely have cerebral edema, whereas cerebral edema is present in about 30% of patients with grade III encephalopathy and about 75% of patients with grade IV encephalopathy.

Table 3. Grades of Encephalopathy

Grade I	Changes in behavior with minimal change in level of consciousness
Grade II	Gross disorientation Drowsiness Possibly asterixis Inappropriate behavior
Grade III	Marked confusion Incoherent speech Sleeping most of the time but arousable to vocal stimuli
Grade IV	Comatose Unresponsive to pain, decorticate or decerebrate posturing

Adapted from: Conn HO, Leevy CM, Vlehevec ZR, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind randomized trial. *Gastroenterology* 1977;72:573-83.

- b. Cardiovascular
 - i. Primary hemodynamic concern in ALF is low systemic vascular resistance, similar to cirrhosis.
 - ii. Most patients are severely volume depleted on admission because of poor nutritional status and third spacing into the extravascular space and will require aggressive fluid resuscitation initially.
 - iii. In patients with elevated ICPs, maintaining adequate perfusion becomes even more important in order to preserve adequate perfusion to the brain, and goals for these patients include maintaining a mean arterial pressure (MAP) of at least 75 mm Hg and a cerebral perfusion pressure (CPP) of 60–80 mm Hg. $CPP = MAP - ICP$.
- c. Coagulopathy
 - i. ALF is defined by the presence of an elevated INR caused by decreased production, together with increased consumption, of coagulation factors.
 - ii. Consumption of platelets is also seen, and thrombocytopenia ($150,000/\text{mm}^3$ or less) is common.
 - iii. However, thromboelastography studies of patients with ALF have shown that overall hemostasis in patients with ALF is maintained by compensatory mechanisms, even in patients with elevated INR values, potentially because of a reduction in hepatic synthesis of natural anticoagulants.
 - iv. Spontaneous bleeding in patients with ALF, though uncommon, is capillary-type bleeding and usually results from mucosal bleeding in the stomach, lungs, or genitourinary system. Unlike chronic liver failure, bleeding from esophageal varices generally does not occur.
 - v. Clinically significant bleeding that requires blood transfusions is rare in ALF.
- d. Renal
 - i. Acute kidney injury with ALF is generally classified as either prerenal injury or acute tubular necrosis.
 - (a) Prerenal azotemia typically is caused by vasodilatation owing to portal hypertension and is worsened by systemic hypoperfusion, similar to hepatorenal syndrome in patients with cirrhosis.
 - (b) Acute tubular necrosis typically occurs secondary to drugs or toxins, such as acetaminophen or *Amanita* poisoning.
- e. Infection
 - i. Patients with ALF are at high risk of infection because of the presence of indwelling catheters in addition to intrinsic monocyte and neutrophil dysfunction. Infections are of particular concern because they may delay transplantation or be problematic during the postoperative period.

- ii. The most common infections in ALF are pneumonia, followed by urinary tract infections and bloodstream infections. The most commonly isolated organisms are gram-positive cocci (e.g., *Staphylococcus*, *Streptococcus*) and enteric gram-negative bacilli. Fungal infections, particularly those caused by *Candida*, occur in about one-third of patients with ALF.
- f. Metabolic abnormalities
 - i. Lack of effective glycogenolysis and gluconeogenesis caused by impaired hepatocyte function places patients at high risk of hypoglycemia.
 - ii. Symptoms of hypoglycemia can often be difficult to identify in patients with severe encephalopathy, whereas profound hypoglycemia can worsen an already altered mental state.
- 2. Therapy must be multimodal to support each of the organ systems affected by ALF.

F. Management of ALF

- 1. Antidotes
 - a. Acetaminophen-induced ALF (see Table 4)
 - i. Although most effective if given within the first hour, GI decontamination with activated charcoal may be of benefit for up to 4 hours after ingestion and does not reduce the effect of acetylcysteine.
 - ii. Administration of acetylcysteine is recommended in all ALF cases in which acetaminophen is suspected as a cause.
 - (a) Acetylcysteine can be given either orally or intravenously. Studies have shown similar outcomes between the two routes; however, in those studies, the main efficacy outcome of interest was development of hepatotoxicity. When patients present already with symptoms of hepatotoxicity (as in ALF), intravenous acetylcysteine is recommended. The U.S. Acute Liver Failure Study Group recommends intravenous therapy for any of the following:
 - (1) Greater than grade I encephalopathy
 - (2) Hypotension
 - (3) If oral therapy cannot be tolerated (e.g., vomiting, compromised airway, ileus)
 - (b) Many poison centers may extend therapy beyond the recommended course if there is a detectable acetaminophen concentration or if ALT concentrations continue to remain elevated at the end of therapy, especially if therapy was initiated more than 8 hours after ingestion and baseline acetaminophen concentrations were greater than 300 mcg/mL.
 - (c) Therapy may continue until the signs and symptoms of encephalopathy or coagulopathy resolve or until the patient receives a liver transplant.
 - (d) Additional information on treatment of acetaminophen-induced ALF can be found in the Toxicology chapter.

Table 4. Acetylcysteine for Acetaminophen-Induced ALF

Route	Dose
Oral	Loading dose: 140 mg/kg × 1 dose Maintenance dose: 70 mg/kg every 4 hr × 17 doses (72 hr total)
IV	150 mg/kg (max 15 g) over 60 min, followed by 50 mg/kg (max 5 g) over 4 hr, followed by 100 mg/kg (max 10 g) over 16 hr (21 hr total)

IV = intravenous.

b. NAI-ALF

- i. Acetylcysteine may improve oxidative stress in NAI-ALF by acting as a free radical scavenger. In addition, acetylcysteine may improve both hepatic and systemic perfusion through its vasodilatory effects.
- ii. A multicenter randomized trial compared acetylcysteine with placebo for 72 hours (see Table 5) for treatment of NAI-ALF. Randomized patients were stratified according to coma grade, with most patients having a low-grade encephalopathy. There was no difference in the primary outcome of overall survival at 3 weeks between acetylcysteine and placebo; however, the transplant-free survival rate significantly increased with the use of acetylcysteine (40% vs. 27%, $p=0.04$).
 - (a) The increase in transplant-free survival with acetylcysteine was mainly confined to the subgroup of patients with coma grade I and grade II (52% vs. 30% with placebo, $p=0.01$).
 - (b) When outcomes were compared on the basis of each etiology of NAI-ALF, patients with DILI and hepatitis B virus had more improvement in overall survival and transplant-free survival from acetylcysteine compared with placebo than with other causes of NAI-ALF.

Table 5. Acetylcysteine for NAI-ALF

Route	Dose
Intravenous	150 mg/kg over 60 min, followed by 12.5 mg/kg/hr for 4 hr, followed by 6.25 mg/kg/hr for 67 hr

Patient Case

1. A 60-year-old woman with rheumatoid arthritis was initiated on azathioprine 3 months ago and now presents with NAI-ALF secondary to DILI. On presentation, her ALT and AST concentrations are 500 IU/L and 350 IU/L, respectively. Her INR is 1.7, and she is mildly confused and drowsy. Which intervention has been shown most effective for the treatment of NAI-ALF?
 - A. Intravenous acetylcysteine 21-hour regimen.
 - B. Intravenous acetylcysteine 72-hour regimen.
 - C. Oral acetylcysteine 72-hour regimen.
 - D. Oral glutamine supplementation.

c. Mushroom poisoning

- i. Gastric lavage and activated charcoal may be beneficial for patients still having GI symptoms indicative of a recent ingestion.
- ii. Although data regarding efficacy are lacking, penicillin G can be used as an antidote to α -amanitin, a toxin released after mushroom ingestion. Penicillin G directly competes with and inhibits the ability of the toxin to bind to plasma protein and penetrate the liver. Dose: 300,000 – 1 million units/kg/day given intravenously
2. Management of neurologic complications
 - a. Encephalopathy
 - i. All medications that can cause sedation or confusion should be avoided (i.e., benzodiazepines, anticholinergics, etc.).
 - ii. Grade I encephalopathy can typically be managed with close monitoring and without medication; grade II–IV encephalopathy should be treated in an ICU setting, if possible.

- iii. Given its ability to decrease serum ammonia concentrations and the experience with treatment of hepatic encephalopathy in patients with cirrhosis, lactulose is recommended for patients with ALF with low-grade encephalopathy. The recommended dose is 20–30 g three or four times daily to produce 2 or 3 soft stools a day.
 - (a) Despite its proposed benefits, retrospective data analyses of patients with ALF who receive lactulose therapy have not shown a benefit on encephalopathy or overall outcome.
 - (b) In addition, lactulose has the potential to cause abdominal distension, which could be a concern for liver transplantation. Moreover, overuse of lactulose has the potential to cause intravascular depletion, which may further contribute to hemodynamic instability. Therefore, its effects may be harmful in the acute setting.
- iv. L-Ornithine-L-aspartate up-regulates urea and glutamine synthesis, during which ammonia is consumed. Theoretically, exogenous supplementation of L-ornithine-L-aspartate should decrease blood ammonia concentrations. One large randomized controlled trial of ALF compared L-ornithine-L-aspartate with placebo and found no differences in serum ammonia concentrations, improvement in encephalopathy, or survival between groups.
- v. Patients with grade III and grade IV encephalopathy should be intubated for airway protection and treated with minimal sedation to allow for more frequent neurologic assessments. If sedation is necessary, propofol is typically used because it can reduce cerebral blood flow and lowers ICP.
- b. Seizures
 - i. Seizures have the potential to increase ICP. Therefore, seizures should be controlled quickly with phenytoin and/or short-acting benzodiazepines.
 - ii. Use of prophylactic antiepileptics is not recommended. Studies have shown that use of prophylactic phenytoin in patients with ALF has no impact on prevention of seizures, cerebral edema, or overall survival.
- c. Elevated ICPs
 - i. ICP should be kept less than 20–25 mm Hg while preserving CPP at 50–60 mm Hg.
 - ii. Routine ICP monitoring has not been shown to reduce mortality in patients with ALF, and routine placement of ICP monitors is not recommended in all patients. Clinicians may choose to place an ICP monitor in patients with high-grade encephalopathy (grades III and IV) to provide close monitoring of cerebral edema.
 - iii. Osmotic agents are used first line for control of ICP.
 - (a) Mannitol has been used effectively in acutely reducing ICP in patients with ALF, though the effect is usually transient.
 - (1) Mannitol is given as 0.5–1 g/kg intravenously once, which may be repeated to effect as long as the serum osmolality is less than 320 mOsm/L; however, it is typically ineffective if the baseline ICP is greater than 60 mm Hg.
 - (2) Adverse effects to consider for mannitol administration include fluid overload, particularly in patients with renal impairment, hyperosmolality, and hypernatremia.
 - (b) In patients with grade III or grade IV encephalopathy, multiorgan failure, or hemodynamic instability, prophylactic hypertonic saline may be used to reduce the risk of cerebral edema.
 - (1) In a small, randomized controlled trial, 30 patients with ALF and grade III or grade IV encephalopathy were randomized to receive prophylactic hypertonic saline to maintain a serum sodium of 145–155 mEq/L compared with standard of care. The primary outcome, incidence of ICP defined as elevations greater than 25 mm Hg, was significantly decreased in the hypertonic saline group (20% hypertonic saline vs. 46.7% control, $p=0.04$).

- (2) Hypertonic saline in this study was administered as a 30% saline infusion by a syringe at 5–20 mL/hour; however, many preparation and dosing strategies have been used (e.g., 23.4% 30-mL bolus, 7.5% 2-mL/kg bolus, 3% 200-mL bolus, or continuously), and the goal should be to target a serum sodium of 145–155 mEq/L.
- iv. When severe ICP elevations do not respond to other measures, barbiturates such as thiopental or pentobarbital may be used to control ICP.
 - (a) Profound hypotension may limit barbiturate use in ALF when patients have hemodynamic instability at baseline. Patients may require vasopressors to maintain adequate MAP (and CPP) while receiving barbiturates.
 - (b) Barbiturate clearance is significantly decreased in patients with ALF, which may limit clinicians' ability to perform neurological assessments for extended periods.
- v. Hyperventilation to a Paco_2 of 25–30 mm Hg can restore cerebral autoregulation, which results in vasoconstriction and decreased ICP.
 - (a) The effects of hyperventilation on ICP appear to be short-lived. A randomized controlled trial of prophylactic hyperventilation showed no benefit on cerebral edema and survival. In addition, there is concern that cerebral vasoconstriction with hyperventilation may worsen cerebral hypoxia.
 - (b) Thus, prophylactic hyperventilation currently plays no role; it is only used for acute control of ICP elevations.
- vi. Hypothermia (33°C–34°C) may control ICP in patients with ALF by lowering the production of ammonia and decreasing the cerebral uptake of ammonia as well as decreasing cerebral blood flow. However, hypothermia for patients with ALF has not been compared with normothermia in controlled trials. In addition, there are concerns about coagulation disturbances and increased risk of infection with hypothermia.

Patient Case

2. A 33-year-old man presents with ALF secondary to acetaminophen overdose. He is now 72 hours post-ingestion and is profoundly encephalopathic and unresponsive to pain on examination. An ICP monitor is placed, which shows acute elevations of 30 mm Hg. Which is most appropriate for the acute management of ICP elevations?
 - A. Hypertonic saline continuous infusion to maintain serum sodium 145–155 mEq/L.
 - B. Mannitol 0.5 mg/kg intravenously $\times$ 1.
 - C. Hyperventilation to Paco_2 of 25–30 mm Hg.
 - D. Thiopental continuous infusion.
3. Management of hemodynamic instability
 - a. Patients should initially be resuscitated with 0.9% sodium chloride (“normal saline”). Hypotonic fluids including lactated Ringer solution (273 mOsm/kg) should be avoided, if possible, in patients with grade III and grade IV encephalopathy because of the risk of cerebral edema.
 - b. Vasopressors should be used if fluid resuscitation fails to maintain a MAP greater than 75 mm Hg or a CPP of 60–80 mm Hg.
 - i. Norepinephrine is the vasopressor of choice in patients requiring vasopressor support.
 - ii. Use of vasopressin is controversial for patients with ALF who have high-grade encephalopathy. One study of six patients with grade IV encephalopathy showed an increased ICP after 1 hour of terlipressin, though systemic hemodynamics were not significantly altered. Although there have been no similar studies of vasopressin in patients with ALF, its use in patients with ALF and high-grade encephalopathy should be cautioned.

4. Management of coagulopathies
 - a. Although the INR may be elevated in patients with ALF, overall hemostasis is maintained through compensatory mechanisms.
 - b. In patients with an elevated INR without signs and symptoms of an acute bleed, INR should not be corrected using fresh frozen plasma. Vitamin K (5–10 mg) may be administered because many patients with ALF are deficient in vitamin K, further contributing to the coagulopathy of ALF. Intravenous administration is usually recommended because subcutaneous administration of vitamin K can lead to erratic absorption, and enteral absorption may also be unreliable.
 - c. If clinically significant bleeding occurs, INR correction with fresh frozen plasma is warranted.
 - i. Guidelines recommend an INR correction to about 1.5 for clinically significant bleeding.
 - ii. If a fresh frozen plasma infusion alone does not adequately lower INR, recombinant activated factor VII (rFVIIa) may be administered. In a small nonrandomized study of 15 patients with fulminant hepatic failure, administration of rFVIIa at a dose of 40 mcg/kg temporarily improved coagulation parameters (INR less than 1.6) compared with patients receiving only fresh frozen plasma (100% vs. 0%, $p < 0.002$). Although the improvements in coagulation were only temporary, patients in the rFVIIa group were able to have invasive procedures performed (e.g., ICP monitors placed) more often than were patients in the control group (100% vs. 38%, $p = 0.03$).
 - d. To reduce the risk of spontaneous intracranial hemorrhage, platelet transfusions should be provided if the count drops to less than 15,000–20,000/mm³ in the absence of bleeding.
 - i. If clinically significant bleeding occurs, patients should be transfused to a target platelet count greater than 50,000/mm³.
 - ii. For invasive procedures, platelet counts should be 50,000–70,000/mm³, though thromboelastography data analyses suggest that a target of 100,000/mm³ is ideal.
 - e. Histamine-2 receptor antagonists or PPIs should be initiated in patients with ALF to reduce the incidence of spontaneous GI bleeding.
5. Management of infectious complications
 - a. Antimicrobial prophylaxis is often given because infection remains the primary cause of death in patients with ALF. However, data analyses are limited on the benefit of antimicrobial prophylaxis in ALF. A retrospective cohort study of 1551 patients with ALF showed that prophylactic antibiotic therapy did not reduce the incidence of bloodstream infections (12.8% in the prophylaxis group vs. 15.7% in the non-prophylaxis group, $p = 0.12$) and did not reduce 21-day mortality.
 - b. Patients should be monitored closely for infection through surveillance cultures, and antimicrobials should be initiated promptly if the patient has any signs or symptoms of a systemic infection. Empiric administration is recommended for any of the following scenarios:
 - i. Positive surveillance cultures
 - ii. Progression to higher-grade encephalopathy
 - iii. Refractory hypotension
 - iv. Development of systemic inflammatory response syndrome (SIRS) criteria
6. Miscellaneous – Corticosteroids
 - a. Corticosteroid therapy may be initiated for patients with ALF caused by autoimmune hepatitis, particularly if they have early-stage disease without multiorgan failure.
 - b. Typical dose is prednisone 40–60 mg/day.
 - c. For patients with late-stage disease (i.e., high-grade encephalopathy, multiorgan failure), decisions regarding liver transplantation should not be delayed while awaiting a response from steroid therapy.

G. Prognosis

1. Predictive models of survival and need for liver transplantation are useful to identify the patients most likely to benefit from liver transplantation.
2. The most important predictor of outcome seems to be cause of ALF. Transplant-free survival is 50% or greater when acetaminophen, hepatitis A, acute ischemic injury, or pregnancy is the cause, whereas other causes confer less than 25% transplant-free survival. In addition, transplant-free survival is significantly decreased when patients present with grade III or grade IV encephalopathy compared with grade I or grade II encephalopathy.
3. King's College criteria, developed from a cohort of about 600 patients with ALF, incorporate parameters such as cause of ALF and clinical parameters, including degree of encephalopathy and liver function tests, in order to evaluate the decision to perform transplantation versus provide medical therapy.

H. Transplantation

1. Orthotopic liver transplantation is the only definitive treatment for patients with ALF.
2. The advance of liver transplantation has improved ALF survival rates to greater than 60%.

II. ACUTE PANCREATITIS**A. Epidemiology**

1. AP is responsible for 220,000 hospitalizations per year in the United States.
2. In 2009, AP was the leading gastroenterology discharge diagnosis in the United States, with an annual cost of \$2.6 billion.
3. AP cases are increasing. Data from the late 1990s showed that admissions for AP were 40 cases per 100,000 individuals, whereas by the early 2000s, that number had increased to 70 cases per 100,000 individuals.
4. AP is classified according to disease severity. Overall, about 20% of patients with AP have a severe course, and up to 30% of patients with severe pancreatitis die of multiorgan failure.

B. Definitions

1. The clinical diagnosis of AP is based on characteristic symptoms (i.e., abdominal pain and nausea), together with elevated serum concentrations of pancreatic enzymes. According to the Acute Pancreatitis Classification Working Group definition, two of the following three criteria must be met for a patient to be given a diagnosis of AP:
 - a. Abdominal pain consistent with AP. This is typically persistent epigastric pain, sometimes radiating to the back.
 - b. Serum lipase (or amylase) concentrations greater than 3 times the upper limit of normal
 - c. Imaging (computed tomography [CT], magnetic resonance imaging [MRI], or transabdominal ultrasonography) consistent with pancreatitis
2. AP is classified according to disease severity as mild, moderately severe, or severe.
 - a. Mild AP: Tends to be self-limiting (less than 48 hours) with no organ failure or necrosis. There is also the absence of local and systemic complications.
 - b. Moderately severe AP: Characterized by local complications and organ failure that lasts less than 48 hours. Local complications for moderately severe AP resolve without intervention.
 - c. Severe AP: Characterized by persistent organ failure for more than 48 hours. Patients with severe AP usually have one or more local complications. Mortality rates are high for severe AP, particularly if persistent organ failure develops within the first few days of disease.

3. AP is further classified according to the phase. There are two distinct phases in this disease: early and late. The early phase usually lasts for the first week, and the late phase can last for weeks to months:
 - a. Early: Symptoms of SIRS with or without transient organ failure during the first week. Inflammatory responses and organ failure are mainly because of a response to local pancreatic injury.
 - b. Late: Complications that occur after 1 week that can last weeks to months. This phase is characterized by persistent organ failure and the presence of local complications. The late phase occurs only in those with moderately severe or severe AP.
 4. Local complications with moderately severe and severe AP may include:
 - a. Peripancreatic fluid collections
 - b. Pancreatic and peripancreatic necrosis (sterile or infected). Pancreatic necrosis is an area of nonviable pancreatic parenchyma identified by lack of enhancement on imaging, generally greater than 30% of the pancreas.
 - c. Pseudocysts
 - d. Walled-off necrosis (sterile or infected)
 5. Organ failure associated with AP is typically cardiovascular, respiratory, or renal dysfunction. The modified Marshall scoring system is recommended to identify patients with AP with organ failure. A score of 2 or more for one of these three systems indicates organ failure.
- C. Pathophysiology – AP is primarily caused by inappropriate activation of trypsinogen to trypsin. Trypsin is the key enzyme responsible for the activation of pancreatic zymogens. When trypsin is inappropriately formed and retained in the pancreas, activation of digestive enzymes inside the pancreas causes pancreatic autodigestion and pancreatic injury.
- D. Causes
1. Gallstones
 - a. Gallstone pancreatitis is the main cause of AP, responsible for 40%–70% of cases.
 - b. Gallstone pancreatitis occurs primarily in white women older than 60 years and in patients with small stones (less than 5 mm in diameter).
 - c. Gallstone pancreatitis is usually an acute event that resolves once the gallstone has been removed or has passed.
 - d. Patients may undergo a cholecystectomy to prevent further episodes in the future.
 2. Alcohol use
 - a. Excessive alcohol use is the etiology of pancreatitis in 25%–35% of cases.
 - b. Symptoms can occur as an acute episode or present as a chronic pancreatitis.
 - c. Alcohol-induced pancreatitis is more common in men than in women.
 - d. Alcohol use and its association with pancreatitis is thought to have a dose-dependent relationship. Alcohol intake for more than 5 years or greater than 50 g daily increases the risk of pancreatitis. However, only about 5% of patients with a history of heavy alcohol consumption develop AP.
 3. Hypertriglyceridemia
 - a. Primary and secondary hypertriglyceridemia causes AP in a few cases (1%–4%).
 - b. If serum triglycerides are greater than 1000 mg/dL, hypertriglyceridemia should be suspected as the cause.
 4. Certain medications can cause pancreatitis through varied mechanisms. Examples include:
 - a. Angiotensin-converting enzyme (ACE) inhibitors
 - b. Estrogens
 - c. HAART (highly active antiretroviral therapy) medications (e.g., didanosine)
 - d. Thiazide diuretics (e.g., hydrochlorothiazide)
 - e. Valproic acid

5. Malignancy – The presence of a pancreatic tumor blocking the main pancreatic duct should be suspected in any patient older than 40 years with signs and symptoms of pancreatitis and no other apparent cause.
6. About 20% of AP cases are idiopathic.

E. Diagnosis

1. Signs and symptoms
 - a. Abdominal pain
 - i. AP pain is usually located in the epigastric region or left upper quadrant; however, it may radiate to the back, chest, or flank. Pain is typically constant and severe.
 - ii. Gallstone pancreatitis–induced pain has been described as knifelike.
 - b. Nausea
2. Laboratory abnormalities
 - a. According to the Acute Pancreatitis Classification Working Group definition of AP, serum lipase (or amylase) concentrations at least 3 times the upper limit of normal are required for diagnosis.
 - b. Serum lipase is preferred for diagnosis because elevations in serum lipase concentrations are more specific to the diagnosis of AP than elevations in amylase and serum lipase concentrations remain elevated longer than amylase concentrations.
 - i. Amylase concentrations rise quickly (within a few hours) in AP; however, they return to normal within a few days.
 - ii. Amylase concentrations may remain normal in alcohol-induced AP and hypertriglyceridemia.
3. Imaging
 - a. Transabdominal ultrasonography should be done to confirm the diagnosis of AP for all patients.
 - b. Contrast-enhanced CT scans of the abdomen are more than 90% sensitive and specific in diagnosing AP; however, routine use is unnecessary.
 - c. Contrast-enhanced CT and/or MRI should be used in patients with an unclear diagnosis or in patients who do not improve after 48–72 hours to evaluate for complications.

F. Management

1. Hydration
 - a. Patients with AP need early aggressive volume resuscitation because they are volume depleted for many reasons, including vomiting, reduced oral intake, third spacing of fluids because of inflammatory response, and diaphoresis. In fact, it has been hypothesized that worsening pancreatic hypoperfusion that develops from pancreatic inflammation in the setting of volume depletion leads to pancreatic necrosis. Thus, early aggressive volume resuscitation may prevent the development of pancreatic necrosis.
 - b. Early aggressive volume resuscitation (within the first 24 hours) has been shown to be more effective than later aggressive volume resuscitation. Studies that have continuously used aggressive hydration strategies beyond the first 24 hours of presentation of AP have not shown benefit.
 - c. Selection of intravenous fluid for initial volume resuscitation in AP appears to be important, favoring pH-balanced fluids. Low pH activates trypsinogen, implying that low-pH fluids exacerbate inflammatory response in AP. In a randomized controlled trial comparing initial resuscitation (within the first 24 hours) with lactated Ringer solution to 0.9% sodium chloride for patients with AP, there was a significant reduction in SIRS after 24 hours in patients resuscitated with lactated Ringer compared with 0.9% sodium chloride (84% reduction vs. 0%, respectively, $p=0.035$). The study also showed a significant reduction in C-reactive protein concentrations with administration of lactated Ringer solution compared with 0.9% sodium chloride.
 - d. Because there can be harm in over-resuscitating patients, especially those with concomitant cardiovascular or renal failure, aggressive hydration may not be beneficial if there is no response within the first 6–12 hours.

2. Endoscopic retrograde cholangiopancreatography (ERCP)
 - a. Although many gallstones are passed through the duodenum and lost in the stool without causing harm to the patient, gallstones that are not cleared can cause an obstruction in some patients in either the biliary tree or the pancreatic duct, which can lead to severe AP or cholangitis.
 - b. An ERCP, together with a sphincterotomy, may be used to extract gallstones from the pancreatic ducts or biliary tree.
 - c. There is considerable risk with ERCP, including bleeding and the potential to worsen AP because of manipulation of the pancreas.
 - d. Three randomized controlled trials have evaluated the effectiveness of early ERCP in reducing the risk of complications in patients with gallstone AP. However, a limitation of these studies was that many of the patients had acute cholangitis, which would be an indication for ERCP without AP. However, a 2004 Cochrane review assessed these three randomized trials, controlling for patients with acute cholangitis. The review showed that, for patients with gallstone-associated AP, early ERCP (within 24–72 hours of admission) with or without sphincterotomy was associated with a significant reduction in complications in patients with severe AP (odds ratio [OR] 0.27; 95% confidence interval [CI], 0.14–0.53), though not for patients with mild AP (OR 0.89; 95% CI, 0.53–1.49).
 - e. AP is the most common complication of ERCP. Although the incidence of post-ERCP pancreatitis has decreased significantly during the past few decades, post-ERCP pancreatitis continues to occur in 2%–4% of patients.
 - i. Risk of post-ERCP pancreatitis is higher for patients without cholangitis and/or jaundice. For these patients, diagnostic endoscopic ultrasonography or MRCP (magnetic resonance cholangiopancreatography) should be used instead of ERCP.
 - ii. Guidewire cannulation reduces post-ERCP pancreatitis by avoiding hydrostatic injury caused by contrast agents.
 - iii. Pancreatic duct stents may be placed to prevent post-ERCP pancreatitis in high-risk patients.
 - iv. Rectal NSAIDs (i.e., 100 mg of indomethacin) after an ERCP can be given to patients at high risk of post-ERCP pancreatitis. In a multicenter randomized controlled trial of 600 high-risk patients undergoing ERCP, 100 mg of rectal indomethacin (administered as two 50-mg suppositories given immediately post-ERCP) reduced the incidence of AP compared with placebo (9.2% vs. 16.9%, $p=0.005$) and, specifically, the development of moderate to severe AP (4.4% vs. 8.8%, $p=0.03$).
3. Infection
 - a. Pancreatic and non-pancreatic infections contribute to mortality in patients with AP. The primary infectious concern with AP is infected necrotizing pancreatitis, which confers a high mortality rate (about 30%); thus, patients with severe acute necrotizing pancreatitis are at highest risk of pancreatic infections.
 - b. The role of prophylactic antibiotics is controversial in AP.
 - i. Early randomized trials showed a potential benefit in the reduction of infectious complications, particularly central line–related bloodstream infections, pulmonary infections, urinary infections, and pancreatic infections; however, the studies were unblinded, and the benefit was mostly confined to patients with severe AP.
 - ii. In more recent literature, the benefit of prophylactic antibiotic is unsupported. The best-designed study randomized 100 patients with necrotizing pancreatitis to receive either meropenem or placebo for 7–21 days. The study showed no difference in the primary end point of developing pancreatic or peripancreatic infections (18% in the meropenem group vs. 12% in placebo, $p=0.401$). There was also no difference in mortality between groups.

- iii. A 2010 Cochrane review evaluated seven studies (with 400 patients) comparing prophylactic antibiotics in AP with CT-proven necrosis. The review showed no effect on mortality (8.4% with antibiotics vs. 14.4% control, $p=0.07$), infected pancreatic necrosis (19.7% vs. 24.4%, $p=0.42$), or non-pancreatic infections (23.7% vs. 36%, $p=0.08$). Studies with imipenem show a significant reduction in infected pancreatic necrosis (10.2% vs. 24.4%, $p=0.02$) but no difference in mortality.
 - c. According to the available information, use of prophylactic antibiotics to prevent the development of infected pancreatic necrosis is not recommended at this time.
 - d. For patients who have not improved after 7–10 days of hospitalization with pancreatic necrosis, an infection should be suspected, and empiric antibiotics should be initiated at that time. Because of penetration issues, only carbapenems, fluoroquinolones, metronidazole, or high-dose cephalosporins should be used.
4. Nutrition
- a. Historically, patients were kept NPO in order to rest the pancreas and prevent the further release of pancreatic enzymes. Patients were given TPN until complete resolution of AP.
 - i. This practice has largely fallen out of favor because several studies have shown that early enteral nutrition is safe and effective for patients with AP. Enteral feeding maintains the gut mucosal barrier and helps prevent infectious complications such as infected necrosis, which may result from bacterial translocation from the gut.
 - ii. A meta-analysis of eight trials comparing enteral nutrition with TPN in patients with AP showed decreased mortality (relative risk [RR] 0.5; 95% CI, 0.28–0.91), infectious complications (RR 0.39; 95% CI, 0.23–0.65), multiorgan failure (RR 0.55; 95% CI, 0.37–0.81), and surgical interventions (RR 0.44; 95% CI, 0.29–0.67) with the use of enteral nutrition. Enteral nutrition in these trials was given by the NJ route.
 - iii. TPN is mainly reserved for patients unable to meet caloric demands with enteral feeding.
 - b. Although the NJ route for enteral feeding has been preferred because it avoids the gastric area where pancreatic enzyme stimulation may occur, the NG route appears to be safe.
 - i. A recent meta-analysis of three randomized controlled trials showed no significant differences in mortality, tracheal aspiration, or proportion meeting energy balance between the two routes; however, the results were limited by small sample sizes.
 - ii. NG feeding is easier than NJ feeding because NJ tubes can be difficult to place, expensive, and inconvenient.
5. Surgery
- a. Cholecystectomy should be performed in patients with gallstones in the gallbladder to prevent the recurrence of AP. For necrotizing biliary AP, cholecystectomy should be delayed until inflammation is resolved and fluid collections are cleared in order to avoid infection.
 - b. Surgery is generally unnecessary for asymptomatic patients with pseudocysts and pancreatic or extrapancreatic necrosis.
 - c. Surgical debridement of sterile necrosis is only necessary if gastric outlet obstruction or bile duct obstruction is present.
 - d. Surgical intervention is the treatment of choice for infected necrotizing pancreatitis.
 - i. For stable patients with infected necrotizing pancreatitis, surgical debridement should be delayed for at least 4 weeks to allow appropriate delineation of necrotic versus non-necrotic tissue, and antibiotics should be tried before surgical intervention.
 - ii. Unstable patients with infected necrosis should undergo immediate debridement, and necrosectomy may be required in patients who do not respond to a combination of antibiotics and debridement.

Patient Case

3. A 44-year-old woman presents to the ED with a 2-day history of diffuse abdominal pain. Amylase is 700 IU/L, and lipase is 800 IU/L. She is given intravenous fluids with lactated Ringer solution and enteral nutrition through an NJ tube. However, after 48 hours, she has still not improved, and CT imaging reveals pancreatic necrosis involving 40% of the pancreas. Which interventions would best be performed at this time?
- A. Piperacillin/tazobactam should be prophylactically administered to prevent infected necrotizing pancreatitis.
 - B. Surgical management of necrotizing pancreatitis is necessary.
 - C. Antibiotics should be deferred unless systemic signs of infection are present.
 - D. Meropenem should be prophylactically administered to prevent infected necrotizing pancreatitis.

III. GASTROINTESTINAL FISTULAS**A. Epidemiology**

1. About 40% of patients with Crohn disease will develop a spontaneous fistula in their lifetime, and up to 12% of patients with diverticulitis will develop a spontaneous fistula.
2. Incidence of postoperative fistula formation varies from less than 1% to about 20%, depending on the type of abdominal surgery, with the rate of fistula increasing with more complex surgical procedures and more complicated resections/anastomoses.
3. In the past 50 years, the mortality rate associated with fistulas has decreased significantly from greater than 40% to currently around 20%, mainly because of improvements in supportive care and the advent of nutritional support.
4. GI fistulas remain a source of considerable morbidity with prolonged hospital courses, infections, and malnutrition.

B. Definition

1. A fistula is any abnormal connection between two epithelialized surfaces. GI fistulas involve an abnormal connection between the GI tract and the skin, another internal organ, or an internal cavity such as the peritoneal or pleural space.
2. Classification systems for fistulas:
 - a. Anatomic: Describe the fistula origin and drainage point
 - i. Internal: Connection to another internal organ or internal cavity (i.e., ileocolic)
 - ii. External: Connection to the skin (i.e., enterocutaneous)
 - b. Physiologic: Classified according to daily fistula output. Daily fistula output is the one of most important determinants of morbidity and mortality, and it generally decreases before spontaneous closure.
 - i. High output: Greater than 500 mL/day. High-output fistulas are associated with a mortality rate of about 35%.
 - ii. Moderate output: 200–500 mL/day
 - iii. Low output: Less than 200 mL/day
 - c. Output classification can be further divided according to anatomic site.
 - i. Pancreatic fistula
 - (a) Low output: Less than 200 mL/day
 - (b) High output: 200 mL/day or greater

- ii. Intestinal fistula
 - (a) Low output: Less than 500 mL/day
 - (b) High output: 500 mL/day or greater
 - d. Fistulas can also be described according to whether they maintain continuity with the GI tract.
 - i. Lateral fistulas divert off the intestines while maintaining the continuity of the intestinal tract. With lateral fistulas, intestinal contents follow normal progression beyond the fistula.
 - ii. End fistulas disrupt the continuity of the intestinal tract beyond the fistula.
- C. Causes
 - 1. Postoperative fistulas
 - a. Most fistulas are formed after surgery (about 80%), most commonly after operations for cancer.
 - b. Postoperative fistulas form because of either infection or breakdown at intestinal anastomoses.
 - c. Postoperative fistulas are more commonly external, often because of the presence of a drain.
 - 2. Spontaneous fistulas
 - a. 15%–25% of GI fistulas occur spontaneously.
 - b. Crohn disease and inflammatory bowel disease are the leading cause of spontaneous fistula formation, though pancreatitis and cancer (particularly if radiation therapy is involved) can also lead to spontaneous fistulas.
 - c. Spontaneous fistulas often form because of local inflammatory processes that can cause local abscess formation or perforation.
 - d. Spontaneous fistulas can be either external or internal.
 - 3. Trauma-induced fistulas
 - a. Some fistulas are caused by trauma (abdominal wounds or blunt trauma).
 - b. Trauma may lead to fistula formation by causing vascular injury.
- D. Diagnosis
 - 1. Common presenting symptoms include pain, abdominal tenderness, leukocytosis, and fever. External fistulas are generally easier to recognize because of the presence of effluent at the drainage sites. Patients with internal fistulas may present with nonspecific symptoms such as diarrhea, dyspnea, or SIRS.
 - 2. In postoperative patients, the first indication of a fistula is delayed recovery, which usually occurs within the first week after surgery.
 - 3. Diagnostic workup should include fistula output volume, fistula output description (e.g., color, consistency), biochemical evaluation of fistula content (e.g., water-electrolyte balance, amylase, lipase, pH), microbiological evaluation of fistula content, and markers of nutritional status.
 - 4. Radiographic contrast studies using CT or MRI are necessary to determine the anatomic aspects of the fistula (e.g., origin, length of fistula, presence of obstruction or abscesses). Barium is generally used for contrast because of its ability to show mucosal surfaces.
- E. Treatment
 - 1. Fluid resuscitation and electrolyte management
 - a. GI fistula fluid is typically iso-osmotic and rich in sodium, potassium, chloride, and bicarbonate. High-output fistulas can result in large fluid and electrolyte imbalances leading to dehydration, hypokalemia, hyponatremia, and metabolic acidosis.
 - b. Fistula output from the upper GI tract is generally more acidic and rich in potassium. Replacement fluid should include a maintenance infusion of 0.9% sodium chloride with potassium and frequent reassessments for potassium corrections.
 - c. Pancreatic and duodenal fistulas result in bicarbonate losses and may require bicarbonate replacement.
 - d. Fistula fluid composition may be analyzed in order to correctly replete fluid and electrolyte deficits.

2. Drainage
 - a. Drainage is used to prevent the accumulation of fluid and the development of infection.
 - b. Most enterocutaneous fistulas will drain to skin spontaneously; however, some fluid may be retained in the fistula tract, which may lead to infection.
 - c. Vacuum-assisted closure (VAC) devices administer negative pressure wound therapy and can increase blood flow and decrease fluid collections. For enterocutaneous fistulas, a VAC system can help protect skin and decrease fistula output. Anecdotal evidence with VAC systems has shown increased spontaneous closure rates within 90 days.
3. Nutrition
 - a. Nutritional deficiencies are present in 55%–90% of patients with GI fistulas, particularly with upper GI fistulas, because there is substantial fluid, electrolyte, and protein loss from the upper GI tract.
 - b. Because of nutritional deficits, patients may need nutritional supplementation in excess of daily demands. Patients with low-output fistulas may need additional protein, and patients with high-output fistulas may need additional daily caloric and protein requirements (e.g., 1.5–2 times basal daily expenditure).
 - c. Enteral feedings are the preferred method for nutritional supplementation because enteral feedings provide direct stimulation to the enterocyte, which may enhance mucosal proliferation.
 - i. In a retrospective cohort study of 335 patients with high-output small intestine fistulas (median output 1350 mL/day), 85% (285) were treated with enteral nutrition. Spontaneous closure rates were acceptable.
 - ii. Tolerability may limit the use of enteral feeding (e.g., high gastric residuals, diarrhea).
 - d. TPN has the potential advantage of improving spontaneous closure rates because of reductions in GI secretions and reduction in fistula output volumes, particularly for patients with high-output fistulas and when combined with antisecretory agents (e.g., octreotide).
 - e. Fistula site may also influence the choice of enteral nutrition compared with TPN. In general, enteral feeding is provided for fistulas from the esophagus, lower small intestine, and colon, whereas TPN is used for fistulas from the stomach, pancreas, or upper small intestine.
 - f. Some evidence supports adding supplements to enteral feeding. These include fish oil, omega-3 fatty acids, and glutamine, which may improve immune function or increase blood flow to the intestinal tissue. In a study of 28 patients with high-output fistulas, patients who received glutamine supplementation (0.3 g/kg/day orally) in addition to TPN were significantly more likely to have spontaneous fistula closure.
4. Somatostatin and octreotide
 - a. Somatostatin is a tetradecapeptide that is naturally found in the GI tract and the nervous system.
 - i. It has several biological effects, including inhibition of hormone secretion (gastrin, cholecystokinin, secretin, insulin, glucagon), inhibition of exocrine secretory response (gastric acid and pancreatic secretion), inhibition of motor activity in the GI tract, inhibition of nutrient absorption, and stimulation of water and electrolyte absorption.
 - ii. Octreotide is an octapeptide synthetic analog of somatostatin with similar activity.
 - iii. Because output volume is correlated with spontaneous closure, drugs such as somatostatin and octreotide are used to reduce output volumes.
 - b. Somatostatin vs. octreotide
 - i. Somatostatin has a very short half-life (about 1–2 minutes), which requires a continuous infusion, whereas octreotide has a half-life of around 113 minutes, allowing for intermittent dosing (three times daily).
 - ii. Effect of octreotide appears to diminish with repeated dosing, possibly because of down-regulation of somatostatin receptors.
 - iii. Somatostatin is active at all somatostatin receptors, whereas octreotide has variable affinity at the somatostatin receptors.

- c. Somatostatin significantly reduces output volumes. One prospective, randomized controlled single-center trial compared somatostatin 250 mcg/hour intravenously continuously with placebo for patients receiving TPN. Somatostatin significantly reduced the time to achieve a 50%, 75%, and 100% reduction in fistula output compared with placebo; also, although there was no difference in the rates of fistula closure (85% vs. 81.25%), the time to fistula closure was significantly reduced with the use of somatostatin (13.9 days vs. 20.4 days, $p < 0.05$).
 - d. Octreotide has been shown to decrease fistula output in some studies, though in other trials, it had no effect on fistula output.
 - i. One small study of 14 patients showed a beneficial effect of octreotide on output volumes. In this crossover study, octreotide at 100 mcg subcutaneously three times daily significantly reduced fistula output compared with placebo for the first 2 days of therapy by about 400 mL/day. When the group that was originally randomized to receive octreotide crossed over to the placebo arm, output increased by about 250 mL/day.
 - ii. Two subsequent studies did not show similar results on fistula output. Possible reasons for decreased efficacy with octreotide include diminished response with repeat dosing and decreased activity at some somatostatin receptors.
 - e. Reduction in fistula output with the use of somatostatin or octreotide should occur within 48 hours. If no noticeable response in fistula response occurs at 48 hours, treatment should be discontinued.
5. Conservative versus surgical management
- a. Conservative management is first line for most patients, with the primary goal of conservative management being spontaneous closure of the fistula. Several prognostic indicators improve the likelihood of spontaneous closure.
 - i. Low-output fistulas
 - ii. Patients younger than 40 years
 - iii. Fistula sites: Oropharyngeal, esophageal, duodenal, pancreatic, jejunal
 - iv. A long fistula tract (greater than 2 cm)
 - v. Intestinal continuity maintained
 - b. Surgery is usually indicated for fistulas that fail to close spontaneously after 30–60 days. Some causes of fistula formation (e.g., bowel injury caused by trauma or certain surgical procedures) may require emergency surgery to repair damage.

Patient Case

4. A 34-year-old woman with morbid obesity presents to the surgical ICU after gastric bypass surgery 1 week prior with an enterocutaneous fistula requiring medical management. Her current output is about 600 mL/day. For the patient's high-output fistula, which best represents the intervention that has not been associated with a reduction in fistula output volume?
- A. Somatostatin 250 mcg/hour intravenously continuously.
 - B. Octreotide 100 mcg subcutaneously three times daily.
 - C. TPN.
 - D. Glutamine 0.3 g/kg/day orally.

IV. POSTOPERATIVE ILEUS

A. Epidemiology

1. Incidence of POI can vary, depending on the type of procedure:
 - a. Abdominal hysterectomy: About 3%
 - b. Bowel resection: About 15%
2. POI can lead to a prolonged hospital stay, prolonged recovery, and increased morbidity including increased postoperative pain, PONV, and risk of postoperative complications (e.g., aspiration pneumonia, thromboembolism, nosocomial infection).

B. Definition

1. POI is a transient impairment of appropriate GI motility after a surgical procedure.
2. The paralytic state in POI is not caused by a mechanical obstruction, and ileus can affect the stomach, small intestine, or large intestine.
3. The duration of POI is typically 2–3 days after a procedure, but POI may last up to 6 days postoperatively. Return to normal bowel function is monitored using objective signs such as passing of flatus, active bowel sounds, or a bowel movement.
 - a. The duration of POI often depends on the surgical site. Return to normal function is fastest for the small bowel, normally within 24 hours. Paralytic state may last on average 24–48 hours in the stomach, whereas it may take up to 3–5 days for the colon to return to normal function.
 - b. If POI persists beyond about 6 days, it is called a paralytic ileus.

C. Causes

1. Bowel motility is controlled by the autonomic nervous system. Parasympathetic stimulation increases bowel motility, whereas sympathetic stimulation inhibits it.
 - a. Increased sympathetic output postoperatively may lead to increased ileus formation. The colon is more dependent on the autonomic nervous system than the stomach or small intestine, which may explain the longer recovery time postoperatively.
 - b. The vagal nerve is important to parasympathetic activity in the stomach. Inadvertent damage to the vagal nerve during abdominal surgery can result in impaired emptying of the stomach.
2. During periods of fasting, upper GI tract motility is controlled by the migrating motor complex, which moves intestinal contents distally.
 - a. During periods of fasting postoperatively, the contractility of the stomach and small intestine is entirely dependent on the migrating motor complex.
 - b. Inflammation of the GI tract after surgery, inhibitory neural reflexes, and the release of inhibitory neurotransmitters such as nitrous oxide, substance P, and vasoactive intestinal peptide may lead to decreased activity of migrating motor complex.
3. Exacerbating factors
 - a. Anesthesia: Delayed gastric emptying has been observed with the use of halothane, enflurane, and atropine.
 - b. Postoperative opioids: Opioids, through agonism at the μ_2 -opioid receptor, slow GI motility mainly by decreasing colonic motility. High doses and prolonged courses postoperatively can contribute to paralytic ileus.
 - c. Other medications known to decrease GI motility are often given perioperatively (e.g., anticholinergics).

D. Diagnosis

1. POI is typically characterized by abdominal distension, lack of bowel sounds, delayed passage of flatus or stool, and accumulation of gas and stool in the bowels, which may lead to nausea and vomiting.
2. All patients should have a physical examination for abdominal distension, followed by plain abdominal radiographs to identify air and dilated loops of bowel.
3. An abdominal CT scan can be used to rule out a mechanical obstruction.

E. Management

1. Use of epidural anesthesia
 - a. Epidural blockade may improve POI by reducing local sympathetic and inflammatory response postoperatively and increasing splanchnic blood flow. It may also reduce postoperative opioid use.
 - b. Several studies of epidural anesthesia have shown reductions in POI. Most studies that showed benefit used thoracic epidural blockade and administered epidural anesthesia for at least 48–72 hours.
2. Use of laparoscopic surgery: Few studies have shown reduced POI rates with laparoscopic surgery compared with open abdominal procedures. However, studies have shown reductions in inflammatory response (e.g., cytokine production) and reduced postoperative pain with laparoscopic procedures, which may affect POI.
3. NG decompression
 - a. Historically, NG tubes were placed in most patients for gastric decompression and used until normal GI function returned.
 - b. In a meta-analysis of 26 trials including 4000 patients, the use of NG tube insertion was routinely associated with fever, atelectasis, and pneumonia, though patients treated without NG tubes did have more abdominal pain and vomiting. The study concluded that for every patient who required NG tube insertion, 20 patients could be treated effectively without NG tube insertion and that NG tubes should be used selectively because of concerns for adverse effects.
4. Enteral feeding
 - a. Traditionally, enteral feeds were delayed postoperatively until after ileus was resolved.
 - b. Recent data from several randomized controlled trials show a modest improvement in POI resolution from early enteral feedings, typically initiated within the first 24 hours postoperatively. This effect probably results from stimulation of the bowel.
5. Sham feeding
 - a. Sham feeding is the process of eliciting the release of hormonal and neuronal GI activity without regular feeding. One way by which this mechanism can occur is through the chewing of gum.
 - b. In a small randomized study of 19 patients, chewing gum three times a day reduced time to first flatus (2.1 days vs. 3.2 days, $p<0.01$) and time to first defecation (3.1 days vs. 5.8 days, $p<0.01$) compared with control.
6. Pharmacologic therapy
 - a. Opioid-sparing analgesia
 - i. NSAIDs have two potential effects on resolving POI: sparing opioids through their analgesic effects and reducing the production of inflammatory mediators (e.g., prostaglandin). Adding an NSAID to opioid therapy reduces the need for opioids by 20%–30%.
 - ii. A randomized, double-blind study of morphine patient-controlled analgesia with or without ketorolac showed decreased morphine use and earlier first bowel movements (1.5 days vs. 1.7 days, $p<0.05$) in the patients who received the additional ketorolac compared with those who did not.
 - iii. Use should be carefully assessed so that the benefit outweighs the risk of postoperative bleeding caused by platelet inhibition.

- b. Prokinetics and laxatives
 - i. Erythromycin
 - (a) Erythromycin is a macrolide antibiotic that has prokinetic activity as a motilin receptor agonist. Motilin induces gastric contractions and migrating motor complex.
 - (b) In randomized controlled trials, erythromycin does not appear beneficial for POI resolution.
 - ii. Metoclopramide. No studies of POI have shown a benefit; however, the antiemetic activity of metoclopramide may be beneficial as an adjunctive therapy for patients with POI.
 - iii. Laxatives
 - (a) Laxatives should play an important role in the management of POI because of their stimulatory action in the GI tract; however, data are limited on the use of laxatives.
 - (b) Most of the data regarding the use of laxatives for POI support the use of bisacodyl suppositories (e.g., 10 mg rectally daily), which have reduced time to return of normal bowel function and some evidence of reduced hospital length of stay.
- c. Peripherally acting mu-opioid receptor antagonists
 - i. Alvimopan (Entereg)
 - (a) Alvimopan has 200-fold selectivity for the peripheral opioid receptors and has poor absorption from the GI tract when administered orally (bioavailability about 6%), decreasing the likelihood of systemic absorption and penetration across the blood-brain barrier.
 - (b) Alvimopan was studied in four North American phase III randomized controlled trials for POI. Each trial included adult surgical patients (generally bowel resection and abdominal hysterectomy) who received standard postoperative care for prevention of POI. In all four trials, patients were randomized to receive placebo, alvimopan 6 mg orally twice daily, or alvimopan 12 mg orally twice daily beginning immediately before surgery and continuing for 7 days (total of 15 doses).
 - (1) Three of the four trials showed significant reductions in return of normal bowel function (considered tolerating solid food and passing bowel movements). The 12-mg dose was especially beneficial in females and patients older than 65.
 - (2) A pooled analysis from the four phase III trials comparing outcomes in patients who received the 12-mg dose with placebo showed a 20-hour reduction in time to return of normal bowel function (102 hours vs. 121.8 hours, $p<0.05$) and a reduction in hospital length of stay (6.6 days vs. 7.6 days, $p<0.001$).
 - (c) Alvimopan was also associated with significantly less POI-related morbidity, including NG tube insertion (6.6% vs. 11.5%, $p<0.001$), and fewer POI complications, including paralytic ileus and adverse events of nausea, vomiting, and abdominal distension (2.9% vs. 8.8%, $p<0.001$).
 - (d) In a 12-month study of alvimopan for opioid-induced bowel dysfunction in patients with chronic non-cancer pain, myocardial infarction rates were higher in patients treated with alvimopan than in placebo (7 [1.3%] vs. 0 [0%]).
 - (1) Although this higher risk did not appear to be related to the therapy duration (12 months), the risk of cardiovascular events has not occurred in other alvimopan studies, including POI studies, and no causal relationship has been established.
 - (2) The FDA has since developed REMS (Risk Evaluation and Mitigation Strategies) for the use of alvimopan. Hospitals that intend to use alvimopan should be enrolled in the EASE (ENTEREG Access Support & Education) program. The EASE program limits the use of alvimopan to short-term inpatient use, and patients cannot receive more than 15 doses.

- ii. Methylnaltrexone
 - (a) Methylnaltrexone is a peripherally acting mu-opioid receptor antagonist approved for treatment of chronic opioid-induced constipation. Methylnaltrexone is not FDA approved for the treatment of POI.
 - (b) Methylnaltrexone is typically given subcutaneously daily or every other day for opioid-induced constipation in a weight-based dose of 0.15 mg/kg rounded to the nearest 2 mg (usually 8 or 12 mg)
 - (c) Results from phase III trials of POI are unavailable, but methylnaltrexone may be an alternative to alvimopan if oral therapy is not an option.

Patient Case

5. A 40-year-old man presents for a large bowel resection. Because of the complexity of the procedure and the anticipated use of perioperative opioids and inhalation anesthesia, the team is creating a plan to prevent POI. Which medication would be best to recommend for reducing the incidence of POI?
- A. Hydromorphone patient-controlled analgesia postoperatively instead of morphine.
 - B. Alvimopan 12 mg orally just before surgery and continued twice daily for 7 days.
 - C. Metoclopramide 5 mg intravenously every 6 hours for 7 days postoperatively.
 - D. Octreotide 100 mcg subcutaneously every 8 hours for 7 days postoperatively.

V. POSTOPERATIVE NAUSEA AND VOMITING**A. Epidemiology**

- 1. Postoperative vomiting occurs in about 30% of overall surgical patients, whereas postoperative nausea occurs in about 50%. In high-risk patients, the incidence of PONV can be as high as 80%.
- 2. Uncontrolled PONV may result in a prolonged stay in the post-anesthesia care unit and, sometimes, unplanned hospital admissions for outpatient procedures.

B. Risk Factors

- 1. The most likely causes of PONV are the use of volatile anesthetics, nitrous oxide, and postoperative opioids.
 - a. The effect of volatile anesthetics on PONV is usually dose-dependent and typically presents within the first 6 hours postoperatively.
 - b. The effect of postoperative opioids similarly increases the risk of PONV in a dose-dependent fashion.
- 2. Surgical factors that increase the risk of PONV:
 - a. Use of general anesthesia
 - b. Duration of anesthesia; each 30-minute increase in duration of anesthesia increases the risk of PONV
 - c. Type of surgery: Cholecystectomy, laparoscopic, gynecological are most commonly associated with PONV

3. Patient-specific factors that increase the risk of PONV:
 - a. Female sex
 - b. History of motion sickness or PONV
 - c. Nonsmoker
 - d. Younger age
4. The estimated risk of PONV is 10%, 20%, 30%, 50%, 60%, and 80% when zero, one, two, three, four, or five of the above risk factors for PONV are present, respectively.

C. Prevention

1. A multimodal strategy that usually targets risk avoidance should be implemented to avoid PONV. The IMPACT study enrolled more than 5000 surgical patients and evaluated six interventions for the prevention of PONV in a factorial design, including avoidance of volatile anesthetics and nitrous oxide, use of short-acting opioids in the postoperative period, and use of ondansetron, dexamethasone, and droperidol for pharmacologic prophylaxis. Each intervention except for choice of opioid was associated with a reduction in the incidence of PONV; however, the study showed that the interventions acted independently of each other, and thus, a benefit with several interventions was seen.
2. Regional anesthetics should be used instead of general anesthetics, when possible, because general anesthetics are associated with an 11-fold increase in PONV. If general anesthesia is required, propofol is preferred to volatile anesthetics for inducing and maintaining anesthesia. In the IMPACT study, the use of propofol compared with volatile anesthetics was associated with a 19% relative risk reduction in the incidence of PONV ($p < 0.001$).
3. Avoiding nitrous oxide as a carrier gas is recommended; use of other carrier gases (e.g., nitrogen, oxygen) is associated with a 12% relative risk reduction in PONV ($p = 0.003$).
4. Perioperative opioid use should be minimized, if possible. Guidelines recommend the use of perioperative NSAIDs for opioid-sparing analgesia. According to data from the IMPACT study, which compared remifentanyl with fentanyl, the use of short-acting opioids does not appear to be associated with the incidence of PONV.
5. Pharmacologic prophylaxis:
 - a. Serotonin-3 antagonists are first-line treatment for pharmacologic prophylaxis. These drugs are most effective for the prevention of PONV when given at the end of surgery.
 - i. Ondansetron, when given at a prophylactic dose of 4 mg intravenously, has more anti-vomiting effects (number needed to treat [NNT] = 6) than antinausea effects (NNT = 7).
 - ii. Granisetron at doses of 0.35–3 mg intravenously is as effective as ondansetron, whereas palonosetron 0.075 mg intravenously was more effective than ondansetron at preventing PONV in a small study of gynecological laparoscopic surgical patients (42% PONV with palonosetron vs. 67% with ondansetron, $p < 0.05$).
 - b. Dexamethasone is most effective for the prevention of PONV when given at the time of induction.
 - i. According to data from the IMPACT study, dexamethasone 4 mg intravenously was associated with a 26% relative risk reduction in the incidence of PONV.
 - ii. There appears to be no clinical advantage of using higher-dose dexamethasone (e.g., 8–10 mg) over the standard dose 4–5 mg intravenously.
 - c. Droperidol at prophylactic doses of 0.625–1.25 mg intravenously is effective for the prevention of PONV when given at the end of surgery.
 - i. Efficacy of droperidol is similar to that of ondansetron and dexamethasone, with a relative risk reduction of about 25% (data from the IMPACT study).
 - ii. FDA black box warnings for cardiovascular risk with droperidol have limited its use; however, the doses used for preventing PONV are very low and should not be associated with cardiovascular effects.

- d. Neurokinin-1 receptor antagonists (e.g., aprepitant) should be given before inducing anesthesia. Data are limited on the use of neurokinin-1 receptor antagonists in PONV; however, they appear to be as effective as ondansetron. One large randomized double-blind trial evaluated 805 abdominal surgery patients who were randomly assigned to receive 40 mg of oral aprepitant, 125 mg of oral aprepitant, or 4 mg of intravenous ondansetron. Although there was no difference in the primary outcome of complete response (considered no vomiting or use of rescue therapy), aprepitant at both doses did reduce the occurrence of vomiting compared with ondansetron.
- e. Transdermal scopolamine can be applied the evening before surgery. When used with ondansetron, adding scopolamine was associated with a 10% absolute reduction in the occurrence of PONV within the first 24 hours postoperatively.
- f. Pharmacologic prophylaxis selection depends on patient risk of PONV: Low-risk patients typically do not require prophylaxis, moderate-risk patients should be provided one or two interventions, and high-risk patients should be provided more than two interventions.

D. Rescue Therapy

1. When rescue therapy is needed within the first 6 hours postoperatively, an antiemetic should be selected from a therapeutic class different from the initial prophylactic drug. Repeat doses of the same drugs that were used for initial prophylaxis can be tried if PONV occurs more than 6 hours after surgery.
2. If patients did not receive a prophylactic agent, rescue treatment with a serotonin-3 antagonist should be tried. Treatment doses for PONV are smaller than the doses for prevention (e.g., ondansetron 1 mg).

Patient Case

6. A 27-year-old woman presents for a total abdominal hysterectomy. She is a nonsmoker who has a significant history of motion sickness. During the procedure, she is expected to receive general anesthesia with volatile anesthetics. She will probably require high-dose opioids perioperatively. Given this patient's risk of developing PONV, which would she best receive for prevention of PONV?
 - A. Patient has a high risk of PONV; she should receive transdermal scopolamine the evening before surgery, dexamethasone 4 mg intravenously at the time of induction, and ondansetron 4 mg intravenously at the end of surgery.
 - B. Patient has a moderate risk of PONV; she should receive dexamethasone 4 mg intravenously at the time of induction and ondansetron 4 mg intravenously at the end of surgery.
 - C. Patient has a high risk of PONV; she should receive dexamethasone 4 mg intravenously at the time of induction and ondansetron 4 mg intravenously at the end of surgery.
 - D. Patient has a low risk of PONV; she should receive ondansetron 4 mg intravenously at the end of surgery.

VI. UPPER GASTROINTESTINAL BLEEDING

A. Definition and Epidemiology

1. Bleeding that occurs within the GI tract proximal to the jejunum (i.e., from the esophagus through the duodenum)
2. In the United States, the annual incidence is 100 hospitalizations per 100,000 adults. Incidence is twice as high in males as in females and increases with age.
3. Accounts for 300,000 hospitalizations per year at a cost of \$2.5 billion per year

4. UGIB is 4 times more common than lower GI bleeding.
5. Mortality at 28 days after hospital admission for non-variceal hemorrhage is about 13%, whereas mortality after variceal hemorrhage is about 20%. Mortality rates after both UGIB classifications seem to be decreasing with advances in care.

B. Etiologies

1. Nonvariceal hemorrhage
 - a. Gastric and/or duodenal ulcer
 - i. Most common cause of severe cases of UGIB, accounting for 21%–60% of all UGIB episodes
 - ii. Gastric ulcers are more common than duodenal ulcers.
 - iii. Most commonly caused by an *H. pylori* infection, but may also be secondary to NSAIDs, hyperacidity (e.g., in Zollinger-Ellison syndrome), or stress-related mucosal disease (stress-related mucosal damage is discussed in detail in the Supportive and Preventive Medicine chapter)
 - b. Gastroduodenal erosions (erosive gastritis/duodenitis): Defects of the gastric/duodenal mucosal layer that lead to inflammation without ulcer formation
 - i. Account for about 12% of severe cases of UGIB
 - ii. Causes similar to those for gastric/duodenal ulcers
 - iii. May progress to ulcer formation
 - c. Mallory-Weiss tear: A longitudinal mucosal laceration in the distal esophagus and proximal stomach (an intramural dissection)
 - i. A sudden increase in intra-abdominal pressure leads to forceful distention of the gastroesophageal junction and a resultant mucosal tear.
 - ii. Typically caused by forceful vomiting
 - d. Less common causes: Vascular malformation, malignant formations, aortoenteric fistulas, gastric antral vascular ectasia, and prolapse gastropathy
2. Variceal hemorrhage
 - a. Relatively few severe cases of UGIB are secondary to variceal hemorrhage (about 5%), but variceal hemorrhage is associated with a high mortality rate (about 20% at 6 weeks).
 - b. Portal hypertension caused by the obstruction of venous blood flow through the cirrhotic liver leads to increased pressure in the portal vein and causes the redirection of blood flow to other areas of the body.
 - c. Varices may be present in any portion of the GI tract, but they are most common in the esophagus and stomach.
 - d. Gastroesophageal varices are present in about 50% of patients with cirrhosis. About 12% of patients with varices will develop variceal hemorrhage within 1 year of diagnosis, and the recurrence rate for variceal hemorrhage within 1 year is about 60%.

C. Initial Assessment and Risk Stratification

1. Most patients (50%) present with both melena and hematemesis; 30% have hematemesis (either red blood or “coffee-ground” emesis) alone, and 20% have melena alone.
2. Hematochezia (bright red blood per rectum) may also be present (in about 5% of patients), which may represent a swift UGIB (about 1 L of blood is needed in the stomach to cause hematochezia, whereas only 50–100 mL is needed to cause melena).
3. Bleeding ulcers may result in right upper quadrant pain; Mallory-Weiss tears may present as emesis, retching, or coughing before hematemesis; and patients with symptoms associated with chronic liver disease will likely have variceal bleeding.
4. Hemodynamic instability may be present in patients with significant hypovolemia. Initial care of these patients should focus on patient stabilization.

5. Insertion of an NG tube and inspection of the aspirate may be useful for patients without frank hematemesis.
 - a. If the aspirate contains bright red blood, urgent endoscopy is likely indicated.
 - b. A normal-appearing aspirate does not rule out UGIB because about 15% of patients with a normal aspirate have high-risk lesions on endoscopy.
 - c. Insertion of an NG tube may be contraindicated in patients with a history of varices, particularly those with recent endoscopic band ligation.
6. Scoring tools may help in patient risk stratification, which can aid in site of care and endoscopy timing decisions.
 - a. The Blatchford scoring system uses clinical and laboratory parameters to predict the need for clinical intervention.
 - b. The Rockall scoring system incorporates endoscopic findings and predicts a patient's risk of rebleeding and death.

D. Management

1. General measures
 - a. Venous access with two large-caliber (at least 16 gauge) peripheral intravenous catheters should be achieved. Access by peripheral intravenous catheters is preferred to central venous catheterization because of their improved ability to deliver intravenous fluids more quickly (because of the Poiseuille law).
 - b. Supplemental oxygen by nasal cannula should be administered to patients with an oxygen saturation below 90%.
 - c. A blood type and cross-match should be sent immediately (in preparation for possible blood transfusion).
2. Hemodynamically unstable patients should be resuscitated immediately with intravenous fluids (with crystalloids) and blood transfusions (if indicated).
 - a. A study of patients with hemodynamic instability secondary to UGIB compared usual care with intensive resuscitation focused on achieving hemodynamic stability, a hematocrit greater than 28%, and an INR less than 1.8. Intensive resuscitation was associated with a lower mortality rate (2.8% vs. 11.1%, $p=0.04$) and a lower incidence of myocardial infarction (5.6% vs. 13.9%, $p=0.04$).
 - b. See the Shock Syndromes and Sepsis chapter for further discussion of hypovolemic shock secondary to hemorrhage.
3. Transfusion
 - a. Packed red blood cell transfusion should be administered if a patient's hemoglobin is below 7 g/dL. In acute UGIB, a restrictive transfusion threshold (hemoglobin less than 7 g/dL), compared with a liberal transfusion threshold (hemoglobin less than 9 g/dL), was associated with higher 6-week survival rates (95% vs. 91%, hazard ratio [HR] 0.55 [95% CI, 0.33–0.92; $p=0.02$]), lower rates of further bleeding (10% vs. 16%, $p=0.01$), and lower rates of adverse effects (40% vs. 48%, $p=0.02$). Notable limitations: Single-center, exclusion of patients with acute coronary syndrome, and unique processes of care
 - b. Patients with an elevated INR (typically greater than 1.5) should receive fresh frozen plasma or vitamin K (if warfarin related). Reversal of target-specific oral anticoagulants is discussed in the Shock Syndromes and Sepsis chapter.
 - c. Platelet transfusion, typically if the platelet count is less than $50,000/\text{mm}^3$, should be considered.
4. Endoscopy
 - a. Diagnostic endoscopy
 - i. Used to diagnose and assess the risk posed by the bleeding lesion(s). Therapeutic endoscopy may also be used for the lesion(s) to reduce the risk of bleeding recurrence (discussed later in the chapter).

- ii. Patients with UGIB should generally have a diagnostic endoscopy within 24 hours.
- iii. Patients who are hemodynamically unstable and those with a suspected variceal UGIB should have a diagnostic endoscopy as soon as possible and no later than 12 hours after presentation.
- iv. Prokinetic therapy should be considered before endoscopy. Erythromycin or metoclopramide may be used when a large amount of blood in the stomach would hinder an endoscopy. Use reduces the need for repeated endoscopy (OR 0.55; 95% CI, 0.32–0.94) but does not alter the need for blood products, length of hospital stay, or need for surgery.
- v. Endotracheal intubation before endoscopy may be indicated to prevent aspiration, but patient selection is controversial.
- vi. Endoscopic findings predict the risk of rebleeding and guide further therapies.
 - (a) Nonvariceal UGIB: Stigmata of recent hemorrhage from a peptic ulcer predict the risk of further bleeding and guide management decisions (Table 6).

Table 6. Endoscopic Findings of Bleeding Peptic Ulcers, Prevalence, and Rebleeding Rate

Risk of Rebleeding	Stigmata of Recent Hemorrhage	Forrest Grade	Prevalence	Rebleeding Rate
High	Active spurting bleeding	IA	9.3% (spurting and oozing)	55% (spurting and oozing)
	Active oozing bleeding	IB		
	Nonbleeding visible vessel	IIA	6.1%	43%
	Adherent clot	IIB	6.5%	22%
Low	Flat pigmented spot	IIC	13.1%	10%
	Clean base	III	52.6%	5%

Information from: Laine L, Peterson W. Bleeding peptic ulcer. *N Engl J Med* 1994;331:717-27; Enestvedt BK, Gralnek IM, Mattek N, et al. An evaluation of endoscopic indication and findings related to nonvariceal upper-GI hemorrhage in a large multicenter consortium. *Gastrointest Endosc* 2008;67:422-9; and Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012;107:345-60.

- (b) Variceal UGIB: If active variceal hemorrhage is confirmed, endoscopic and pharmacologic therapy should be initiated.
- b. Therapeutic endoscopy
 - i. Can be used in conjunction with a diagnostic endoscopy to treat the source of UGIB once it has been identified
 - ii. Non-variceal UGIB
 - (a) Peptic ulcer
 - (1) Endoscopic therapy should be used for lesions with active spurting, active oozing, or a non-bleeding visible vessel.
 - (2) Endoscopic therapy for an adherent clot resistant to vigorous irrigation is controversial. Patients with clinical features associated with a higher risk of rebleeding (e.g., older age) may benefit from endoscopic therapy.
 - (3) Endoscopic therapy should not be used for ulcers with a flat pigmented spot or clean base.
 - (4) Endoscopic therapy includes hemostatic clips, epinephrine injection, and thermal therapy. Often, these therapies are combined. Epinephrine injection should not be used alone but should be combined with a second modality.
 - (b) Other findings (e.g., erosions or Mallory-Weiss tear) are typically unamenable to endoscopic therapy.

- iii. Variceal UGIB
 - (a) The primary endoscopic therapy for varices is endoscopic band ligation, which is preferred to sclerotherapy.
 - (b) Sclerotherapy is recommended in patients for whom endoscopic band ligation is unfeasible.
 - (c) Gastric varices are often unamenable to endoscopic band ligation, and rescue therapies may be necessary (discussed later in the chapter).
- 5. Pharmacologic management
 - a. Non-variceal UGIB
 - i. Acid-suppressive therapy is the mainstay of pharmacologic therapy for acute non-variceal UGIB.
 - ii. Gastric acid inhibits platelet aggregation, impairs clot formation, and promotes fibrinolysis; therefore, inhibiting gastric acid and raising the intragastric pH to 6 or higher may promote clot formation and decrease the risk of rebleeding.
 - iii. Histamine-2 receptor antagonists are ineffective at achieving a pH greater than 6; therefore, these agents are not recommended for patients with acute ulcer-related UGIB.
 - iv. Octreotide is not routinely recommended for patients with acute ulcer-related UGIB.
 - v. High-dose PPIs should be used as an adjunct to endoscopic therapy.
 - (a) PPI therapy, with an initial bolus followed by a continuous infusion, should be initiated before endoscopy. In a study of patients admitted for UGIB, omeprazole, compared with placebo, initiated before endoscopy was associated with a lower need for endoscopic therapy (19.1% vs. 28.4%, $p=0.007$) and fewer actively bleeding ulcers (6.4% vs. 14.7%, $p=0.01$). Furthermore, more patients receiving omeprazole had a hospital stay less than 3 days (60.5% vs. 49.2%, $p=0.005$).
 - (b) Patients with high-risk stigmata of recent hemorrhage should have the PPI infusion continued for 72 hours. In patients with high-risk stigmata, intravenous PPI bolus plus infusion therapy, compared with histamine-2 receptor antagonists or placebo, has been associated with reduced rebleeding (OR 0.43; 95% CI, 0.24–0.67), surgery (OR 0.60; 95% CI, 0.37–0.96), and mortality (OR 0.57; 95% CI, 0.34–0.96).
 - (c) Controversy exists regarding intermittent (i.e., twice-daily intravenous push) versus bolus plus continuous infusion PPI administration methods for patients with high-risk stigmata of recent hemorrhage.
 - (1) Current guidelines recommend PPI bolus plus continuous infusion over intermittent therapy because a mortality benefit has been shown with the bolus plus infusion strategy versus alternative therapies (histamine-2 receptor antagonists or placebo). This mortality benefit has not been shown with intermittent therapy.
 - (2) A recent systematic review and meta-analysis of these two approaches determined that intermittent PPI therapy was noninferior to bolus and continuous infusion PPI therapy for rebleeding within 7 days (absolute risk difference -2.64%; upper bound of 1-sided 95% CI, -0.28%; noninferiority margin 3%) and mortality (absolute risk difference -0.74%; upper bound of 1-sided 95% CI, 0.43%). The authors concluded that intermittent PPI therapy should be the administration method of choice and that guidelines should be revised to reflect the study findings.
 - (d) Patients with low-risk stigmata of recent hemorrhage should have the PPI infusion discontinued and enteral daily PPI initiated.

- b. Variceal UGIB
 - i. Octreotide, a somatostatin analog, should be initiated promptly when variceal UGIB is suspected and continued for 3–5 days after the diagnosis is confirmed.
 - (a) Octreotide causes selective splanchnic vasoconstriction through inhibition of the release of vasodilatory peptides (mainly glucagon). Octreotide may also have a local vasoconstrictive effect. Splanchnic vasoconstriction decreases portal inflow, which indirectly reduces variceal blood flow and hemorrhage volume.
 - (b) Typically given as a 50-mcg bolus, followed by a 50-mcg/hour continuous intravenous infusion
 - (c) When used without therapeutic endoscopy, octreotide is only marginally beneficial (reduction of packed red blood transfusion by 0.7 unit with no benefit on rebleeding or mortality).
 - (d) Compared with endoscopic therapy alone, a somatostatin analog combined with endoscopic therapy is associated with improved initial control of bleeding (relative risk [RR] 1.12; 95% CI, 1.02–1.23) and hemostasis at 5 days (RR 1.28; 95% CI, 1.18–1.39) with no difference in mortality or serious adverse events.
 - (e) Patients should be monitored for bradycardia and hyperglycemia during octreotide infusion.
 - ii. Vasopressin infusion is not recommended for variceal UGIB because of the high incidence of adverse events (cardiac, peripheral, and bowel ischemia) with doses necessary to reduce splanchnic blood flow (0.2–0.8 unit/minute).
 - iii. Because of the high incidence of peptic ulcer–related UGIB, a PPI bolus and continuous infusion should be initiated, even when variceal UGIB is suspected, until the diagnosis of variceal UGIB is confirmed.
 - iv. There is no evidence that high-dose PPI therapy reduces the risk of rebleeding after endoscopic therapy for variceal UGIB.
 - c. Patients with cirrhosis, with or without ascites, and UGIB (whether variceal or non-variceal) should be initiated on short-term prophylactic antibiotics.
 - i. Antibiotics are associated with a lower risk of infection and higher survival rates.
 - ii. Guidelines recommend therapy with norfloxacin (which is no longer marketed in the United States) or ciprofloxacin. Ceftriaxone may be preferred to ciprofloxacin in patients with advanced cirrhosis (Child-Pugh class B or C), particularly in centers with a high prevalence of quinolone-resistant organisms.
 - iii. Prophylactic antibiotic therapy should be continued for no more than 7 days.
 - d. Treatment of *H. pylori* infection is beyond the scope of this chapter; however, a 14-day treatment should be given to all patients with suspected or diagnosed infection, and eradication should be confirmed 4 weeks after therapy.
6. Rescue therapies
- a. For patients in whom endoscopic therapy has failed or who are not candidates for endoscopy, angiographic intervention (typically selective arterial embolization) may be required.
 - b. For variceal UGIB, balloon tamponade may be used as a temporizing method (maximum 24 hours) while definitive therapy is planned.
 - c. Transjugular intrahepatic portosystemic shunt is indicated in patients in whom hemorrhage from esophageal varices cannot be controlled or in whom bleeding recurs, despite pharmacologic and endoscopic therapy.

Patient Case

7. A 27-year-old man with a medical history of Crohn disease presents to your ED with frank bloody output from his rectum. The patient has hypotension (systolic blood pressure 85 mm Hg, MAP 58 mm Hg), and an NG lavage reveals “coffee-ground” material. The resident on call is in the process of calling the endoscopy team to help diagnose and intervene on an UGIB with an esophagogastroduodenoscopy. Which statement is most accurate regarding the care of this patient?

- A. An endoscopy is the appropriate course of action and should be completed as soon as possible.
- B. A PPI continuous infusion should be initiated as soon as possible and continued for 72 hours post-endoscopy.
- C. The patient, who likely has a lower GI bleed, would benefit from a colonoscopy as opposed to an esophagogastroduodenoscopy.
- D. An endoscopy and a PPI continuous infusion should be initiated as soon as possible.

E. Resuming Antithrombotic and/or Antiplatelet Therapy After Hemorrhage

1. Patients who do not have a strong indication for continued anticoagulation at the time of the bleeding event should have antithrombotic therapy discontinued.
2. Most patients who develop UGIB while receiving long-term antithrombotic therapy continue to be at risk of thrombosis; these patients should be resumed on antithrombotic therapy.
 - a. In a retrospective cohort study of patients who had a GI hemorrhage during warfarin therapy, those who resumed warfarin within 90 days after the hemorrhagic event had a lower adjusted risk of death (HR 0.31; 95% CI, 0.15–0.62) and thrombosis (HR 0.05; 95% CI, 0.01–0.58), without a significant increase in the risk of recurrent GI hemorrhage (HR 1.32; 95% CI, 0.50–3.57). In this study, warfarin was resumed a median of 4 days (interquartile range 2, 9) after presentation for UGIB. These data suggest that for many patients with warfarin-associated GI hemorrhage, the benefits of resuming warfarin therapy outweigh the risks.
 - b. Antithrombotic therapy should be withheld at minimum until the source of bleeding is found and controlled.
 - c. The patient’s short-term risk of rebleeding should be weighed against the short-term risk of thrombosis when deciding to resume antithrombotic therapy.
 - d. Some experts recommend that warfarin be resumed 4–7 days after presentation for UGIB.
 - e. The risks, benefits, and timing of resuming target-specific oral anticoagulants are unclear.
3. Low-dose aspirin should be resumed in patients who develop ulcer-related UGIB as soon as the risk of cardiovascular complication is thought to outweigh the risk of bleeding. In a small randomized trial, continuation of low-dose aspirin after peptic ulcer–related UGIB was not noninferior to placebo for recurrent bleeding within 30 days (risk difference 4.9%; 95% CI, -3.6% to 13.4%; noninferiority margin 10%) but was associated with a lower mortality rate (risk difference 11.6%; 95% CI, 3.7%–19.5%). These data suggest that low-dose aspirin therapy can be resumed in most patients, with careful monitoring for hemorrhage.

VII. ENDOCRINE EMERGENCIES

A. Epidemiology

1. Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the most common diabetic emergencies.
 - a. DKA accounts for 500,000 hospital days and costs \$2.4 billion per year in the United States.
 - b. Between 1996 and 2006, there was a 35% increase in the incidence of DKA in the United States, with most cases occurring in patients 18–44 years of age.
 - c. Most patients who develop DKA have type 1 diabetes, and DKA is considered the most important contributor to mortality rates in children and adolescents with diabetes.
 - d. Mortality rates for DKA are 1%–5%, depending on age and other comorbidities, and can be as high as 5%–20% for HHS.
2. Hyperglycemia (blood glucose [BG] above 140 mg/dL) occurs commonly in the setting of critical illness, with prevalence rates depending on the level of hyperglycemia and patient population evaluated.
 - a. About 27% of critically ill patients have a BG above 200 mg/dL on ICU admission, and about 90% of patients will have at least one BG reading above 110 mg/dL during their ICU stay.
 - b. Hyperglycemia has consistently been associated with increased mortality in critically ill patients, most notably in patients without diabetes. The link between hyperglycemia and worse outcomes seems strongest for patients with acute coronary syndrome or stroke.
 - c. Glucose variability (BG fluctuation over time) has also been associated with ICU mortality.
3. Hypoglycemia also occurs commonly in the ICU, both with and without intensive glucose control.
 - a. In a large international cohort of patients, moderate hypoglycemia (BG less than 70 mg/dL) occurred in 37% of patients and was independently associated with mortality on multivariable regression (OR 1.78; 95% CI, 1.39–2.27).
 - b. In a secondary analysis of the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, moderate hypoglycemia occurred in 45% of patients (74.2% in the intensive-control group and 15.8% in the conventional-control group), and severe hypoglycemia (BG below 40 mg/dL) occurred in 3.7% of patients (6.9% in the intensive-control group and 0.5% in the conventional-control group). Both moderate and severe hypoglycemia (HR 1.41; 95% CI, 1.21–1.62 and HR 2.10; 95% CI, 1.59–2.77, respectively) were independently associated with death compared with the absence of hypoglycemia.
4. Thyroid crisis, also known as thyroid storm or critical thyrotoxicosis, is an uncommon manifestation of hyperthyroidism known to occur in less than 10% of patients admitted for thyrotoxicosis. Thyrotoxicosis has been associated with mortality rates of 20%–50%, if treated, and up to 100%, if untreated.
5. Myxedema coma is an uncommon severe manifestation of hypothyroidism, with mortality rates of about 20%–25% with appropriate treatment and up to 80% without treatment.
6. Adrenal crisis (i.e., acute adrenal insufficiency or Addisonian crisis) is a life-threatening disorder caused by glucocorticoid (and possibly mineralocorticoid) deficiency.
 - a. Adrenal crisis necessitating hospital admission has an incidence of 3.3 per 100 patient-years in those with chronic adrenal insufficiency.
 - b. Critical illness–related corticosteroid insufficiency (CIRCI) is a separate entity from adrenal crisis. The prevalence of CIRCI is about 10%–20% but depends on the definition used and the population evaluated. Prevalence rates as high as 60% for patients with septic shock have been reported.

B. DKA and HHS**1. Clinical presentation of DKA**

- a. DKA is a combination of hyperglycemia (BG greater than 250 mg/dL), ketosis (positive urine or serum ketones), and acidosis (pH less than 7.30) with a serum bicarbonate less than 18 mmol/L and anion gap greater than 10. Patients with severe DKA present with severe acidemia (pH 7), a serum bicarbonate less than 10 mmol/L, and an anion gap greater than 12 together with depressed mental status (stupor or coma).
- b. A lack of insulin leads to reduced glucose uptake, which, together with increased counterregulatory hormone (catecholamines, cortisol, glucagon, and growth hormone) release, leads to increased lipolysis. The released free fatty acids are metabolized in the liver to ketone bodies (β -hydroxybutyrate and acetoacetate), resulting in ketonemia and elevated anion gap metabolic acidosis.
- c. Although symptoms may exist for a few days, ketoacidosis occurs quickly, and patients may deteriorate rapidly.
- d. Typically occurs in young, leaner patients with type 1 diabetes
- e. Patients may present with symptoms of nausea and vomiting (80% of patients; more indicative of DKA than of HHS), polyuria, polydipsia, weight loss, abdominal pain (30% of patients), and fruity breath from acetone in the blood. Signs of DKA include tachycardia, poor skin turgor, hypotension (because of intravascular volume loss from osmotic diuresis), and Kussmaul respirations (because of severe acidemia).
- f. Serum potassium may be high, given the shift of intracellular potassium to the extracellular space because of the lack of endogenous insulin. However, patients typically have a relative deficiency of total body potassium, which can be worsened with treatment.

2. Clinical presentation of HHS

- a. HHS is similar to DKA and is defined as BG greater than 600 mg/dL and serum osmolality greater than 320 mOsm/L with pH greater than 7.30 and serum bicarbonate greater than 18 mmol/L. Typically, ketonemia or ketonuria is not present (if present, only in small amounts).
- b. HHS presentation is often later in the disease course than DKA (because of the lack of ketosis), and symptoms evolve over days to weeks. Patients also have higher degrees of dehydration owing to osmotic diuresis.
- c. Typically occurs in older patients with obesity with type 2 diabetes
- d. Signs and symptoms, including electrolyte abnormalities, are similar to those in DKA. However, confusion is much more apparent in HHS and is directly related to the serum osmolality.
- e. Patients with HHS do not develop ketoacidosis. Although there is an overall insulin deficiency in both DKA and HHS, there is enough insulin secretion to prevent ketogenesis in patients with HHS.
- f. Lack of access to water, either because of the illness itself or because of an altered thirst response in older adult patients, can worsen the severity of dehydration in the setting of hyperglycemia.

3. Typically, DKA and HHS are caused by an insufficiency of insulin in patients with diabetes combined with another potential trigger such as infection, pancreatitis, and certain drugs (steroids, diuretics, vasopressors, antipsychotics, cocaine).**4. Management**

- a. Typically involves fluid resuscitation, correction of hyperglycemia, and electrolyte (mainly potassium) replacement. Correction of acidemia may also be indicated.
- b. Patients are often profoundly hypovolemic. Total body water deficits may be as high as 10–12 L and should be replaced within the first 24 hours.
 - i. In the absence of concomitant cardiogenic shock, 0.9% sodium chloride should be administered at a rate of 15–20 mL/kg (typically 1–1.5 L) for the first hour. Thereafter, fluid administration is titrated to hemodynamic parameters and urine output (typically 250–500 mL/hour).

- ii. Patients with mild dehydration and normal or high sodium concentrations can be changed to 0.45% sodium chloride infused at a rate of 250–500 mL/hour.
- iii. Maintenance fluids can be switched to a dextrose-containing fluid (often 5% dextrose with 0.45% sodium chloride) once BG concentrations have dropped to less than 200 mg/dL in DKA and less than 300 mg/dL in HHS.
- c. Insulin therapy is the main treatment modality of DKA and HHS.
 - i. Insulin corrects hyperglycemia and inhibits the release of free fatty acids, which decreases ketone formation and corrects acidosis.
 - ii. Intravenous regular insulin is preferred to subcutaneous insulin because of its short half-life and ease of titration.
 - iii. Initiate with a 0.1-unit/kg intravenous bolus, followed by a 0.1-unit/kg/hour continuous infusion. An alternative approach, without an initial bolus but initiated at a higher continuous infusion rate (0.14 unit/kg/hour), provides a time similar to DKA resolution.
 - iv. The insulin infusion should subsequently be titrated on an hourly basis to decrease BG concentrations by 50–75 mg/dL/hour.
 - v. DKA: Decrease dose to 0.02–0.05 unit/kg/hour once BG concentrations drop to 200 mg/dL, and maintain a BG of 150–200 mg/dL until ketoacidosis has resolved.
 - vi. HHS: Decrease dose to 0.02–0.05 unit/kg/hour once BG concentrations drop to 300 mg/dL, and maintain a BG of 200–300 mg/dL until mental status changes have resolved.
 - vii. Continuous insulin infusions should be continued until ketoacidosis resolves in DKA and abnormal serum osmolality and mental status in HHS resolve; then, change to subcutaneous insulin.
 - (a) Doses of 0.5–0.8 units/kg of subcutaneous insulin per day can be used.
 - (b) Electrolyte replacement: Potassium, phosphate, and bicarbonate should be monitored closely and repleted as needed (replete bicarbonate only if pH is less than 6.9).
- d. Potassium should be replaced aggressively (assuming adequate renal function) with a goal serum potassium of 4–5 mEq/L.
 - i. Patients with initial serum potassium less than 3.3 mEq/L should have insulin withheld and potassium administered until their serum potassium is above 3.3 mEq/L.
 - ii. Patients with serum potassium of 3.3–5.2 mEq/L should have 20–30 mEq of potassium added to each liter of intravenous fluid administered.
 - iii. Patients with initial serum potassium greater than 5.2 mEq/L should not receive potassium, but they should be monitored closely (with potassium administered if the patient's serum falls below 4 mEq/L). Of importance, patients with DKA and initial hyperkalemia should not receive therapy directed toward total body potassium removal (e.g., sodium polystyrene sulfonate or furosemide). The patient's serum potassium will typically decrease as insulin is administered.
- e. Intravenous sodium bicarbonate should not be administered routinely.
 - i. Acidemia will typically quickly correct as ketosis is resolved, and bicarbonate may have deleterious effects (e.g., hypokalemia).
 - ii. Studies of patients with DKA with a pH of 6.9 or greater have not supported a benefit with sodium bicarbonate administration.
 - iii. If a patient's pH is below 6.9, sodium bicarbonate should be administered.
 - (a) Prospective studies of this patient population have not been reported, and this level of acidemia may lead to severe sequelae.
 - (b) Guidelines recommend that 100 mEq of sodium bicarbonate be placed in 400 mL of sterile water with 20 mEq of potassium chloride, administered at a rate of 200 mL/hour. The infusion should be discontinued if the patient's pH is above 7.
- f. Phosphorus repletion should be initiated in patients with serum phosphate below 1 mg/dL or in those with severe cardiac or respiratory dysfunction associated with hypophosphatemia.

C. Hyperglycemia

1. Clinical presentation

- a. Because hyperglycemia is so prevalent in critically ill patients, there is no specific clinical presentation.
- b. Critically ill patients often do not have the “classic triad” of diabetes symptoms of polyuria, polydipsia, and polyphagia.
- c. Stress-induced hyperglycemia has been associated with illness severity.

2. Causes

- a. Critically ill patients have increased release of “stress hormones” (e.g., cortisol and epinephrine) and cytokines. These responses lead to both increased glucose production and insulin resistance, which results in hyperglycemia.
- b. Hyperglycemia is further exacerbated by infusions of dextrose-containing fluids, corticosteroids, and exogenous sympathomimetic medication administration.

3. Management

- a. Hyperglycemia was once considered a beneficial adaptive response in the critically ill population and was not considered a treatment priority. In general, BG was only treated if it exceeded 200 mg/dL.
- b. Tighter glucose control garnered increased interest because hyperglycemia has independently been associated with increased ICU mortality.
- c. A treatment paradigm shift occurred in 2001 with the publication of the landmark “intensive insulin therapy” study.
 - i. In this single-center study, surgical ICU patients who were receiving parenteral nutrition were randomized to intensive intravenous insulin therapy (goal BG 80–110 mg/dL) or conventional insulin therapy (goal BG 180–200 mg/dL).
 - ii. Patients randomized to intensive insulin therapy had a significantly lower ICU mortality rate than did patients receiving conventional insulin therapy (4.6% vs. 8.0%, $p<0.04$). The ICU mortality benefit was most pronounced in patients who stayed in the ICU (and received intensive insulin therapy) for greater than 5 days (10.6% vs. 20.2%, $p=0.005$).
 - iii. Patients randomized to intensive insulin therapy also less commonly developed bloodstream infections, acute kidney injury, and ICU-acquired weakness (at the time termed *critical-illness polyneuropathy*).
 - iv. A study of medical ICU patients with an identical design from the same center was published in 2006. The study detected no in-hospital mortality benefit with intensive insulin therapy (37.3% vs. 40.0% with conventional insulin therapy, $p=0.33$). Patients in the intensive insulin therapy arm less commonly developed acute kidney injury, had a shorter time to liberation from mechanical ventilation, and had earlier discharge from the ICU and hospital. For patients who stayed in the ICU for 3 days or more, in-hospital mortality was lower in the intensive insulin therapy arm (43.0% vs. 52.5%, $p=0.009$), but the validity of this subgroup analysis has been called into question because patients were not defined by a baseline characteristic.
 - v. In light of these findings, intensive insulin therapy was widely recommended by treatment guidelines (including the 2008 Surviving Sepsis Campaign guidelines) and often implemented into practice as a standard of care.
- d. Multicenter trials have not confirmed the mortality benefit of intensive insulin therapy.
 - i. Because of concern with the single-center nature of the aforementioned studies, unblinded design, and large relative mortality benefit, three multicenter trials were designed and conducted.
 - ii. One multicenter study was terminated early because of safety concerns. Patients randomized to intensive insulin therapy more commonly developed severe hypoglycemia (BG of 40 mg/dL or less) than those allocated to conventional insulin therapy (17.0% vs. 4.1%, $p<0.001$). Intensive insulin therapy was not associated with a benefit in 28-day mortality (24.7% vs. 26.0%, $p=0.74$), but the study was inadequately powered to assess this outcome.

- iii. A second multicenter study was terminated early because of several protocol violations. Intensive insulin therapy was not associated with a benefit in ICU mortality (17.2% vs. 15.3%, $p=0.41$), but patients allocated to intensive insulin therapy more commonly developed severe hypoglycemia (BG of 40 mg/dL or less; 8.7% vs. 2.7%, $p<0.0001$).
- iv. The largest multicenter study, NICE-SUGAR, evaluated intensive insulin therapy (target BG 81–108 mg/dL) or conventional glucose control (BG of 180 mg/dL or less) in more than 3000 patients.
 - (a) At 90 days, intensive insulin therapy was associated with increased mortality (27.5% vs. 24.9%, $p=0.02$).
 - (b) Severe hypoglycemia (BG of 40 mg/dL or less) was more common in patients allocated to intensive insulin therapy (6.8% vs. 0.5%, $p<0.0001$).
 - (c) Intensive insulin therapy was not associated with a benefit in ICU or hospital length of stay, days of mechanical ventilation, or need for renal replacement therapy.
- e. A meta-analysis that included seven randomized controlled trials and 11,425 patients found that intensive insulin therapy was not associated with a difference in 28-day mortality (OR 1.04; 95% CI, 0.93–1.17) but was associated with a significant increase in the incidence of hypoglycemia (OR 7.7; 95% CI, 6.0–9.9).
- f. Clinical practice guidelines from the American College of Critical Care Medicine regarding insulin infusions for the management of hyperglycemia recommend the following.
 - i. A BG of 150 mg/dL or greater should trigger initiation of an intravenous insulin infusion, which should be titrated by protocol to keep BG less than 150 mg/dL for most adult ICU patients and absolutely less than 180 mg/dL.
 - ii. Cardiac surgery and adult trauma patients should have a BG target less than 150 mg/dL.
 - iii. Patients who are admitted with a diagnosis of ischemic stroke, intraparenchymal hemorrhage, aneurysmal subarachnoid hemorrhage, or traumatic brain injury should have BG values absolutely less than 180 mg/dL, with avoidance of BG values less than 100 mg/dL.
 - iv. The insulin infusion protocol should achieve a low rate of hypoglycemia (BG less than 70 mg/dL).
 - v. BG should be monitored every 1–2 hours but may be liberalized to no less often than every 4 hours given the stability of BG values within the target range for an individual patient, or if the protocol has been shown to lead to a low frequency of hypoglycemia.
 - vi. Subcutaneous insulin may be used for select ICU patients.
 - vii. Stable ICU patients should be transitioned to subcutaneous basal/bolus insulin therapy before the intravenous insulin infusion is discontinued.

D. Hypoglycemia

1. Clinical presentation

- a. Glucose is an obligate molecule for brain function.
- b. Because the brain cannot produce glucose, hypoglycemia leads to counterregulatory hormonal changes to correct the fall in BG. These complex changes are multifaceted and include pancreatic (decreased insulin and increased glucagon), central nervous system (CNS) (increased norepinephrine and acetylcholine), adrenal medulla (increased epinephrine), and liver (increased glycogenolysis and gluconeogenesis) involvement.
- c. In the early stages of hypoglycemia, symptoms such as sweating, anxiety, hunger, palpitations, tremor, and arousal are present. As hypoglycemia persists and worsens, confusion, dizziness, and difficulty speaking develop. Severe hypoglycemia leads to seizures and hypoglycemic coma.
- d. Typically, complete recovery of symptoms occurs with glucose administration, but permanent brain damage may occur in patients with severe prolonged hypoglycemia.

- e. Hypoglycemia, a reversible cause of cardiac arrest, should be considered for patients with an unclear reason for cardiac arrest.
 - f. Neurologic symptoms of hypoglycemia may be masked by sedation, and the counterregulatory response may be impaired or masked (e.g., in circulatory shock).
2. Causes
- a. Hypoglycemia can be caused by excessive insulin administration, reduced intake of glucose (rarely the cause of severe hypoglycemia in the absence of insulin administration), decreased insulin resistance (weight loss, adrenal or pituitary insufficiency), decreased clearance of insulin (renal or hepatic insufficiency), or other drugs (commonly sulfonylureas, meglitinides, and ethanol; possibly pentamidine, quinine, quinolones, insulin-like growth factor 1, β -blockers, or ACE inhibitors).
 - b. In a retrospective cohort study of mixed ICU patients, independent predictors of hypoglycemia (BG less than 45 mg/dL) included continuous venovenous hemofiltration with bicarbonate-based replacement solution (OR 14; 95% CI, 1.8–106), a decrease of nutrition without adjustment for insulin infusion (OR 6.6; 95% CI, 1.9–23), diabetes mellitus (OR 2.6; 95% CI, 1.5–4.7), insulin use (OR 5.3; 95% CI, 2.8–11), sepsis (OR 2.2; 95% CI, 1.2–4.1), and inotropic support (OR 1.8; 95% CI, 1.1–2.9).
 - c. Other studies of critically ill patients have identified renal insufficiency, diabetes, mechanical ventilation, female sex, greater severity of illness, longer ICU stay, liver disease, immunocompromised state, and medical or nonelective admission as risk factors for hypoglycemia.
 - d. Renal insufficiency in the setting of insulin administration should be particularly noted because patients with renal failure have decreased clearance of insulin, which may prolong the duration of hypoglycemia.
3. Management
- a. For conscious patients without severe symptoms, oral glucose should be ingested (milk, juice, or dextrose tablets).
 - i. The typical initial glucose dose is 20 g, which should be repeated in 15–20 minutes if symptoms have not improved or if BG remains low.
 - ii. Because the response to this “rescue glucose” is transient (less than 2 hours), it should be followed by more substantial glucose intake as a snack or meal.
 - b. Parenteral therapy is necessary for patients unable to take glucose orally or hospitalized patients with moderate or severe hypoglycemia.
 - i. Glucagon (typical dose 1 mg) promotes hepatic glucogenesis and glycogenolysis. It is a useful therapy for patients with type 1 diabetes (often outside a health care setting) and those without diabetes, but it is less useful in patients with type 2 diabetes because it stimulates insulin secretion and glycogenolysis.
 - ii. Hospitalized patients with severe hypoglycemia (either severe symptoms or BG less than 40 mg/dL) or those receiving an insulin infusion with BG less than 70 mg/dL (less than 100 mg/dL in neurologic injured patients) should be treated with intravenous dextrose.
 - (a) Insulin infusion should be discontinued, as appropriate.
 - (b) Administer 10–20 g of 50% dextrose solution (20–40 mL of 50% dextrose in water).
 - (c) The BG measurement should be repeated in 15 minutes, with additional dextrose doses administered to achieve a BG greater than 70 mg/dL.
 - (d) Care should be taken to avoid excessive dextrose administration in order to avoid iatrogenic hyperglycemia and because glucose variability has been associated with adverse outcomes.

E. Thyroid Crisis

1. Clinical presentation

- Typically occurs in a patient with undiagnosed or inadequately treated hyperthyroidism who has a precipitating event such as trauma, infection, or surgery
- Fever (temperature greater than 38.5°C) is the principal symptom, and significant tachycardia is often present.
- Cardiac arrhythmias (e.g., atrial fibrillation), heart failure, and myocardial ischemia often accompany thyroid crisis.
- Tachypnea, nausea and vomiting, diarrhea, mental status changes (psychosis or coma), and hemodynamic instability may also occur.
- Serum TSH is often below the detectable range, and free T₃ and total and free T₄ will be elevated. Other laboratory abnormalities may include hyperglycemia (because of catecholamine-induced glycolysis), leukocytosis, hypercalcemia, and elevated liver function tests.
- Typically, the diagnosis of thyroid crisis must be based on suggestive but nonspecific clinical findings.
- Thyroid function tests do not reliably differentiate patients with thyroid crisis from those with uncomplicated thyrotoxicosis.
- The Burch and Wartofsky criteria (see Table 7) have been used to help identify a potential thyroid storm.

Table 7. Burch and Wartofsky Criteria for Thyroid Storm

Criteria	Points
Temperature (°F)	
• 99–99.9	5
• 100–100.9	10
• 101–101.9	15
• 102–102.9	20
• 103–103.9	25
• ≥ 104	30
Heart rate (beats/minute)	
• 99–109	5
• 110–119	10
• 120–129	15
• 130–139	20
• ≥ 140	25
Atrial fibrillation	
• Absent	0
• Present	10
Congestive heart failure	
• Absent	0
• Mild (edema)	5
• Moderate (rales)	10
• Severe (pulmonary edema)	20
GI signs	
• Absent	0
• Moderate (nausea, vomiting, diarrhea, abdominal pain)	10
• Severe (jaundice)	20

Table 7. Burch and Wartofsky Criteria for Thyroid Storm (*continued*)

Criteria	Points
CNS disturbance	
• Absent	0
• Mild (agitation)	10
• Moderate (delirium, psychosis, extreme lethargy)	20
• Severe (seizure, coma)	30
Precipitant history	
• Positive	0
• Negative	10
Score	
• > 45: Thyroid storm	
• 25–44: Suggestive/impending storm	
• < 25: Storm unlikely	

Information from: Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid* 2011;21:593-646.

2. Causes
 - a. Although a history of hyperthyroidism is common, hyperthyroidism by itself does not typically cause thyroid storm; the illness is typically aggravated by a severe external trigger or abrupt discontinuation of antithyroid drugs.
 - b. In some cases, thyroid storm is the initial presentation for patients with undiagnosed hyperthyroidism.
 - c. Sepsis and infection are leading exacerbating causes of thyroid storm.
 - d. Radioiodine therapy for severe hyperthyroidism may occasionally precipitate thyroid crisis.
3. Management: The treatment goals for thyroid crisis and the specific therapies are as follows (initiated simultaneously).
 - a. Decrease thyroid hormone synthesis.
 - i. Propylthiouracil is preferred to methimazole for the treatment of thyroid storm because it can decrease the peripheral conversion of T_4 to T_3 . Propylthiouracil is also preferred to methimazole in pregnant or lactating women.
 - ii. However, no data show the superiority of propylthiouracil to methimazole for the treatment of thyroid storm.
 - iii. Typical propylthiouracil dose: 200–300 mg every 4–6 hours. The dose may be administered by the enteral or rectal route.
 - iv. Propylthiouracil has been associated with agranulocytosis, allergic hepatitis, and vasculitis; these should be included as part of the monitoring plan for a patient initiated on this therapy.
 - v. If methimazole must be initiated because of allergy or intolerance to propylthiouracil or adverse events, it is typically dosed at 20–30 mg every 8 hours. Methimazole may also be administered by the enteral or rectal route.
 - b. Inhibit thyroid hormone release with inorganic iodine.
 - i. Administration of inorganic iodine leads to a rapid decrease in both T_4 and T_3 .
 - ii. These therapies should be initiated at least 1 hour after the first dose of propylthiouracil or methimazole to reduce the risk of providing more substrate for thyroid hormone production.
 - iii. Typically, oral potassium iodide (“Lugol solution”) is administered as 5 drops four times daily.
 - iv. Alternatively, sodium iodide may be administered as a 1-g infusion over 24 hours.

- c. Reduce heart rate (block the effects of circulating T_4 and T_3).
 - i. Because cardiovascular collapse leads to systemic decompensation, β -blockers should be initiated as quickly as possible.
 - ii. The β -blocker dose should be titrated to achieve heart rate control (typically below 90 beats/minute).
 - iii. Traditionally, propranolol is the preferred therapy because it may block T_4 to T_3 conversion at high doses. The initial propranolol dose is 60 mg orally every 4 hours (with an optional initial loading dose of 80 mg).
 - iv. Alternative agents include metoprolol, esmolol, and diltiazem. Diltiazem should be reserved for patients with active bronchospasm or for those who do not tolerate β -blockers.
- d. Support circulation.
 - i. Patients should be provided with aggressive fluid resuscitation until they are no longer fluid responsive.
 - ii. Intravenous steroids (dexamethasone 2–4 mg intravenously every 6 hours or hydrocortisone 100 mg intravenously every 6–8 hours) block the conversion of T_4 to T_3 and can improve patient outcomes.
 - iii. Targeted temperature management (with surface cooling methods) to prevent fever will decrease tissue oxygen demand.
- e. Treat precipitating cause. Salicylates should be avoided in thyroid storm because use can decrease binding of thyroid hormones to proteins and therefore increase the concentrations of free thyroid hormones.

F. Myxedema Coma

1. Clinical presentation

- a. Patients with myxedema coma present with an acute change in mental status and hypothermia. No absolute diagnostic criteria distinguish myxedema coma from severe hypothyroidism. Nonspecific symptoms may predominate, often making the diagnosis difficult. Identifying the telltale signs of hypothyroidism is key to appropriate diagnosis in a timely manner.
- b. Signs of depressed metabolic activity, as evidenced by severe hypothermia, mental status changes (somnolence or coma), hemodynamic compromise (bradycardia and hypotension), respiratory acidosis, and pericardial effusions, are associated with myxedema coma.
- c. Patients may present with shock and arrhythmias; evidence suggests that a prolongation of the QT interval occurs that can lead to torsades de pointes.
- d. If a patient presents with signs of infection without the typical systemic inflammatory response syndrome (absence of fever or tachycardia), myxedema coma should be suspected.
- e. Typically, patients have elevated TSH and markedly decreased or undetectably low T_3 and T_4 , but the level of change in thyroid hormones does not correlate well with the severity of the clinical presentation.
- f. An inappropriately low TSH may be observed if hypothyroidism is caused by TSH deficiency (e.g., secondary hypothyroidism in patients with panhypopituitarism).
- g. Myxedema coma is more common in older women and occurs commonly during winter months because of altered temperature regulation.
- h. Discussion of nonthyroidal illness syndrome (“euthyroid sick syndrome” or “SICU thyroid”) is beyond the scope of this chapter.

2. Causes

- a. Myxedema coma may present as the first symptom of new hypothyroidism. Often, the presentation is triggered by cold exposure, infection, trauma, or surgery requiring anesthesia.

- b. Infection is a common precipitator of myxedema coma, and all patients with suspected myxedema coma should have an extensive workup for an underlying infection.
 - c. Medications (e.g., sedatives, anesthetics, narcotics, amiodarone, or lithium) or changes to levothyroxine therapy (or abrupt discontinuation) can precipitate myxedema coma.
3. Management
- a. General treatment measures include rewarming of the patient and treatment of the precipitating illness.
 - b. Guidelines from the American Thyroid Association recommend the following for patients with myxedema coma.
 - i. Because patients may have an underlying adrenocorticotrophic hormone deficiency and restoration of thyroid hormone can accelerate cortisol metabolism, empiric intravenous corticosteroids at doses appropriate for the stressed state should be given before levothyroxine administration (strong recommendation). Typically, hydrocortisone 200–300 mg daily (50 mg every 6 hours or 100 mg every 8 hours) is given.
 - ii. Initial thyroid hormone replacement with intravenous levothyroxine. A loading dose of 200–400 mcg should be given, with doses on the lower end of the range if the patient is smaller, is older in age, or has a history of cardiac disease or arrhythmia (strong recommendation).
 - iii. Daily replacement dose of intravenous levothyroxine of 1.6 mcg/kg/day after the initial loading dose (strong recommendation). Daily therapy may be changed to the enteral route after the patient improves clinically.
 - iv. Given that T_4 to T_3 conversion may be decreased in myxedema coma, intravenous liothyronine may be given in addition to levothyroxine (weak recommendation). High doses should be avoided, given the association between high serum T_3 during treatment with liothyronine and mortality. A loading dose of 5–20 mcg can be given, followed by a maintenance dose of 2.5–10 mcg every 8 hours, with lower doses selected if the patient is smaller, is older in age, or has a history of cardiac disease or arrhythmia. Intravenous liothyronine can continue until the patient is clearly recovering (e.g., until the patient regains consciousness and clinical parameters have improved).
 - v. The therapeutic end points of myxedema coma should be improved mental status, improved cardiac function, and improved pulmonary function. Optimal concentrations of TSH, T_4 , and T_3 are not well defined, but failure of TSH to trend down or for T_4 and T_3 concentrations to improve could be considered indications to increase levothyroxine therapy and/or add liothyronine therapy. High serum T_3 could be considered an indication to decrease therapy, given safety concerns (weak recommendation).
 - c. Patients may need supportive care with vasoactive medications. Typically, a catecholamine agent with β_1 -adrenergic receptor agonist properties (epinephrine or dopamine) is preferred to increase the patient's heart rate and blood pressure.

Patient Case

8. A 23-year-old man (weight 80 kg) presents to the ED with an acute mental status change and a core body temperature of 94°F (34.4°C). He has a history of hypothyroidism, but according to his family, he had decided to stop taking all of his thyroid medications 1 week earlier. The team has given him a diagnosis of myxedema coma. Which is the most appropriate treatment option for this patient?
- A. Intravenous levothyroxine 400 mcg × 1 followed by 125 mcg daily.
 - B. An insulin infusion titrated to a BG of 140–180 mg/dL.
 - C. Propylthiouracil 200 mg every 4 hours.
 - D. Propranolol 60 mg orally every 4 hours.

G. Adrenal Crisis**1. Clinical presentation**

- a. Patients with acute adrenal insufficiency typically present with severe hypotension, altered mental status, acute abdominal pain, vomiting, and fever. As such, patients often receive a misdiagnosis of an acute abdomen.
- b. Accompanying symptoms may include fatigue, lethargy, confusion, weakness, and pain in the muscles or joints. Patients with primary adrenal insufficiency may also have salt craving (because of mineralocorticoid deficiency secondary to a lack of aldosterone).
- c. Characteristic skin hyperpigmentation from primary adrenal insufficiency may also be present.
- d. Adrenal crisis is a rare cause of vasodilatory shock.
- e. Laboratory findings will include low serum cortisol (below 18 mcg/dL in an acutely stressed patient is suggestive of adrenal insufficiency); hyponatremia, hyperkalemia, hypoglycemia, and normocytic anemia may also be present.
- f. CIRCI is a complication of an underlying disease. Most commonly, patients have septic shock, but severe respiratory diseases (e.g., acute respiratory distress syndrome) may also be present. Patients with CIRCI often have hypotension refractory to fluids that requires vasopressors. Laboratory assessment may show hypoglycemia and eosinophilia; hyponatremia and hyperkalemia are uncommon.
 - i. Historically, CIRCI was diagnosed according to either a low serum cortisol concentration or an inadequate increase in cortisol after a cosyntropin stimulation test. These tests have significant limitations in critically ill patients, such as poor reproducibility of the cosyntropin stimulation test and lack of agreement of commercially available cortisol assays with analytic standards.
 - ii. Despite these limitations, an increase in cortisol after a cosyntropin stimulation test less than 9 mg/dL is the best predictor of adrenal insufficiency (as determined by metyrapone testing in patients with severe sepsis/septic shock). A serum cortisol value less than 10 mg/dL has a high positive predictive value for adrenal insufficiency but a low sensitivity.
 - iii. Corticosteroids should only be given for patients with septic shock and suspected CIRCI who do not achieve resuscitation goals despite fluid administration and vasopressors.
 - iv. Of importance, clinical practice guidelines for the treatment of CIRCI recommend against using cortisol-based testing in determining a patient's candidacy for corticosteroid therapy. As such, using cortisol assays or a cosyntropin stimulation test to diagnose CIRCI and influence treatment decisions is not recommended.

2. Causes

- a. May result from either primary adrenal failure or secondary adrenal disease because of impairment of the hypothalamic-pituitary axis
- b. Acute-onset primary adrenal insufficiency is usually caused by adrenal hemorrhage or infarction, whereas acute-onset secondary adrenal insufficiency is usually caused by pituitary apoplexy, pituitary or hypothalamic surgery, or traumatic brain injury.
- c. Several medications may contribute to inadequate serum cortisol concentrations, including etomidate and ketoconazole.
- d. Patients receiving corticosteroids who have acute stress (e.g., infection or surgery) will be unable to increase their cortisol appropriately because of suppression of corticotropin-releasing hormone and corticotropin.
- e. An abrupt decrease in dose or cessation of corticosteroids in patients receiving moderate glucocorticoid doses (equivalent to prednisone 7.5 mg daily or above) for 3 weeks or more may precipitate adrenal crisis.
- f. CIRCI is caused by inadequate circulating cortisol concentrations combined with tissue resistance.

3. Management

- a. Acute adrenal crisis
 - i. Patients with acute adrenal crisis should receive intravenous fluids and vasopressors (typically crystalloids and norepinephrine) for the treatment of shock (if present).
 - ii. Corticosteroids should be administered, but the optimal dose is unclear. Typically, intravenous hydrocortisone at 200–300 mg/day (50 mg every 6 hours or 100 mg every 8 hours) is initiated. Some experts have advocated that lower doses are sufficient.
 - iii. After the patient is clearly improved (e.g., shock resolution), the corticosteroid dose can be tapered.
- b. Patients receiving chronic corticosteroids who have an acute stressor should receive an increased glucocorticoid dose (“stress dose”) of corticosteroids to prevent adrenal crisis.
 - i. The corticosteroid dose recommended in this setting depends on the level of stress.
 - ii. In febrile patients, those undergoing major dental procedures, and those undergoing invasive diagnostic procedures (e.g., colonoscopy), a doubling of the maintenance dose for 1–2 days may be sufficient.
 - iii. Patients experiencing severe infection, undergoing major surgery, or presenting with shock should have intravenous hydrocortisone at 200–300 mg/day (50 mg every 6 hours or 100 mg every 8 hours) initiated. This dose should be tapered to the patient’s home regimen after the patient clinically improves or after surgery.
- c. Treatment of CIRCI in the setting of septic shock is discussed in the Shock Syndromes and Sepsis chapter. Use of corticosteroids for the treatment of acute respiratory distress syndrome is discussed in the Pulmonary Diseases chapter.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Intravenous acetylcysteine increases transplant-free survival rates for patients with NAI-ALF, particularly for patients with low-grade encephalopathy, as for this patient. Oral acetylcysteine has not been studied for NAI-ALF (Answer C is incorrect), and the dosing strategy for NAI-ALF is different from the 21-hour intravenous regimen for acetaminophen overdose (Answer A is incorrect). The dosing strategy for NAI-ALF is a 72-hour regimen with a 150-mg/kg bolus, followed by a 12.5-mg/kg/hour dose for 4 hours and then a 6.25-mg/kg/hour dose for 67 hours (Answer B is correct). Oral glutamine is not used for NAI-ALF; it has been studied to aid in the healing of GI fistulas (Answer D is incorrect).

2. Answer: B

Osmotic agents are first-line treatment for control of ICP. Although hypertonic saline prevents ICP elevations, the continuous infusion is not used for acute control (Answer A is incorrect). For acute control of ICP elevations, mannitol boluses are used first line (Answer B is correct). Hyperventilation and barbiturates are only used to control ICP elevations when other options have failed (Answers C and D are incorrect).

3. Answer: C

This patient has severe acute necrotizing pancreatitis because she has not improved after the first 48 hours, and her CT reveals pancreatitis involving more than 30% of her pancreas. There appears to be no benefit with using prophylactic antibiotics for patients with necrotizing AP, in reducing either mortality rates or rates of pancreatic and extrapancreatic infections (Answers A and D are incorrect). Surgical management for sterile necrosis is only recommended if patients have gastric outlet obstruction and/or bile duct obstruction (Answer B is incorrect). For patients with severe acute necrotizing pancreatitis, it is recommended to defer antibiotics unless there is suggestion of infection or if patients have not improved within 7–10 days (Answer C is correct).

4. Answer: D

Somatostatin significantly decreases fistula output compared with placebo (Answer A is incorrect). Total parenteral nutrition increases spontaneous closure rates by reducing GI secretions (Answer C is incorrect), and octreotide had a beneficial effect on fistula output in one

small study (Answer B is incorrect). Although glutamine has been associated with spontaneous rates of fistula closure, it has been not been associated with reduced fistula output (Answer D is correct).

5. Answer: B

Of the possible answers, only alvimopan has been shown to reduce the incidence of ileus postoperatively (Answer B is correct). Metoclopramide has shown mixed results, though the antiemetic properties may be beneficial as adjunctive therapy in POI, and octreotide is not used in the prevention of POI (Answers C and D are incorrect). All opioids can contribute equally to POI (Answer A is incorrect).

6. Answer: A

This patient has seven risk factors for developing PONV (young age, female sex, gynecologic procedure, non-smoker, history of motion sickness, general anesthesia with volatile anesthetics, and perioperative opioids). These risk factors place her at high risk of developing PONV, estimated at greater than 80% (Answers B and D are incorrect). Patients with a high risk of PONV should receive more than two pharmacologic interventions to prevent PONV (Answer A is correct; Answer C is incorrect).

7. Answer: D

Frank bloody output from the rectum is more indicative of a lower GI bleed than an UGIB. However, patients with a brisk UGIB may present with bright red blood per rectum. Although a lower GI bleed is more likely, the patient should be initiated on a PPI infusion and undergo an esophagogastroduodenoscopy as soon as possible (Answer D is correct). The approach of initiating a PPI infusion before endoscopy has been associated with fewer actively bleeding ulcers on endoscopy and more frequent hospital stays less than 3 days. After the esophagogastroduodenoscopy, the patient should have a colonoscopy. The priority in this patient's case is to evaluate for an UGIB because the finding of "coffee-ground" material on NG lavage suggests that the bleeding source is UGIB (Answer C is incorrect). In patients with a suspected UGIB, a PPI infusion should be initiated before endoscopy (Answer A is incorrect) and should only be continued if a high-risk lesion is identified on endoscopy (Answer B is incorrect).

8. Answer: A

The patient, who presented with signs and symptoms of myxedema coma, was given this diagnosis by the treating team. Of the possible answers listed, only levothyroxine is appropriate for the treatment of myxedema coma (Answer A is correct). Insulin, propylthiouracil, and propranolol play no role in the treatment of myxedema coma (Answers B–D are incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

The most recent guidelines from the American Association for the Study of Liver Diseases and the U.S. Acute Liver Failure Study Group define ALF as a coagulopathy, usually an INR of 1.5 or more, with any degree of encephalopathy in patients without preexisting liver disease (Answer C is correct). Although jaundice, thrombocytopenia, and leukocytosis can occur in patients with ALF, they are not currently defined as hallmark signs of the disease that exist in all patients (Answers A, B, and D are incorrect).

2. Answer: A

Administration of acetylcysteine is recommended in all ALF cases when acetaminophen is suspected as a cause, regardless of the acetaminophen concentration (Answer B is incorrect). Although oral and intravenous formulations have efficacy for the treatment of acetaminophen overdose, the intravenous formulation is recommended when patients have greater than grade I encephalopathy or hypotension or when they cannot tolerate oral therapy (Answers C and D are incorrect). Intravenous acetylcysteine is recommended for most patients who present with liver failure and can be extended beyond the 21-hour regimen, especially if therapy was initiated more than 8 hours after ingestion or baseline concentrations were greater than 300 mg/dL (Answer A is correct).

3. Answer: D

Patients with AP should not be kept NPO (Answer A is incorrect). Studies that have compared TPN with enteral feeding in AP have shown that enteral feeding is associated with reduced mortality and infectious complications. Thus, enteral feeding is recommended over TPN for AP, if it is tolerated (Answer B is incorrect). Enteral feeding can be given by either the NJ or the NG route for AP, though the NG route may increase the risk of aspiration. Because this patient has several admissions for aspiration, it is safer to use the NJ route over the NG route; also, there are more data on the NJ route of enteral feeding in AP because it prevents stimulation of pancreatic enzymes (Answer C is incorrect, Answer D is correct).

4. Answer: C

Fistula output is defined as high if the output is greater than 500 mL/day, moderate if it is 200–500 mL/day, and low if it is less than 200 mL/day. This patient's fistula output has decreased significantly (Answers A and D are incorrect) from 570 mL/day to 250 mL/day, but it is still not enough to classify her fistula output as low (Answer B is incorrect). Her output has decreased from high to moderate (Answer C is correct).

5. Answer: B

In a long-term study of alvimopan for opioid-induced bowel dysfunction, alvimopan was associated with higher rates of myocardial infarction than was placebo. To mitigate this risk, the FDA has limited the use of alvimopan to short-term, inpatient use, and patients cannot receive more than 15 doses (Answer B is correct); however, its use is not contraindicated in patients with a history of myocardial infarction (Answer D is incorrect). The FDA-approved dose is 12 mg twice daily, and there is no requirement for QTc monitoring with alvimopan (Answers A and C are incorrect).

6. Answer: D

Dexamethasone and aprepitant should be given before inducing anesthesia for the prevention of PONV (Answers A and C are incorrect). Ondansetron and other serotonin-3 antagonists are most effective if given at the end of surgery (Answer B is incorrect). Droperidol is effective for the prevention of PONV when given at the end of surgery (Answer D is correct).

7. Answer: A

H. pylori is a recognized carcinogen and should be eradicated using a 14-day PPI/antibiotic combination (Answer B is incorrect). Patients with an acute UGIB who present with a high-risk bleed should have a diagnostic and therapeutic endoscopy within 24 hours of admission (Answer C is incorrect). Blood transfusions should be administered to keep the hemoglobin concentration greater than 7 g/dL (Answer D is incorrect). Therefore, the only inappropriate treatment option is using octreotide (Answer A is correct).

8. Answer: B

Thyroid storm is an uncommon but deadly manifestation of hyperthyroidism; therefore, TSH will be low, whereas T_4 and T_3 will be high (Answer B is correct). Myxedema coma is a manifestation of hypothyroidism; therefore, patients will typically have high TSH and low T_4/T_3 . When TSH is high, both T_3 and T_4 are typically low (Answer A is incorrect). Conversely, if TSH is low, both T_3 and T_4 are typically high (Answers C and D are incorrect).

Appendix 1. Most Common or Well-Described Drugs Associated with DILI and the Patterns of Liver Injury

Drug Class	Typical Pattern of Injury
Antibiotics • Amoxicillin/clavulanate • Isoniazid • Trimethoprim/sulfamethoxazole • Fluoroquinolones • Macrolides • Nitrofurantoin • Minocycline	• Cholestatic injury • Hepatocellular injury • Cholestatic injury, can also be hepatocellular injury • Hepatocellular, cholestatic, or mixed injury • Hepatocellular injury • Hepatocellular injury • Hepatocellular injury
Antiepileptics • Phenytoin • Carbamazepine • Lamotrigine • Valproate	• Hepatocellular, cholestatic, or mixed injury • Hepatocellular, cholestatic, or mixed injury • Hepatocellular injury • Hepatocellular injury, may also cause hyperammonemia
Nonsteroidal anti-inflammatory drugs	• Hepatocellular
Immune modulators • Interferon • Anti-TNF agents • Azathioprine	• Hepatocellular injury • Hepatocellular injury • Cholestatic injury, can also be hepatocellular injury
Herbal medications and dietary supplements • Green tea extract • Flavocoxid	• Hepatocellular injury • Hepatocellular, cholestatic, or mixed injury
Miscellaneous • Methotrexate • Allopurinol • Amiodarone • Androgen-containing steroids • Inhaled anesthetics • Sulfasalazine • Proton pump inhibitors	• Fatty liver • Hepatocellular or mixed injury • Hepatocellular, cholestatic, or mixed injury • Cholestatic injury • Hepatocellular injury • Hepatocellular, cholestatic, or mixed injury • Hepatocellular injury

TNF = tumor necrosis factor.

Information from: Chalasani NP, Hayashi PH, Bonkovsky HL, et al. ACG clinical guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol 2014;109:950-66.

SUPPORTIVE AND PREVENTIVE MEDICINE

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Learning Objectives

1. Identify the importance of the key components of intensive care medicine that can be applied to all critically ill patients.
2. Recommend therapeutic options to prevent stress-related mucosal disease.
3. Recommend therapeutic options to prevent venous thromboembolism in a critically ill patient.
4. Discuss therapeutic options for patients with heparin-induced thrombocytopenia.
5. Discuss medications that can be used to provide comfort to a critically ill patient at the end of life.

Abbreviations in This Chapter

aPTT	Activated partial thromboplastin time
CDI	<i>Clostridium difficile</i> infection
DVT	Deep venous thrombosis
H ₂ RA	Histamine-2 receptor antagonist
HIT	Heparin-induced thrombocytopenia
ICU	Intensive care unit
NGT	Nasogastric tube
PF4	Platelet factor 4
PPI	Proton pump inhibitor
SRMD	Stress-related mucosal disease
SUP	Stress ulcer prophylaxis
VTE	Venous thromboembolism

Self-Assessment Questions

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

1. On rounds, you have a “checklist” of interventions that will benefit all critically ill patients in an intensive care unit (ICU). Which interventions would be most effective to implement?
 - A. Initiate stress ulcer prophylaxis (SUP) in patients who are admitted to the ICU, and if appropriate, discontinue sedation.
 - B. Initiate enteral nutrition, when appropriate, and initiate mechanical venous thromboembolism (VTE) prophylaxis.
 - C. If appropriate, initiate sedation interruption, and ensure that patients’ heads are elevated 45 degrees above the bed, if not contraindicated.
 - D. Assess the need for VTE prophylaxis in patients admitted to the ICU, and initiate an insulin infusion to maintain a blood glucose of 120 mg/dL.
2. Regarding pharmacologic prophylaxis for stress-related mucosal injury, which would be the most appropriate statement?
 - A. Sucralfate neutralizes gastric pH.
 - B. Proton pump inhibitors (PPIs) are superior to histamine-2 receptor antagonists (H₂RAs) in preventing clinically significant bleeding.
 - C. Tolerance will occur with continued administration of H₂RAs.
 - D. Antacids are effective when used up to three times daily.
3. A 66-year-old man is admitted to the ICU with abdominal pain, nausea, and altered mental status. He has a history of alcoholic cirrhosis, atrial fibrillation, and erosive esophagitis. He is intubated and stabilized on the ventilator. A nasogastric tube (NGT) is placed, and the patient is tolerating enteral tube feedings. Which would be best to recommend for preventing stress-related bleeding?
 - A. Pantoprazole 40 mg intravenously twice daily.
 - B. Ranitidine 50 mg intravenously three times daily.
 - C. Famotidine 20 mg twice daily by NGT.
 - D. Omeprazole suspension 20 mg once daily by NGT.
4. A 51-year-old woman is admitted to the ICU for hypovolemic shock secondary to severe dehydration. She reports a 5-day history of diarrhea and malaise. She has no recent history of illnesses or contact with health care personnel. Her medical history includes hypothyroidism and gastroesophageal reflux disease. Her medications include levothyroxine 25 mcg orally daily and famotidine 20 mg orally at bedtime. Recently, her primary care physician changed famotidine to omeprazole 20 mg orally at bedtime for increased gastroesophageal reflux disease symptoms. While she is in the ICU, testing for *Clostridium difficile* infection (CDI) comes back positive. Which would be the most appropriate statement regarding PPI use and CDI?
 - A. Sucralfate neutralizes gastric pH.
 - B. Proton pump inhibitors (PPIs) are superior to histamine-2 receptor antagonists (H₂RAs) in preventing clinically significant bleeding.
 - C. Tolerance will occur with continued administration of H₂RAs.
 - D. Antacids are effective when used up to three times daily.

- A. PPIs are a potential risk factor for CDI by producing hypochlorhydria and increasing the host susceptibility to infections.
- B. Prospective randomized controlled trials have shown that the risk of CDI is associated with PPI use.
- C. There is no association between PPI use and CDI risk.
- D. Studies reporting on CDI and PPI use have used the same definition of CDI and implemented the same infection control practices.
5. A 50-year-old woman (weight 70 kg) is admitted to the ICU for worsening mental status. Her medical history is significant for hypertension, tobacco use, and osteoporosis. The next morning, she is intubated and stabilized on a ventilator. An NGT is placed. Her current medications include ceftriaxone 2 g intravenously every 12 hours, vancomycin 1250 mg intravenously every 12 hours, acyclovir 800 mg intravenously every 8 hours, famotidine 20 mg by NGT twice daily, and a bowel regimen. Serum creatinine is normal. Which would be the most appropriate VTE prophylaxis for this patient?
- A. Intermittent pneumatic compression devices.
- B. Enoxaparin 40 mg subcutaneously daily.
- C. Unfractionated heparin continuous infusion to maintain a therapeutic activated partial thromboplastin time (aPTT).
- D. No VTE prophylaxis at this time.
6. A 34-year-old woman (weight 65 kg) is admitted to the ICU with several fractures, a closed-head injury, and a grade 4 liver laceration after sustaining a motor vehicle crash. Her medical history is non-significant. She is admitted to the ICU on a ventilator after surgery. Current laboratory values are as follows: sodium 145 mEq/L, potassium 3.1 mEq/L, chloride 97 mEq/L, carbon dioxide 18 mEq/L, blood urea nitrogen (BUN) 70 mg/dL, and serum creatinine (SCr) 3.5 mg/dL. Which would be the most appropriate VTE prophylaxis on the day of admission for this patient?
- A. Provide intermittent pneumatic compression devices.
- B. Give dalteparin 5000 units subcutaneously daily.
- C. Give fondaparinux 2.5 mg subcutaneously daily.
- D. No VTE prophylaxis is indicated at this time.
7. A 34-year-old man (weight 70 kg) is admitted to the surgical ICU for acute respiratory failure from pancreatitis. He has no pertinent medical history. His current medications include norepinephrine at 0.07 mcg/kg/minute, dexmedetomidine at 0.7 mcg/kg/hour, ampicillin/sulbactam 3 g intravenously every 6 hours, famotidine 20 mg intravenously twice daily, and heparin 5000 units subcutaneously three times daily. On day 3 of his ICU admission, the team suspects heparin-induced thrombocytopenia (HIT). His platelet count was 360,000/mm³ on admission, and today, it is 180,000/mm³. The 4T score is used to determine the probability of HIT. The score is calculated as 3: low risk. The team would like to send the heparin-platelet factor 4 (PF4) immunoassay and initiate argatroban. Which is the most appropriate response?
- A. Discontinue all heparin products, but do not initiate argatroban.
- B. Discontinue all heparin products, and initiate argatroban.
- C. Send the heparin-PF4 immunoassay, and continue low-dose unfractionated heparin until the results come back.
- D. Do not send the heparin-PF4 immunoassay, and continue low-dose unfractionated heparin.
8. Which would be the most important considerations in a critically ill patient approaching the end of life?
- A. Provision of pain management, tight glucose management, and control of secretions.
- B. Provision of routine vital sign checks, discontinuation of unnecessary medications, and control of secretions.
- C. Provision of pain management, control of secretions, and discontinuation of unnecessary medications.
- D. Discontinuation of unnecessary medications, insertion of a Foley catheter, and treatment of nausea and vomiting.

I. KEY ASPECTS IN THE GENERAL CARE OF ALL CRITICALLY ILL PATIENTS

- A. FAST-HUG is a mnemonic emphasizing important aspects of ICU medicine that can be applied at least daily to all critically ill patients to ensure safe, effective, and efficient care (Crit Care Med 2005;33:1225-9).

Table 1. Key Elements of the FAST-HUG Approach

Element	Importance	Considerations
F eeding	Malnutrition can lead to impaired immune function, in turn leading to increased susceptibility to infection, inadequate wound healing, bacterial overgrowth in the GI tract, and increased propensity for decubitus ulcers	Initiate oral or enteral feeding (preferred to parenteral feedings) as soon as possible, typically within the first 24–48 hr after stabilization
A nalgesia	Analgesic and sedative administration optimizes patient comfort and minimizes the acute stress response (hypermetabolism, increased oxygen consumption, hypercoagulability, and alterations in immune function)	- Pain should regularly be assessed with a validated tool such as the BPS or the Critical-Care Pain Observation Tool - Preemptive analgesia should be considered for invasive or potentially painful clinical procedures
S edation		- Sedation should be assessed and reassessed with a validated tool such as the Richmond Agitation-Sedation Scale or the Sedation Agitation Scale - Maintain light levels of sedation - If appropriate, execute daily sedative interruption
T hromboembolic prophylaxis	Most ICU patients carry at least one risk factor for VTE	- Initiate appropriate prophylaxis, considering VTE and bleeding risks - Mechanical prophylaxis (graduated compression stockings or intermittent pneumatic compression devices) is an alternative nonpharmacologic option in patients at high risk of bleeding
H ead of bed elevation	Elevating the head and thorax above bed to a 30–45 degree angle reduces the occurrence of GI reflux and nosocomial pneumonia in patients who are receiving mechanical ventilation	Ensure patient position periodically throughout the day, especially after procedures that require the patient to lie flat

Table 1. Key Elements of the FAST-HUG Approach (*continued*)

Element	Importance	Considerations
Stress <u>U</u> lcer prophylaxis	Critically ill patients develop stress-related mucosal damage, potentially leading to clinically significant bleeding	Consider discontinuing acid-suppressive medications when risk factors are no longer present
<u>G</u> lycemic control	Glycemic control is necessary in critically ill patients to decrease the incidence of complications such as decreased wound healing, increased infection risk, and increased risk of polyneuropathy	Maintaining blood glucose at 140–180 mg/dL should be considered in the acutely ill patient when blood glucose concentrations are ≥ 150 mg/dL

BPS = behavioral pain scale; GI = gastrointestinal; ICU = intensive care unit; VTE = venous thromboembolism.

B. Updated mnemonic: FAST-HUGS BID

1. S = spontaneous breathing trial
2. B = bowel regimen
3. I = indwelling catheter removal
4. D = de-escalation of antimicrobials

C. Daily Checklists

1. Checklists aim to provide a framework of standardization and regulation of interventions in a systematic manner, allowing individuals to assess the presence or absence of the items.
2. Provides structure to important ICU-related interventions in an effort to reduce errors of omission and increase compliance with evidence-based practices to improve outcomes in the ICU patient population (N Engl J Med 2009;360:491-9; N Engl J Med 2006;355:2725-32)

Patient Case

1. A 68-year-old man (weight 85 kg) is admitted to the ICU for management of severe hypoxemic respiratory failure associated with community-acquired pneumonia. He is endotracheally intubated and placed on mechanical ventilation. His medical history consists of Child-Pugh class B cirrhosis secondary to alcohol abuse, heart failure, and myocardial infarction. His laboratory values show a white blood cell count (WBC) of 15×10^3 cells/mm³, platelet count 150,000/mm³, BUN 15 mg/dL, SCr 1.1 mg/dL, potassium 4.5 mEq/L, international normalized ratio (INR) 1.0, aspartate aminotransferase (AST) 58 IU/mL, and alanine aminotransferase (ALT) 49 IU/mL. His current medications include azithromycin 500 mg intravenously daily, ceftriaxone 1 g intravenously daily, vancomycin 1250 mg intravenously every 12 hours, heparin 5000 units subcutaneously every 8 hours, fentanyl drip at 50 mcg/hour, midazolam drip at 1 mg/hour titrated to a Richmond Agitation-Sedation Scale (RASS) of 0 to -1, and a regular insulin drip at 1.5 units/hour titrated to maintain blood glucose 140–180 mg/dL. Currently, on day 3 of his ICU stay, the patient's head is 30 degrees above the bed, his RASS is documented as -4, he is on minimal ventilator settings, and an NGT is placed. As the clinical pharmacist rounding on this patient, you go through the FAST-HUG mnemonic. Which are the best recommendations to make to the team?
 - A. Initiate enteral nutrition by NGT, add SUP, and discontinue fentanyl and midazolam drips.
 - B. Initiate enteral nutrition by NGT, discontinue deep venous thrombosis (DVT) prophylaxis, and transition insulin drip to sliding scale.
 - C. Transition insulin drip to sliding scale, add SUP, and discontinue fentanyl and midazolam drips.
 - D. Discontinue fentanyl and midazolam drips, discontinue DVT prophylaxis, and add SUP.

II. STRESS ULCER PROPHYLAXIS

A. Epidemiology of Stress-Related Mucosal Disease (SRMD)

1. Endoscopic evidence of superficial mucosal damage occurs in 75%–100% of patients within 1–2 days after ICU admission.
2. Mortality from stress-related bleeding is 50%–70% in the critically ill population, with a 20% mortality rate attributable to SRMD.
3. Clinically significant stress-related bleeding has decreased during the past decade because of factors that include early resuscitation and SUP.

B. Characteristics of SRMD

1. Multiple superficial erosive lesions occurring early in the course of critical illness, potentially progressing to deep ulcers.
2. Stress ulcers are diffuse in nature and unamenable to endoscopic therapy; they generally heal over time, without intervention, as the patient's clinical status improves.

Table 2. Stress vs. Peptic Ulcers

Stress Ulcers	Peptic Ulcers
Multiple superficial lesions at the proximal stomach bulb; involves superficial capillaries; results from splanchnic hypoperfusion	Few deep lesions in the duodenum; typically involves a single vessel; results from break in gastric, duodenal, or esophageal lining from the corrosive action of pepsin

C. Pathophysiology of SRMD

1. Decreased gastric blood flow and mucosal ischemia are the primary causes of stress ulcer–related bleeding.
2. Reduced splanchnic blood flow is caused by mechanisms common to critical illness:
 - a. Hypovolemia
 - b. Reduced cardiac output
 - c. Proinflammatory mediator release
 - d. Increased catecholamine release
 - e. Visceral vasoconstriction
3. Additional factors leading to stress ulcer–related bleeding:
 - a. Decreased gastric mucosal bicarbonate production
 - b. Decreased gastric emptying of irritants and acidic contents
 - c. Acid back-diffusion
 - d. Reperfusion injury that may occur after restoration of blood flow after prolonged periods of hypoperfusion

Table 3. Categories of Stress-Related Bleeding

Outcome	Incidence in ICU Patients	Definition
Endoscopically evident mucosal damage	75%–100%	Superficial lesions identified on endoscopy
Occult bleeding	15%–50%	Presence of guaiac-positive stools or nasogastric aspirate
Overt or clinically evident bleeding	5%–25%	Appearance of coffee grounds in nasogastric aspirate, hematemesis, melena, or hematochezia
Clinically significant bleeding	1%–5%	Presence of overt bleeding with hemodynamic instability and/or blood transfusion within 24 hr of the event

D. Risk Factors for Stress-Related Bleeding (N Engl J Med 1994;330:377-81)

1. Independent risk factors for SRMD and bleeding are respiratory failure requiring mechanical ventilation for 48 hours or longer OR coagulopathy (platelet count less than 50,000 cells/mm³, INR greater than 1.5, or aPTT greater than 2 times the control).
 - a. Patients with at least one risk factor had a 3.7% incidence of bleeding compared with 0.1% if risk factors were absent.
 - b. Most of the 2252 patients enrolled in this study were cardiothoracic patients, potentially making extrapolations to other ICU settings inaccurate.
2. Variables associated with the risk of gastrointestinal (GI) bleeding while receiving prophylaxis:
 - a. Renal failure (Crit Care Med 1999;27:2812-7)
 - b. Age (50 years or older), male sex, acute respiratory failure, myocardial infarction, acute kidney injury, neurologic injury, sepsis, shock, acute or chronic hepatic failure, and coagulopathy (JAMA Intern Med 2014;174:564-74)
 - c. Severity of illness, liver disease, and renal replacement therapy (Intensive Care Med 2015;41:833-45)
3. Other risk factors for SRMD and bleeding (Am J Health Syst Pharm 1999;56:347-79; J Trauma 1995;39:289-94):
 - a. Spinal cord/head trauma
 - b. Thermal injury affecting more than 35% of total body surface area
 - c. History of GI bleed within the past year
 - d. Postoperative transplantation
 - e. Ulcerogenic medications (nonsteroidal anti-inflammatory drugs, aspirin, corticosteroids)

E. Pharmacologic Therapy for Preventing Stress Ulcers

1. Antacids
 - a. Dose-dependent neutralization of gastric acid
 - b. Not recommended for routine use because of frequency of administration (up to every hour), adverse effects (diarrhea, constipation, electrolyte abnormalities), and interactions (interferes with the absorption of some drugs)
2. Sucralfate (Carafate)
 - a. Complexes with albumin and fibrinogen to form a viscous, adhesive substance that adheres to ulcers in the presence of a pH less than 4
 - b. Not recommended for routine use because of adverse effects (constipation, aluminum toxicity, hypophosphatemia) and interactions by chelation
 - c. Sucralfate is less efficacious than H₂RAs.

3. H₂RAs

- a. Competitive blockade of histamine subtype 2 receptors on the basolateral membrane of the parietal cells. In addition, H₂RAs inhibit gastrin secretion to reduce acid production; however, they do not reliably inhibit vagally induced acid secretion.
- b. In animal models, H₂RAs may also attenuate reperfusion injury by decreasing interleukin-6 and neutrophil activation, reducing inflammation by enhancing cell-mediated immunity, and acting as a weak free radical scavenger.
- c. Dose-dependent increase in gastric pH
- d. Previous studies of SRMD-related bleeding used either continuous infusion H₂RAs or combined H₂RAs with intermittent antacids to maintain a pH greater than 4. Current practice is to use intermittent administration of H₂RAs without pH monitoring.
- e. Adverse effects
 - i. Mental status changes such as confusion, hallucinations, agitation, and headaches (mainly associated with cimetidine)
 - ii. Thrombocytopenia (occurs over several days from hapten formation; may occur within hours if patient is sensitized)
 - iii. Rapid infusion-related hypotension
 - iv. Sinus bradycardia
 - v. Risk of nosocomial pneumonia
- f. Drug interactions
 - i. Cimetidine inhibits cytochrome P450 (CYP) isoenzymes 3A4, 2D6, 2C9, 2C19, and 1A2.
 - ii. pH-dependent interactions

Table 4. Available H₂RAs

Drug Name	Dose ^a
Cimetidine ^b (Tagamet)	300 mg IV/PO every 6 hr or continuous infusion at 37.5–50 mg/hr
Famotidine (Pepcid)	20 mg IV/PO every 12 hr
Nizatidine (Axiid)	150 mg PO every 12 hr
Ranitidine (Zantac)	150 mg PO every 12 hr or 50 mg IV every 8 hr

^aDose based on clinical data; all are renally eliminated, and all require dose adjustments for renal dysfunction.

^bCimetidine continuous infusion is the only H₂RA approved by the U.S. Food and Drug Administration (FDA) for stress ulcer prophylaxis, and it competitively inhibits tubular secretion of creatinine.

H₂RA = histamine-2 receptor antagonist; IV = intravenous(ly); PO = orally.

4. PPIs

- a. Prodrugs activated in the acidic environment of the stimulated parietal cell inhibiting both histamine-induced and vagally mediated gastric acid by binding and inhibiting active proton pumps
- b. Dose-dependent increase in gastric pH, with maximal activity reached 3 days after initiation
- c. Most trials evaluated the effectiveness of enteral PPIs.
- d. Despite short elimination half-lives, PPIs suppress acid secretion for 20 hours or more, permitting once-daily dosing without requiring gastric pH monitoring.
- e. Tachyphylaxis does not occur with PPIs.

- f. Rebound acid hypersecretion may occur after discontinuation; however, clinical relevance is unknown.
- g. Adverse effects
 - i. Diarrhea, abdominal pain, constipation, nausea
 - ii. Headaches
 - iii. Rash
 - iv. Interstitial nephritis
 - v. Hypomagnesemia (3 months or more of therapy)
 - vi. Neurologic effects with high-dose intravenous omeprazole (hearing and vision disturbances)
 - vii. Hypophosphatemia and metabolic alkalosis when administered with sodium bicarbonate
 - viii. Vitamin B₁₂ deficiency
 - ix. Increased risk of fractures (hip, waist, and spine)
 - x. CDI (definitive cause-effect relationship is not well established)
 - xi. Risk of nosocomial pneumonia
- h. Drug interactions
 - i. All agents are hepatically metabolized by CYP isoenzymes 3A4 and 2C19.
 - ii. Omeprazole is an inhibitor of 3A4, 2C19, 2C9, and 1A2.
 - iii. Lansoprazole may induce CYP1A2.
 - iv. pH-dependent interactions

Table 5. Available PPIs

Agent	Dose (mg/day) ^a	Dosage Forms
Dexlansoprazole (Dexilant)	20	Delayed-release capsule
Esomeprazole (Nexium)	40	Delayed-release capsule Delayed-release oral suspension granules IV
Lansoprazole (Prevacid)	30	Delayed-release capsule Packet for oral suspension Delayed-release orally disintegrating tablet Delayed-release suspension (xanthan gum will clog nasogastric or orogastric tube)
Omeprazole (Prilosec)	20	Delayed-release capsule Delayed-release tablet Immediate-release capsule ^b Powder for oral suspension
Pantoprazole	40	Packet for oral suspension IV
Rabeprazole (AcipHex)	20	Delayed-release capsule Delayed-release tablet

^aDose based on clinical data.^bOnly PPI approved by the FDA for stress ulcer prophylaxis.

PPI = proton pump inhibitor.

F. Clinically Significant GI Bleeding

1. Most trials define clinically significant GI bleeding as overt bleeding accompanied by one of the following:
 - a. Decrease in blood pressure of 20 mm Hg within 24 hours of the first GI bleeding episode

- b. Decrease in blood pressure of 10 mm Hg and an increase in heart rate of 20 beats/minute on orthostatic change
 - c. Decrease in hemoglobin of 2 g/dL and transfusion of 2 units of blood within 24 hours of bleeding OR failure of the hemoglobin concentration to increase after transfusion by at least the number of units transfused minus 2 g/dL
2. Antacids, sucralfate, H₂RAs, and PPIs have all reduced clinically significant SRMD-related bleeding compared with placebo.
3. Randomized placebo-controlled trial showed significantly less clinically important GI bleeding with H₂RAs than with sucralfate (relative risk [RR] 0.44 [95% confidence interval {CI}, 0.21–0.92]; p=0.02) (N Engl J Med 1998;338:791-7).
4. Three meta-analyses favored PPIs to H₂RAs for GI bleeding; however, the studies that were included lacked methodological quality with unexpectedly high baseline bleeding rates, a disproportionate number of risk factors between patient groups, inconsistent definitions of bleeding, and different routes and dosing of agents.
5. Retrospective cohort including more than 35,000 mechanically ventilated patients reported an odds ratio (OR) of GI bleeding greater with PPIs than with H₂RAs (2.24; 95% CI, 1.81–2.76) (JAMA Intern Med 2014;174:564-74).

Table 6. Results of Meta-analyses on Clinically Important Bleeding Rates^a

	Antacids vs. Sucralfate	H₂RAs vs. Antacids	H₂RAs vs. Sucralfate	PPIs vs. H₂RAs
Am J Med 1991;91:519-27	0.65 (0.16–2.49)	0.84 (0.45–1.56)	0.95 (0.06–15.40)	—
Crit Care Med 1991;19:942-9	0.87 (0.45–1.67)	—	0.53 (0.3–0.93) ^b favoring sucralfate	—
Infect Control Hosp Epidemiol 1994;15:437-42	1.39 (0.67–3.21)	0.84 (0.45–1.56)	1.05 (0.12–16.36)	—
JAMA 1996; 275:308-14	1.49 (0.42–5.27)	0.86 (0.46–1.59)	1.28 (0.27–6.11)	—
Crit Care 2010;14:R194 ^c	—	—	0.87 (0.49–1.53)	—
Crit Care Med 2010;38:1197-205	—	—	—	-0.04 (-0.09 to 0.01) favoring PPIs
Am J Gastroenterol 2012;107:507-20	—	—	—	0.30 (0.17–0.54) favoring PPIs
Crit Care Med 2013;41:693-705	—	—	—	0.36 (0.19–0.68) favoring PPIs

^aAll results reported as OR or RR (95% CI).^bMacroscopic hemorrhages only; meta-analysis directly contradicts findings from Cook et al. (N Engl J Med 1998;338:791-7), in which intermittent administration of IV ranitidine resulted in a lower rate of clinically significant bleeding than sucralfate.^cNot all trials included in the analysis used a standard definition of clinically significant bleeding.

G. Infectious Complications

1. Increases in gastric pH promote bacterial overgrowth, potentially leading to infectious complications.
2. Both H₂RAs and PPIs will cause changes in gastric pH; however, PPIs have a greater propensity to maintain a sustained higher pH.
3. PPIs may also have immunosuppressive effects through the inhibition of neutrophils.
4. Pneumonia
 - a. Meta-analyses have shown lower pneumonia rates with sucralfate than with H₂RAs alone or H₂RAs combined with antacids (JAMA 1996;275:308-14; Crit Care Med 1991;19:942-9).
 - b. Meta-analyses have failed to show an association between H₂RAs and PPIs on the risk of pneumonia (Crit Care Med 2013;41:693-705; Am J Gastroenterol 2012;107:507-20; Crit Care Med 2010;38:1197-205).
 - c. The incidence of pneumonia was higher with PPIs than with H₂RAs (38.6% vs. 27.0%, respectively; p<0.001) in a large pharmacoepidemiologic cohort (JAMA Intern Med 2014;174:564-7).
 - d. Many of the trials included in these analyses had varying definitions of pneumonia.
5. CDI
 - a. A pharmacoepidemiologic cohort study found that CDI rates were significantly higher with PPIs than with H₂RAs (3.8% vs. 2.2%; p<0.001) (JAMA Intern Med 2014;174:564-7).
 - b. A large retrospective study observed PPI use to be an independent risk factor for developing CDI in medical ICU patients (OR 3.11; 95% CI, 1.11–8.74) (J Crit Care 2014;29:696).
 - c. There are no prospective trials evaluating the risk of CDI in ICU patients. Furthermore, many published trials have different definitions of CDI, unclear association of antisecretory therapy initiation and CDI diagnosis, and variable infection control practices.
6. Duration of SUP should be evaluated daily, and SUP should be continued only as long as one or more risk factors are present.

H. Pharmacoeconomics

1. According to the landmark trial comparing H₂RAs with sucralfate, H₂RAs may be more cost-effective because of a reduced incidence of bleeding without an increase in pneumonia rates (N Engl J Med 1998;338:791-7).
2. Cost-effectiveness models have compared H₂RAs with PPIs in relation to clinically important bleeding and adverse effects (ventilator-associated pneumonia [VAP] and CDI).
 - a. Use of PPI therapy for SUP resulted in a \$1250 net cost savings per patient compared with H₂RAs. Univariate sensitivity analysis observed that PPI therapy was not as cost-effective when the probability of VAP rates was altered (Value Health 2013;16:14-22).
 - b. Use of H₂RA therapy for SUP resulted in a \$1095 net cost savings compared with PPIs. Univariate sensitivity analysis showed that assumptions of pneumonia and bleeding rates were the primary drivers of incremental costs (Crit Care Med 2014;42:809-15).
3. Initiating SUP in patients at risk and appropriately discontinuing SUP when a patient no longer has any of the risk factors for stress-related bleeding is best practice for cost minimization.

I. Guideline Recommendations

1. In 1999, the first guideline from the American Society of Health-System Pharmacists was published (Am J Health Syst Pharm 1999;56:347-79). The guideline recommended that institutions decide on H₂RAs, antacids, or sucralfate according to safety profile, costs, and ease of administration.
2. In 2008, the Eastern Association for the Surgery of Trauma published a guideline recommending cytoprotective agents, H₂RAs, or PPIs; antacids were not recommended (www.east.org).
3. In 2012, the Surviving Sepsis Campaign guidelines commented on SUP, recommending H₂RAs or PPIs, with PPIs as the preferred agent (Crit Care Med 2013;41:580-637).

4. In 2014, the Danish Society of Intensive Care Medicine and the Danish Society of Anaesthesiology and Intensive Care Medicine published guidelines suggesting PPIs as the preferred agent (Dan Med J 2014;61:C4811).
5. Society of Critical Care Medicine/American College of Critical Care Medicine guidelines on SUP – to be released

Patient Cases

Questions 2–4 pertain to the following case.

A 45-year-old woman is admitted to the ICU for severe respiratory failure from community-acquired pneumonia. She is endotracheally intubated and placed on mechanical ventilation. An NGT is placed to begin enteral nutrition. She is currently receiving fluid boluses, norepinephrine and vasopressin infusions, and appropriate antimicrobial agents. Her WBC is 20×10^3 cells/mm³, platelet count 45,000/mm³, BUN 70 mg/dL, SCr 4.5 mg/dL (baseline 0.9 mg/dL), potassium 4.5 mEq/L, INR 1.4, AST 30 IU/mL, and ALT 46 IU/mL.

2. Which best reflects this patient's number of risk factors for stress-related bleeding?
 - A. One.
 - B. Three.
 - C. Four.
 - D. Five.
3. Which would be most appropriate for preventing stress-related bleeding?
 - A. Sucralfate 1 g four times daily by NGT.
 - B. Magnesium hydroxide 30 mL every 4 hours by NGT.
 - C. Pantoprazole 40 mg intravenously twice daily.
 - D. Famotidine 20 mg intravenously daily.
4. One week later, the patient's respiratory status has greatly improved. She has been off sedation and vasopressors for the past 4 days, working with physical therapy, and is now extubated. Her only medications include ceftriaxone, heparin subcutaneously, and SUP. Her current laboratory values are as follows: WBC 6×10^3 cells/mm³, platelet count 256,000/mm³, BUN 10 mg/dL, SCr 1.1 mg/dL, potassium 4.0 mEq/L, INR 0.8, AST 15 IU/mL, and ALT 10 IU/mL. Which would be the most appropriate recommendation to make regarding this patient's SUP regimen?
 - A. SUP should be continued until hospital discharge.
 - B. SUP should be continued until ICU discharge.
 - C. SUP should be discontinued now.
 - D. SUP should be discontinued once the patient is off antimicrobials.

III. PROPHYLAXIS AGAINST DEEP VENOUS THROMBOSIS OR PULMONARY EMBOLISM**A. Epidemiology**

1. Reported occurrence of DVT is 10%–80% (J Crit Care 2002;17:95-104). Precise incidence in the critically ill population is challenging because of inconsistencies in patient populations, different diagnosis strategies, and variable study methodologies.

2. Rates of DVT in the absence of prophylaxis varies, depending on patient population.
 - a. In the absence of prophylaxis: 30% in medical-surgical patients, 50%–60% in trauma patients, up to 80% in orthopedic surgical patients, and 20%–50% in neurosurgical patients (Arch Intern Med 2001;161:1268-79)
 - b. A recent randomized controlled trial of medical-surgical ICU patients receiving pharmacologic prophylaxis found proximal DVT rates of 5%–6% (N Engl J Med 2011;364:1305-14).
- B. Risk Factors**
1. Malignancy, previous VTE, immobility, known thrombophilia, recent (1 month or less) surgery or trauma, older age (70 years or older), heart or respiratory failure, sepsis, obesity (body mass index of 30 kg/m² or more), pregnancy, erythropoiesis-stimulating agents with hemoglobin of 12 g/dL or more, hormonal therapy, recent transfusions of concentrated clotting factors, central venous lines, and long-distance travel (Chest 2012;141:S195-226)
 2. Additional VTE risk factors in critically ill patients: A single-center prospective cohort (n=261) identified four independent risk factors for ICU-acquired VTE: personal or family history of VTE (multivariate hazard ratio [HR] 4.0; 95% CI, 1.5–10.3; p=0.004), end-stage renal failure (HR 3.7; 95% CI, 1.2–11.1; p=0.02), platelet transfusion (HR 3.2; 95% CI, 1.2–8.4; p=0.02), and vasopressor use (HR 2.8; 95% CI, 1.1–7.2; p=0.03) (Crit Care Med 2005;33:1565-71).
 3. In the critically ill patient population, there are no validated risk assessment models to estimate the risk of VTE.
- C. Prevention of VTE in the General Critically Ill Patient Population**
1. Routine ultrasound screening is not recommended (Chest 2012;141:S195-226).
 2. Prophylactic use of inferior vena cava filters is not recommended (Chest 2012;141:S195-226).
 3. Mechanical VTE prophylaxis should be used in a critically ill patient if bleeding or at high risk of bleeding. Once bleeding risk abates, initiate pharmacologic VTE prophylaxis.
 - a. Intermittent pneumatic compression devices and graduated compression stockings (GCS) significantly reduce the risk of symptomatic VTE compared with no prophylaxis (Chest 2012;141:S195-226).
 - b. A recent Cochrane review evaluated the results from 19 studies of GCS (Cochrane Database Syst Rev 2014;12:1-72).
 - i. Rates of DVT were 9% in the GCS group and 21% in the control group (OR 0.33; p<0.00001), and rates of pulmonary embolism were 2% in the GCS group and 5% in the control group (OR 0.38; p=0.04).
 - ii. The patient population was largely limited to those undergoing orthopedic and general surgery.
 - c. Limited data in medical critically ill patients
 4. Either low-dose unfractionated heparin or low-molecular-weight heparin should be initiated in a critically ill patient over no prophylaxis.

Table 7. Randomized Trials of VTE Prophylaxis in Critically Ill Patients

Citation	Study Type	Population	Intervention	Screening Methods	VTE Rates	Major Bleeding Rates
Crit Care Med 1982;10: 448-50	Single-center	119 medical-surgical ICU patients	LDUH 5000 units SC twice daily vs. placebo	Daily 125I-labeled fibrinogen leg scanning	DVT: 13% in LDUH group vs. 29% in placebo group; p<0.05	NR

Table 7. Randomized Trials of VTE Prophylaxis in Critically Ill Patients (*continued*)

Citation	Study Type	Population	Intervention	Screening Methods	VTE Rates	Major Bleeding Rates
N Engl J Med 1996;335:701-7	Single-center	344 patients with major trauma	Enoxaparin 30 mg twice daily vs. LDUH 5000 units twice daily	Venography on day 10–14 and US if VTE suspected	Proximal DVT: 14.7% in LDUH group vs. 6.2% in enoxaparin group; p=0.012 PE: 0% in LDUH group vs. 0.8% in enoxaparin group; p=NR	0.6% in LDUH group vs. 2.9% in enoxaparin group; p=0.12
Am J Respir Crit Care Med 2000;161:1109-14	Multicenter, double-blind	221 MV patients with COPD (169 patients evaluated)	Nadroparin (weight based) SC daily vs. placebo	Weekly US and venography	DVT: 15.5% in nadroparin group vs. 28.2% in placebo group; p=0.045	5.6% in nadroparin group and 2.7% in placebo group; p=0.28
Thromb Haemost 2009;101:139-44	Multicenter, double-blind	1935 patients with severe sepsis receiving drotrecogin alfa (activated)	LDUH 5000 units SC twice daily vs. enoxaparin 40 mg SC daily vs. placebo	US on day 4–6	DVT: 5.6% in LDUH group vs. 5.9% in enoxaparin group vs. 7.0% in placebo group; p=NS PE: 0.4% in LDUH group vs. 0.4% in enoxaparin group vs. 0.8% in placebo group; p=NS	NR
Blood Coagul Fibrinolysis 2010;21:57-61	Single-center, double-blind	156 surgical patients undergoing major elective surgery	LDUH 5000 units SC twice daily vs. enoxaparin 40 mg SC daily	US 5–7 days after surgery and when clinically indicated	DVT: 2.7% in LDUH group vs. 1.2% in enoxaparin group; p=0.51	2.7% in LDUH group vs. 1.2% in enoxaparin group; p=0.48
N Engl J Med 2011;364:1305-14	Multicenter, double-blind	3746 medical-surgical ICU patients expected to remain in the ICU for ≥ 3 days (90% medical, 76% MV)	LDUH 5000 units SC twice daily vs. dalteparin 5000 international units SC daily	US 2 days after admission, twice weekly, and as clinically indicated	Proximal DVT: 5.8% in LDUH group vs. 5.1% in dalteparin group; p=0.57 PE: 2.3% in LDUH group vs. 1.3% in dalteparin group; p=0.01	5.6% in LDUH group vs. 5.5% in dalteparin group; p=0.98

COPD = chronic obstructive pulmonary disease; DVT = deep venous thrombosis; LDUH = low-dose unfractionated heparin; MV = mechanically ventilated; PE = pulmonary embolism; NR = not reported; NS = not significant; SC = subcutaneously; US = ultrasonography.

D. Prevention of VTE in the Non-orthopedic Surgical Patient (Chest 2012;141:S227-77)

Table 8. VTE Prophylaxis Recommendations in Trauma Patients

Risk Level for VTE	Risk of Bleeding	Prophylaxis
Low-moderate	Low	LMWH, ^a LDUH, ^a or IPCD (all preferred to no prophylaxis)
High ^b	Low	LMWH ^a or LDUH ^a with elastic stockings or IPCD

^aIf LDUH or LMWH is contraindicated, mechanical prophylaxis with IPCD is preferred to no prophylaxis in the absence of lower-extremity injury.

^bIncludes acute spinal cord injury, traumatic brain injury, and spinal surgery from trauma; pharmacologic prophylaxis should be initiated as soon as possible, typically 24–48 hours after the event, but this may depend on the extent of bleeding on head computed tomography.

IPCD = intermittent pneumatic compression device; LMWH = low-molecular-weight heparin.

Table 9. VTE Prophylaxis Recommendations in the General and Abdominal-Pelvic Surgical Patient

Risk Level for VTE	Risk of Bleeding	Prophylaxis
Very low	Low	Early ambulation
Low	Low	IPCD
Moderate	Low	LMWH, LDUH, or IPCD
	High	IPCD
High	Low	LMWH or LDUH with elastic stockings or IPCD
	Low with contraindications to LMWH or LDUH	Low-dose aspirin, fondaparinux, or IPCD
	High	IPCD until risk of bleeding abates; then pharmacologic prophylaxis should be initiated

Table 10. Available Agents and Dosing

	Dose in Patients with Normal Renal Function	Dose in Patients with Renal Impairment ^a
Enoxaparin	40 mg SC daily	30 mg SC daily
Dalteparin	5000 units SC daily	Specific dosage adjustments have not been recommended; accumulation was not observed in critically ill patients with severe renal insufficiency. No adjustment needed for CrCl $\geq$ 20 mL/min/1.73 m ² (Arch Intern Med 2008;168:1805-12)
LDUH	5000 units SC every 8–12 hr: Choosing between every 8 hr and every 12 hr should be based on the patient's risk of thrombosis and bleeding	
Fondaparinux	2.5 mg once daily for patients weighing 50 kg or more	Contraindicated; however, doses of 2.5 mg SC every 48 hr have been used

^aEstimated CrCl 20–30 mL/min/1.73 m².

CrCl = creatinine clearance.

E. Considerations for Critically Ill Patients

1. Inability to communicate symptoms (impaired consciousness) and altered physical examination (edema) make diagnosis of symptomatic VTE challenging in the critically ill patient population. Routine screening for VTE with ultrasonography is not recommended.

2. Dosing frequency of low-dose unfractionated heparin (twice vs. thrice daily)
 - a. Large randomized controlled trials have only assessed twice-daily dosing, and no direct comparisons have been made in any population, including the critically ill population.
 - b. Indirect comparisons from a meta-analysis suggest no difference in thrombosis or major bleeding rates with twice- compared with thrice-daily regimens (Chest 2011;140:374-81).
 3. The bioavailability of subcutaneously administered drugs is reduced in critically ill patients with the concomitant use of vasoactive drugs or the presence of edema, thereby potentially providing a reduced effect.
 4. Renal impairment. Critically ill patients (n=138) administered prophylactic subcutaneous dalteparin with an estimated creatinine clearance (CrCl) of less than 30 mL/minute/1.73 m² were evaluated in a prospective study. No evidence of accumulation or an increased risk of bleeding (Arch Intern Med 2008;168:1805-12)
 5. Bleeding
 - a. Bleeding rates in critically ill patients are variable, depending on the type of pharmacologic prophylaxis.
 - b. Patients at high risk of bleeding are often excluded from studies.
 - c. Patients at high risk of bleeding with a moderate to high risk of VTE may be considered for mechanical VTE prophylaxis; however, pharmacologic prophylaxis should be reassessed when the bleeding risk is no longer present.
 6. Limited evidence exists to guide dosing in the critically ill patient population with obesity. An inverse relationship between body weight and anti-factor Xa (anti-Xa) concentration may exist in patients with obesity; however, the risk of VTE and optimal anti-Xa concentrations to achieve is unclear.
- F. Oral Anticoagulants for VTE Prophylaxis
1. No studies to date of critically ill ICU patients with direct thrombin inhibitors (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)
 2. Rivaroxaban is noninferior to standard treatments in other settings such as orthopedic surgery.
 3. Rivaroxaban 10 mg orally once daily was compared with enoxaparin 40 mg subcutaneously daily for 10 days, followed by placebo in acutely ill, hospitalized patients. The rates of asymptomatic or symptomatic VTE, pulmonary embolism, or death were comparable; however, increased bleeding rates occurred in the rivaroxaban group (N Engl J Med 2013;368:513-23).
 4. Low-molecular-weight heparin is preferred to vitamin K antagonists such as warfarin for prophylaxis; however, it may be used in patients who refuse injections (Chest 2011;140:374-81).
- G. Heparin-Induced Thrombocytopenia (Chest 2012;141(2 suppl):495S-530S)
1. HIT is a severe, immune-mediated reaction potentially leading to life-threatening complications such as myocardial infarction, skin necrosis, stroke, and VTE (around 50%–75% of patients with HIT develop symptomatic thrombosis).
 2. A rare manifestation is delayed-onset HIT, affecting patients exposed to heparin in the recent past (prior 2 weeks) who present with a new thrombosis and low platelet counts.
 3. Frequency of HIT
 - a. Higher in patients receiving unfractionated heparin compared with low-molecular-weight heparin, occurring in 1%–5% of patients versus less than 1%, respectively
 - b. Occurs in less than 1% of ICU patients
 - c. Higher risk in cardiac or orthopedic surgical patients receiving unfractionated heparin (15%) than in medical patients (0.1%–1%)

4. Alternative causes of thrombocytopenia in critically ill patients include extracorporeal devices, intra-aortic balloon pumps, sepsis, disseminated intravascular coagulation, bleeding, and medications. Platelet counts may decrease post-cardiac bypass surgery and subsequently recover. A secondary drop in platelet count may signal potential HIT.
5. Clinical diagnosis of HIT
 - a. Suspected when a patient has a decrease in absolute platelet count to less than 150,000/mm³ or a relative decrease of at least 50% from baseline, skin lesions at injection sites, or systemic reactions after intravenous boluses
 - b. Typical onset is 5–10 days after heparin exposure, though onset can be delayed and occur up to 3 weeks after therapy cessation
 - c. Recent heparin exposure may result in rapid-onset HIT, occurring within hours after rechallenge.
 - d. Patients with recent unfractionated heparin/low-molecular-weight heparin exposure and a new thrombosis should have their platelet counts checked before starting anticoagulant therapy.
6. Probability of HIT
 - a. The 4T pretest clinical scoring system has a high negative predictive value; however, it requires further investigation in ICU patients.
 - b. The HEP (HIT Expert Probability) score has not been assessed in ICU patients.
7. Laboratory testing
 - a. Antigen assays
 - i. Examples: GTI-PF4 (Genetic Testing Institute, Waukesha, WI) and ID-PaGIA (Bio-Rad, Berkeley, CA)
 - ii. Antibody present if sample from patient binds to the heparin-PF4–coated wells, leading to a color-producing reaction. A higher antibody concentration leads to greater color production and a higher optical density reading. Optical density readings of 0.4 or greater are considered positive and indicative of the presence of HIT antibodies.
 - iii. High sensitivity (greater than 90%) and low to moderate specificity
 - (a) Clinically insignificant HIT antibodies are often detected among patients who have received heparin 5–100 days earlier.
 - (b) Detects a range of immunoglobulin (Ig) A and IgM antibodies that are not pathogenic
 - b. Functional assays
 - i. Examples: Heparin-induced platelet aggregation (HIPA) and C14 serotonin release assay
 - ii. Detect platelet activation in the presence of heparin. Patient serum is mixed with washed platelets from healthy volunteers and low and high concentrations of heparin. In the presence of HIT antibodies, platelets are activated in low concentrations of heparin and detected using radioactive serotonin (serotonin release assay) or visually (HIPA).
 - iii. High sensitivity and specificity
 - iv. Technically challenging and not readily available
8. Treatment of HIT
 - a. Immediately discontinue all sources of heparin, and initiate an alternative non-heparin anticoagulant.
 - b. Parenteral direct thrombin inhibitors are the agents of choice for anticoagulation in acute HIT because they have no cross-reactivity with heparin. Some studies support the use of the factor Xa inhibitor fondaparinux for the treatment of HIT, though there are reports of fondaparinux-induced HIT.
 - c. Parenteral direct thrombin inhibitors are associated with a higher rate of major bleeding complications than is unfractionated heparin.
 - d. Initiate warfarin once the platelet count has recovered and is within normal limits (at least 150,000/mm³) and after at least 5 days of therapy with an alternative anticoagulant. Alternatively, conservative warfarin dosing may begin once the platelet count is recovering. If a patient is receiving warfarin at the time of HIT diagnosis, reversing with vitamin K is recommended.

- e. Argatroban dosing in the critically ill population (Crit Care 2010;14:R90; Ann Pharmacother 2007;41:749-54)
 - i. Mean dose in critically ill patients was 0.24 ± 0.16 mcg/kg/minute and 0.22 ± 0.15 mcg/kg/minute in critically ill patients with multiple organ dysfunction.
 - ii. In patients with severe liver impairment, consider 0.5 mcg/kg/minute.
 - iii. Target aPTT is 1.5–3 times baseline.
- f. Bivalirudin dosing in the critically ill population (Pharmacotherapy 2006;26:452-60)
 - i. Dose reduced to 0.05–0.1 mg/kg/hour, depending on renal function and bleeding risks
 - ii. Target aPTT is 1.5–2.5 times baseline.

Table 11. Parenteral Agents for the Treatment of HIT

	Argatroban	Desirudin (Iprivask)	Bivalirudin (Angiomax)	Fondaparinux (Arixtra)
FDA approved for the treatment of HIT	Yes	No	Yes (percutaneous coronary intervention with HIT)	No
Mechanism of action	Direct thrombin inhibitor	Direct thrombin inhibitor	Direct thrombin inhibitor	Factor Xa inhibitor
Elimination half-life	40–50 min	120 min	25 min	17–20 hr
Elimination	Hepatobiliary	Renal	80% enzymatic 20% renal	Renal
Dosing	2 mcg/kg/min (see above for dosing in the critically ill population)	Unlabeled dose for HIT: 15–30 mg SC every 12 hr	Unlabeled dose for HIT: 0.15–0.2 mg/kg/hr (see above for dosing in the critically ill population)	Unlabeled dose for HIT: 5–10 mg SC daily (depending on weight); 2.5 mg/day for prophylaxis
Monitoring	aPTT	aPTT	aPTT	Anti-Xa concentration
Effect on INR	Excessive	Minimal	Moderate	None

aPTT = activated partial thromboplastin time; HIT = heparin-induced thrombocytopenia.

Patient Cases

5. A 93-year-old man (weight 45 kg) confined to his bed is admitted from a nursing home with a chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation. He has a history of diabetes mellitus and heart failure. His laboratory values are all within normal limits except for a BUN of 35 mg/dL and an SCr of 2.8 mg/dL (baseline 0.5). Which would be the most appropriate recommendation for VTE prophylaxis in this patient?
- A. Intermittent pneumatic compression devices.
 - B. Enoxaparin 30 mg subcutaneously once daily.
 - C. Heparin 5000 units subcutaneously twice daily.
 - D. Fondaparinux 2.5 mg subcutaneously daily.

Questions 6 and 7 pertain to the following case.

A 55-year-old man (weight 60 kg) with a medical history of diabetes mellitus, hyperlipidemia, and a DVT 2 months ago secondary to trauma to the lower extremity is admitted today to the ICU for acute respiratory failure from influenza virus. His current laboratory values are as follows: WBC 13.1×10^3 cells/mm³, platelet count 250,000/mm³, BUN 13 mg/dL, SCr 0.9 mg/dL, INR 1.2, AST 22 IU/mL, and ALT 11 IU/mL. His current medication regimen includes fentanyl and midazolam boluses for pain and agitation, piperacillin/tazobactam, vancomycin, regular insulin infusion, SUP, and a heparin drip. Five days later, the patient remains intubated on the same medications. At this time, his platelet count has dropped to 112,000/mm³, and his BUN and SCr have increased to 45 mg/dL and 2.7 mg/dL, respectively. The team sends a heparin-PF4 immunoassay; however, the results will not come back for 48 hours.

6. Which would be the best course of action?
- A. Discontinue heparin drip, and initiate argatroban continuous infusion at 0.5 mcg/kg/minute.
 - B. Do nothing because the patient has several other reasons to be thrombocytopenic.
 - C. Discontinue heparin drip, and initiate fondaparinux at 10 mg subcutaneously daily.
 - D. Do nothing until the heparin-PF4 immunoassay results return.
7. Three days later, both the heparin-PF4 immunoassay and the serotonin release assay return positive, and the patient has a new DVT. The team would like to initiate warfarin. The patient's current platelet count is 130,000/mm³. Which would be the most appropriate response?
- A. Discontinue argatroban and initiate warfarin at 5 mg orally daily.
 - B. Discontinue argatroban and initiate warfarin at 10 mg orally daily.
 - C. Warfarin should never be used in patients with HIT.
 - D. Warfarin should not be initiated now.

IV. END-OF-LIFE CARE

- A. Clinicians commonly provide end-of-life and palliative care in ICUs.
- B. The World Health Organization describes palliative care as “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual” (Global Atlas of Palliative Care at the End of Life).
- C. Goals of Palliative Care
 - 1. To improve the quality of life for individuals who have severe diseases
 - 2. To offer a diverse array of assistance and care to the patient
- D. Categories of Support
 - 1. Pain management is of paramount importance for comfort and reduction of distress. Providers and families can collaborate to identify the sources of pain and relieve them with drugs and other forms of therapy.
 - 2. Symptom management involves treating symptoms other than pain such as nausea, thirst, bowel and bladder problems, depression, anxiety, dyspnea, and secretions.
 - 3. Emotional and spiritual support is important for both the patient and the family in dealing with the emotional demands of critical illness.
- E. General Considerations
 - 1. Minimization of uncomfortable or unnecessary procedures, tests, or treatments
 - 2. Minimizing or discontinuing routine vital sign checks, patient weights, cardiac or other electronic monitoring, fingersticks, and intermittent pneumatic compression devices
 - 3. Consider discontinuing routine blood tests, radiologic imaging, and other diagnostic procedures.
 - 4. Consider discontinuing all medications not necessary for patient comfort.
- F. Symptom Management
 - 1. Pain
 - a. No evidence supports that unconscious patients do not experience pain.
 - b. Opioids are the mainstay of treatment for patients experiencing pain at the end of life.
 - c. Administer opioid as an intravenous bolus dose, and begin an intravenous continuous infusion, adjusting rates to maintain comfort; avoid using subcutaneous or enteral routes because the onset is delayed.
 - d. Bolus and titrate infusion to control labored respirations; specific dosages of medications are less important than the goal of symptom relief. Optimal dose is determined by assessing the patient and rapidly increasing dose as needed until symptoms are no longer present. Dose is determined by symptom relief and adverse effects (excessive sedation, respiratory depression [rare]).
 - e. Suggested goals include keeping the respiratory rate at or below 30 breaths/minute and keeping the patient pain free. Assessment of pain should include using the behavioral pain scale (BPS) or the Critical-Care Pain Observation Tool (see the chapter on Management of Pain, Agitation, Delirium and Neuromuscular Blockade in Adult Intensive Care Unit Patients for further details on these scales).
 - f. Never use neuromuscular blocking agents to treat pain.
 - g. Morphine is most commonly used; hydromorphone and fentanyl are alternatives.
 - h. In addition, opioids will reduce dyspnea.

- i. Tolerance may develop over time.
 - j. Evidence is good that pain can be improved with correct dosing and titration without causing respiratory depression or hastening death (Chest 2004;126:286-93; Crit Care Med 2004;32:1141-8; JAMA 1992;267:949-53).
2. Anxiety/agitation/delirium
- a. Symptoms at the end of life can relate to acute or chronic anxiety, delirium, or terminal delirium.
 - b. Nonpharmacologic treatments for agitation and anxiety can include frequent reorientation to the environment and reduction in noise and other bothersome or stimulating environmental factors.
 - c. Intravenous haloperidol may be used without electrocardiographic (ECG) monitoring because the benefits outweigh the risks of prolonged QTc (corrected QT interval), given the goals of care.
 - d. Benzodiazepines (midazolam and lorazepam):
 - i. Dose is determined by assessing the patient and increasing the dose as needed until symptoms are no longer present if haloperidol fails to relieve significant agitation.
 - ii. Determining what would be perceived as an acceptable level of sedation with the patient and/or family or surrogate decision-maker is important before initiating sedatives.
 - iii. Tolerance may develop over time.
3. Fever
- a. Acetaminophen is an effective therapy for improving comfort and decreasing the incidence of fever. If the patient cannot swallow, this agent may be administered per rectum.
 - b. A nonsteroidal anti-inflammatory drug may be used when acetaminophen is ineffective.
 - c. Dexamethasone, which is also known to have antipyretic properties, could be considered.
4. Nausea and vomiting
- a. Underlying causes such as medications, uremia, ascites, gastroparesis, and intestinal or gastric obstruction should be treated or eliminated, if possible.
 - b. Agents to consider include metoclopramide, ondansetron, and dexamethasone.
 - c. Lorazepam can be considered as an adjunct, especially with anticipatory vomiting.
 - d. Use of more than one agent may be necessary for symptom relief.
5. Cough
- a. Excessive coughing can lead to exacerbation of dyspnea and spells of nausea and vomiting, in addition to disturbing sleep and exacerbating pain.
 - b. Non-opioid antitussives such as benzonatate and dextromethorphan may be considered.
 - c. All opioids have intrinsic antitussive action by inhibiting the brain stem cough center; however, if the patient is receiving an opioid for other reasons, adding another opioid has not shown additional benefit.
 - d. For refractory cough, consider nebulized lidocaine.
6. Secretions
- a. Near the end of life, the ability to clear oral and tracheobronchial secretions diminishes.
 - b. Secretions are usually too low in the tracheobronchial tree for gentle oral suctioning to help, and suctioning can be disturbing.
 - c. The mainstay of treatment includes anticholinergic and antimuscarinic medications.
 - i. Scopolamine and atropine cross the blood-brain barrier and can be more sedating than glycopyrrolate.
 - ii. Glycopyrrolate (0.1 mg intravenously every 4 hours) or atropine (1% ophthalmic solution 2 drops sublingually every 4 hours as needed) should be used to manage acute symptoms.
 - iii. Scopolamine patch is more gradual in onset (12 hours).
 - iv. More than one scopolamine patch may be used for unrelieved symptoms.

Patient Case

8. An 88-year-old woman is admitted to the ICU for decompensated heart failure, acute kidney injury, and uncontrollable pain from rib fractures she sustained 1 month ago from a fall. This is her fourth admission to the ICU in the past 5 months. Speaking with the patient, you find that she wishes not to be resuscitated or intubated but only to be comfortable. Her blood pressure is currently 119/70 mm Hg, heart rate 120 beats/minute, and respiratory rate 55 breaths/minute. Her pain is 9/10 using the BPS. In a meeting with the patient's family, all members agree that they do not want to see her suffer any longer. It is decided to initiate a morphine drip at 2 mg/hour. Titration parameters include giving a bolus dose equivalent to the current rate and increasing the infusion by 25% to maintain a score of 3 (no pain) using the BPS. Her laboratory values are all within normal limits including BUN 10 mg/dL and SCr 0.6 mg/dL. The nurse taking care of the patient believes that the titration parameters are too aggressive. Which would be the most appropriate change in titration parameters?
- A. Change the parameters to increase the morphine drip when the patient shows signs of discomfort, such as an increase in blood pressure or heart rate.
 - B. Discontinue titration parameters, keeping the morphine infusion at the current rate.
 - C. Discontinue titration parameters, keeping the morphine infusion at the current rate and adding a midazolam infusion at 2 mg/hour.
 - D. Do not change the titration parameters at this time; however, assess the patient's response after the first dose increase.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

The mnemonic FAST-HUG stands for Feeding, Analgesia, Sedation, Thromboembolic prophylaxis, Head of bed elevation, stress Ulcer prophylaxis, and Glycemic control. Using this mnemonic as a “check-list” every day for each critically ill patient will assist in maximizing therapeutic interventions and promote patient safety. This patient would benefit from initiation of enteral nutrition (he has an NGT already placed and has a working GI tract), interruption in sedative (current RASS score is above the designated goal), and addition of SUP (risk factors include mechanical ventilation) (Answer A is correct). Critically ill patients with risk factors for VTE should remain on VTE prophylaxis (Answers B and D are incorrect); moreover, sliding-scale insulin should be initiated when the patient is not critically ill, adding another reason why Answer B is incorrect, as well as making Answer C incorrect.

2. Answer: C

Two independent risk factors for SRMD are respiratory failure requiring mechanical ventilation for 48 hours or longer and coagulopathy (platelet count less than 50,000/mm³, INR greater than 1.5, or aPTT time greater than 2 times the control). This patient has both of these risk factors. In addition, she has septic shock, as evidenced by end-organ dysfunction and acute kidney injury (Answer C is correct). Answers A, B, and D are incorrect because this patient has four risk factors for SUP.

3. Answer: D

Antacids are not recommended for routine use because of their frequency of administration, adverse effects, and interactions (Answer B is incorrect). In a large randomized controlled trial, sucralfate was inferior to H₂RAs in preventing clinically significant bleeding from SRMD and is generally not recommended because of its adverse effect profile (Answer A is incorrect). Proton pump inhibitors are no better than H₂RAs in preventing SRMD and are associated with increased infectious complications, including pneumonia and CDI (Answer D is correct). Meta-analyses have favored PPIs to H₂RAs for GI bleeding; however, the individual trials included lacked methodological quality (Answer C is incorrect).

4. Answer: C

Once the risk factors are no longer present, SUP should promptly be discontinued (Answer C is correct). This patient no longer has risk factors (mechanical ventilation, coagulopathy acute kidney failure, and severe sepsis). In addition, there is no evidence that SUP should be continued until hospital or ICU discharge or when antimicrobial therapy is complete (Answers A, B, and D are incorrect).

5. Answer: C

The patient has several risk factors for VTE, including immobility and respiratory failure, making heparin 5000 units subcutaneously twice daily an appropriate choice for VTE prophylaxis (Answer C is correct). Neither enoxaparin nor fondaparinux is appropriate for this patient, who has acute kidney injury with an estimated CrCl less than 20 mL/minute/1.73 m² (Answers B and D are incorrect). Intermittent pneumatic compression would be insufficient in a patient with no contraindication to pharmacologic prophylaxis (Answer A is incorrect).

6. Answer: A

Diagnosing HIT is difficult in a critically ill patient because there are many alternative causes of thrombocytopenia. Clinical assessment is essential in diagnosing HIT because of the immediate need for treatment and the delay in laboratory testing (Answers B and D are incorrect). Clinically, this patient has had a greater than 50% drop in platelet count within 5 days of receiving heparin. This patient had a DVT 2 months ago, when he was probably exposed to heparin products. In managing suspected HIT, first ensure that all forms of heparin are discontinued, including flushes and heparin-coated catheters. Next, initiate an alternative form of anticoagulation. Direct thrombin inhibitors are the agents of choice for anticoagulation in acute HIT because they have no cross-reactivity with heparin (Answer A is correct). Factor Xa inhibitors have been used in managing HIT; however, they would not be the best choice in this patient, who has acute kidney injury (Answer C is incorrect).

7. Answer: D

Warfarin can be initiated (Answer C is incorrect) once the platelet count has recovered to at least 150,000/mm³ and after at least 5 days of therapy with an alternative anticoagulant (Answer D is correct). Because this patient's platelet counts have not reached 150,000/mm³ and only 3 days of argatroban have been completed, warfarin therapy should not be initiated at this time (Answers A and B are incorrect). Argatroban should be continued, and warfarin may be considered at low doses (maximum 5 mg) as the platelet count continues to recover (Answer B is incorrect).

8. Answer: D

Up to 50% of seriously ill, hospitalized patients will experience moderate or severe pain. Opioids are the mainstay of treatment for patients experiencing pain and dyspnea at the end of life. Assessing pain in the ICU can be particularly challenging because many patients have impaired cognition and communication. Vital signs alone should not be used for pain assessment (Answer A is incorrect). Evidence suggests that pain can be improved with correct dosing and titration (Answers B and C are incorrect) without causing respiratory depression or hastening death (Answer D is correct).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

The FAST-HUG mnemonic can serve as a “checklist” for every patient admitted to the ICU. Every patient should be assessed for a sedation interruption in an effort to minimize sedative exposure and maintain a light level of sedation (Answer C is correct). To decrease the risk of nosocomial pneumonia, each patient should have his or her head 30–45 degrees above the head of the bed (Answer C is correct). Enteral nutrition should be initiated as soon as possible—typically, once the patient is stabilized; however, thromboprophylaxis should be initiated in every patient, using pharmacologic agents preferentially to mechanical prophylaxis (Answer B is incorrect). Stress ulcer prophylaxis should be initiated only in patients who have risk factors present and should be discontinued when the risk factor does not exist (Answer A is incorrect). Insulin infusions should be initiated only if blood glucose readings are not 140–180 mg/dL (Answer D is incorrect).

2. Answer: C

Sucralfate forms a protective barrier over the surface of the stomach, reducing exposure to acidic gastric contents; therefore, sucralfate has no effect on gastric pH (Answer A is incorrect). Compared with H₂RAs, PPIs seem to be more effective at reducing gastric acidity, but no well-conducted trial has shown PPIs to be superior in preventing clinically significant bleeding (Answer B is incorrect). Tolerance to any H₂RA may occur, but not with PPIs (Answer C is correct). Antacids have some effect on reducing stress ulceration, provided the gastric pH is kept around 3.5, but frequent dosing (up to every 2 hours) is required to achieve this goal, making their use impractical (Answer D is incorrect).

3. Answer: D

The patient has an indication for SUP (mechanical ventilation). He has an NGT in place and is tolerating tube feedings, indicating a functioning gut; therefore, intravenous therapy is not required (Answers A and B are incorrect). The patient has erosive esophagitis, for which a PPI will be more effective than an H₂RA (Answer C is incorrect). Omeprazole suspension is effective in the prevention of SRMD; therefore, omeprazole suspension would be the most appropriate choice for this patient (Answer D is correct).

4. Answer: A

Proton pump inhibitors are potent inhibitors of gastric acid production and are the drug of choice for the treatment of gastroesophageal reflux disease. To date, no prospective randomized controlled trials have evaluated the risk of CDI with PPI use (Answer B is incorrect); however, several cohort studies have observed an association (Answer C is incorrect). All published trials assessing the risk of CDI with PPI use have been limited by the inconsistent definitions of CDI and the variable infection control practices (Answer D is incorrect). Gastric juice is strongly bactericidal for microorganisms. Proton pump inhibitors are commonly used to increase the gastric pH; therefore, they act as a potential risk factor for CDI (Answer A is correct).

5. Answer: B

Low-dose unfractionated heparin or low-molecular-weight heparin should be initiated for VTE prophylaxis in a critically ill patient over no prophylaxis (Answer D is incorrect). Intermittent pneumatic compression devices would be insufficient prophylaxis in a patient with several risk factors for VTE (Answer A is incorrect). A continuous infusion of heparin is inappropriate for the prevention of VTE (Answer C is incorrect). Enoxaparin may be used in a critically ill patient with stable renal function for VTE prophylaxis (Answer B is correct).

6. Answer: A

This patient sustained a closed-head injury, placing her at high risk of VTE (Answer D is incorrect). She is at high risk of having major bleeding and experiencing acute kidney injury; therefore, use of a low-molecular-weight heparin or a factor Xa inhibitor would not be the best option in this patient (Answers B and C are incorrect). Mechanical prophylaxis with intermittent pneumatic compression devices is preferred to no prophylaxis in the absence of lower-extremity injury until the bleeding risk is no longer present (Answer A is correct).

7. Answer: D

Clinical assessment is essential in diagnosing HIT because of the immediate need for treatment and the delay in laboratory testing. Although this patient did have a 50% decrease in his platelet count, the characteristic onset of the platelet count decline in HIT is 5–10

days after heparin initiation. Clinical prediction rules to assist in determining the probability of HIT (e.g., 4T score) have been developed. Patients with a low 4T score (0–3) have a very low probability of HIT (Answer D is correct). Direct thrombin inhibitors are the agents of choice for anticoagulation in acute HIT because they have no cross-reactivity with heparin. Initiating these agents in those with a low probability of HIT could lead to an unnecessary increase in bleeding risk (Answer B is incorrect). If HIT were highly suspected in this patient, the first step in managing it would be to ensure that all forms of heparin are discontinued, including flushes and heparin-coated catheters (Answer C is incorrect). The next step would be to initiate an alternative form of anticoagulation (Answer A is incorrect).

8. Answer: C

General considerations in the critically ill patient at the end of life include minimizing uncomfortable or unnecessary procedures, tests, or treatments, including fingersticks, Foley catheters, and routine vital signs (Answers A, B, and D are incorrect). Symptom management of pain and anxiety, fever, cough, secretions, nausea and vomiting, and delirium should be considered in the dying patient (Answer C is correct).

ACUTE CARDIAC CARE

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Learning Objectives

1. Manage cardiac arrest from the initiation of basic life support to the use of post-cardiac arrest care.
2. List the indications and contraindications for medication administration during cardiac arrest.
3. Recognize the utility of therapeutic hypothermia and the patient groups to which it should be applied.
4. State the common complications of therapeutic hypothermia and explain how to ameliorate them.
5. Define the different presentations of hypertensive emergency.
6. Outline the therapeutic goals and clinical indications for the medications used in hypertensive emergency.

Abbreviations in This Chapter

ACLS	Advanced cardiac life support
AED	Automated external defibrillator
BLS	Basic life support
BPV	Blood pressure variability
CPR	Cardiopulmonary resuscitation
DBP	Diastolic blood pressure
ED	Emergency department
ICP	Intracranial pressure
ICU	Intensive care unit
IO	Intraosseous
MAP	Mean arterial pressure
MICU	Medical intensive care unit
PEA	Pulseless electrical activity
ROSC	Return of spontaneous circulation
SCA	Sudden cardiac arrest
SBP	Systolic blood pressure
TTM	Targeted temperature management
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Self-Assessment Questions

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

Questions 1–5 pertain to the following case.

T.B. is a 72-year-old man with a history of atrial fibrillation, coronary artery disease with drug-eluting stent placement in 2009, heart failure with reduced ejection fraction (most recent ejection fraction was 45% on

echocardiogram in 2013), and gastroesophageal reflux disease. T.B. is sent to the catheterization laboratory for suspected acute myocardial infarction. Laboratory values for T.B. are as follows: international normalized ratio (INR) 1, platelet count 200,000/mm³, hemoglobin 12 g/dL, serum creatinine (SCr) 1.7 mg/dL (baseline 1.5 mg/dL), white blood cell count (WBC) 17 x 10³ cells/mm³, and aspartate aminotransferase (AST) 100 IU/L. He is admitted to the coronary care unit for observation after catheterization when he suddenly loses consciousness and becomes pulseless. The coronary care unit team of which you are part is called to the bedside. Of note, T.B. has peripheral intravenous access, and before this event, he was on room air by nasal cannula.

1. Which is the most appropriate first step in T.B.'s resuscitation?
 - A. Promptly intubate because this is likely a hypoxic pulmonary arrest
 - B. Place central line for vasopressor administration.
 - C. Initiate cardiopulmonary resuscitation (CPR), beginning with chest compressions.
 - D. Initiate CPR, beginning with 2 breaths by bag-mask ventilator.
2. The monitor reveals that T.B. is in ventricular fibrillation (VF), and T.B. remains pulseless. Which is the most appropriate management of T.B.'s VF arrest?
 - A. Provide an unsynchronized shock/defibrillation at 120 J from a biphasic defibrillator.
 - B. Give intravenous amiodarone at a dose of 300 mg.
 - C. Give intravenous atropine at a dose of 0.4 mg.
 - D. Provide emergency transcutaneous pacing.
3. T.B.'s rhythm changes from VF to pulseless electrical activity (PEA) on the monitor. Which is the most appropriate management of T.B.'s PEA arrest?
 - A. Provide an unsynchronized shock/defibrillation at 120 J from a biphasic defibrillator.
 - B. Begin high-quality chest compressions, and consider treatable causes of cardiac arrest.
 - C. Give intravenous lidocaine 1 mg/kg x 1, followed by an infusion at 1 mg/minute.
 - D. Give intravenous atropine at a dose of 0.4 mg.

4. T.B. has return of spontaneous circulation (ROSC) after 15 minutes of total resuscitation. The team is deciding whether targeted temperature management (therapeutic hypothermia) would be appropriate for T.B. Which is the most accurate statement regarding targeted temperature management for T.B.?
 - A. He should not be considered because his initial presentation was VF arrest.
 - B. He should not be considered because he has transaminitis.
 - C. He should be considered with vigilant SCr monitoring.
 - D. He should be considered, but thrombolysis should be initiated concurrently because of the associated risk of clotting.
5. The medical team wants further information about the literature regarding therapeutic hypothermia. Which is the most appropriate information regarding the data to support therapeutic hypothermia?
 - A. Improves survival in PEA cardiac arrests
 - B. Shown to improve neurologic outcomes
 - C. Superiority found when targeting a core temperature of 36°C compared with 33°C
 - D. Most studied in patients with asystole
6. Which is most accurate regarding the classification of J.H.'s BP?
 - A. Hypertensive urgency because she has no signs of target organ damage
 - B. Hypertensive urgency because she has signs of target organ damage
 - C. Hypertensive emergency because she has no signs of target organ damage
 - D. Hypertensive emergency because she has signs of target organ damage
7. Which is the most appropriate initial treatment strategy for J.H.'s BP?
 - A. Phentolamine 1 mg intravenously every 30 minutes
 - B. Metoprolol 25 mg orally every 12 hours
 - C. Nitroprusside 0.25 mcg/kg/minute by continuous intravenous infusion
 - D. Enalaprilat 10 mg intravenously every 6 hours
8. Which is the most appropriate goal for J.H.'s BP reduction?
 - A. Goal mean arterial pressure (MAP) reduction of 25% during the first 60 minutes
 - B. Goal MAP reduction of 50% during the first 60 minutes
 - C. Goal MAP reduction of 25% during the first 24 hours
 - D. Goal MAP reduction of 50% during the first 24 hours

Questions 6–8 pertain to the following case.

J.H. is a 48-year-old woman with no known medical history who presents to the emergency department (ED) for acute onset of shortness of breath, side pain, and some blurry vision. She denies any illicit drug or cigarette use, but she confirms social alcohol intake (about 3 drinks per week). Urine toxicology is negative. Initial vital signs are as follows: blood pressure (BP) 202/140 mm Hg, heart rate (HR) 88 beats/minute, respiratory rate (RR) 22 breaths/minute, and pain 4/10 (chest and side pain). Initial laboratory values are as follows: SCr 0.8 mg/dL, AST 608 U/L, ALT 458 U/L, lipase 20 U/L, total bilirubin (Tbil) 1 mg/dL, direct bilirubin (Dbil) 0.4 mg/dL, WBC 6×10^3 cells/mm³, hemoglobin 11 mg/dL, troponin T less than 0.01 ng/mL, and D-dimer less than 0.5 mcg/mL. Chest radiography shows moderate bilateral pleural effusions and no focal consolidations. Chest computed tomography (CT) is negative for pulmonary embolism. Of note, J.H. is taking no prescription or over-the-counter medications.

I. ADVANCED CARDIAC LIFE SUPPORT**A. Background**

1. Foundation of advanced cardiac life support (ACLS) is effective and timely basic life support (BLS).
2. Sudden cardiac arrest (SCA) continues to be a leading cause of death in many parts of world.
3. SCA can vary in etiology (noncardiac vs. cardiac), circumstances (unwitnessed vs. witnessed), and setting (in vs. out of hospital).
4. Because of heterogeneity, action links that are denoted the “chain of survival” were developed for guidance and include (Circulation 2016;26:133(4):447-454)
 - a. Immediate recognition of SCA and activation of the emergency response system
 - b. Early CPR that emphasizes chest compressions
 - c. Rapid defibrillation, if indicated
 - d. Basic and advanced emergency medical services
 - e. Advanced life support and post–cardiac arrest care
5. Following the chain of survival effectively can improve survival (e.g., with out-of-hospital, witnessed VF arrest survival rates can approach 50%) (Circulation 2006;114:2760-5). Because BLS and ACLS are often experienced as a team approach in the hospital setting, it is imperative to be familiar with all aspects of BLS and ACLS in order to fulfill any role during the arrest situation.

B. Basic and advanced emergency medical services

1. Immediate recognition of SCA and activation of emergency response system (chain of survival): Unresponsive patient or witnessed sudden collapse with absent or gasping abnormal breathing (Circulation 2016;26:133(4):447-454; Acad Emerg Med 2007;14:877-83).
 - a. Ensure that the scene is safe.
 - b. Check for response by tapping on shoulder and shouting at victim; simultaneously check for normal breathing.
 - c. Activate emergency response system (e.g., facility emergency response team), and follow instructions from trained dispatchers/responders (Ann Emerg Med 1993;22:354-65).
2. Early CPR. Follow the sequence of C-A-B (compressions-airway-breathing) (chain of survival).
 - a. C - Chest compressions are an essential component of CPR.
 - i. Often not provided by laypeople until professional emergency responders arrive (Circ Cardiovasc Qual Outcomes 2010;3:63-81)
 - ii. Both an increase in intrathoracic pressure and a direct compression of the heart lead to perfusion and oxygen delivery to the brain and myocardium.
 - iii. All patients with SCA should receive chest compressions (Acta Anaesthesiol Scand 2008; 52:914-9).
 - iv. Place patient on a hard surface, use backboard (unless it will cause interruptions in chest compressions, delay in initiation of CPR, or dislodgment of lines/tubing), and/or deflate air-filled mattresses (J Intensive Care Med 2009;24:195-9; Acta Anaesthesiol Scand 2007;51:747-50; Resuscitation 2004;61:55-61).
 - v. Compress at a rate of 100–120 compressions per minute at a depth of 2–2.4 inches, and allow chest recoil after each compression to avoid decreases in coronary perfusion, cardiac index, myocardial blood flow, and cerebral perfusion (Crit Care Med 2010;38:1141-6; Resuscitation 2006;71:137-45; Resuscitation 2006;71:341-51; Resuscitation 2005;64:363-72, Circulation 2015;132(suppl 2):S315-S367).

- vi. Without the use of a compression feedback device, it may be difficult to judge compression rate and depth. In randomized study, compression feedback devices were shown to increase adherence to CPR guidelines, increase CPR quality, increase rates of ROSC, and decrease morbidity (rib fractures) seen with CPR (Critical Care 2016;20:147:1-8).
- vii. Actual number of chest compressions given per minute is a function of the compression rate and proportion of time without interruption. Goal is to minimize interruptions to chest compressions.
 - (a) Increasing the number of compressions given per minute can affect survival from cardiac arrest (JAMA 2008;299:1158-64) and is a determinant of ROSC and neurologically intact survival (Circulation 2009;120:1241-7; Circulation 2005;111:428-34).
 - (b) Rescuer fatigue is common and may lead to inadequate compression quality (Resuscitation 2009;80:918-4). Recommended to change compressors every 2 minutes (or after five cycles of compressions at a rate of 30:2 compressions/ventilation) with no more than 5 seconds between changes (Resuscitation 2009;80:1015-8).
 - (c) Providers have difficulty and take too long to check for a pulse (Resuscitation 2000;44:195-201). Pulse checks (including initial) should last no more than 10 seconds.
 - (d) Duration of the single longest interruption to chest compressions (regardless of reason) and prolonged pauses have both been negatively associated with survival (Circulation 2015;132:1030-7), reemphasizing the need to minimize interruptions to chest compressions.
 - (e) Compression-first (or “compression only”) CPR decreases time until first compression (Resuscitation 2004;62:283-9) and for suspected out-of-hospital cardiac arrest is now recommended for layperson rescuers (Circulation 2015;132(suppl 2):S315-S367).
- viii. Mechanical chest compressions devices have not been shown to be superior to conventional CPR. They can be considered when prolonged CPR is used, being mindful of interruptions in CPR during device deployment and removal (Circulation 2015;132(suppl 2):S315-S367).
- ix. Emerging data suggests patients can have ROSC with meaningful neurological recovery even after prolonged (>25 min) pre-hospital resuscitation efforts. (Circulation. 2016;133:1386-1396; Resuscitation 2016 <http://dx.doi.org/10.1016/j.resuscitation.2016.05.004>).
- x. End-tidal CO₂ (ETCO₂), coronary perfusion pressure (aortic diastolic pressure - right atrial diastolic pressure), arterial relaxation pressure, regional cerebral oxygenation and central venous oxygen saturation (Scvo₂) correlate with cardiac output and myocardial blood flow during CPR. Threshold values have been reported at which ROSC is rarely achieved, and an abrupt increase in any of these variables is a sensitive indicator of ROSC (Table 1 - Circulation 2015;132(suppl 2):S315-S367; Ann Emerg Med 1992;21:1094-101; JAMA 1990;263:1106-13; Am J Emerg Med 1985;3:11-4; J Emerg Med 2010;38:614-21; Crit Care 2008;12:R115; Crit Care Med 2016; Apr 11[Epub ahead of print]):

Table 1. Useful Physiologic Variables During CPR

Variable	ROSC Rarely Achieved
ETCO ₂	< 10 mm Hg
Coronary perfusion pressure	< 15–20 mm Hg
Arterial relaxation (diastolic) pressure	< 20–40 mm Hg
Regional cerebral oxygenation	< 25%
Scvo ₂	< 30%

Patient Case

1. A.C., a 50-year-old man with a history of gastroesophageal reflux disorder and chronic obstructive lung disease, was admitted for shortness of breath, palpitations, and presumed exacerbation of his lung disease. On hospital admission day 4, A.C. has witnessed cardiac arrest on the medicine unit. The emergency response team of which you are part is called, and when you arrive, the bedside nurse has already begun chest compressions. Which insight would be best shared regarding chest compressions for A.C.?
 - A. Because the nurse has already begun chest compressions, she should continue chest compressions for the duration of CPR.
 - B. Compressions increase intrathoracic pressure and directly compress the heart, which can generate cardiac output and deliver oxygen.
 - C. Because increasing the intrathoracic pressure is vital to oxygen delivery, chest recoil is unnecessary and should be avoided.
 - D. Number of chest compressions given per minute has no impact on any outcomes, so pulse checks, line placements, and airways can be placed as needed without respect to interrupting chest compressions.
- b. A - Airway
 - i. To place an artificial airway in patients without an advanced airway, use the head-tilt, chin-lift technique if patients have no evidence of head or neck trauma and the jaw thrust alone if cervical spine injury is suspected (JACEP 1976;5:588-90; JAMA 1960;172:812-5) (see “Rescue Breaths” following).
 - ii. Cricoid pressure is the technique of applying pressure to the victim’s cricoid cartilage to push the trachea posteriorly and compress the esophagus with the goal of preventing aspiration.
 - (a) May help in visualizing vocal cords during tracheal intubation
 - (b) Recommend against use for adult cardiac arrest because of possible delay or prevention of advanced airway, lack of protection from aspiration, and lack of mastery from “expert” and nonexpert rescuers (Emerg Med Australas 2005;17:376-81; Br J Anaesth 1994;72:47-51)
 - iii. If a foreign body airway obstruction (FBAO) occurs:
 - (a) Do not act if the patient is coughing forcefully because this is a mild FBAO.
 - (b) Signs of severe FBAO include a silent cough, stridor, or increasing respiratory difficulty. If these occur, ask the patient, “Are you choking?” If patients clutch their neck (universal sign of choking) or nod without answering verbally, consider severe FBAO:
 - (1) Activate the emergency response system.
 - (2) Administer abdominal thrusts to nonobese adults.
 - (3) In adults with obesity or women in the late stage of pregnancy, administer chest thrusts.
 - (c) If the patient becomes unresponsive:
 - (1) Place on ground and begin CPR as chest compressions have been shown to generate higher airway pressure than abdominal thrusts (Resuscitation 2000; 44:105-8).
 - (2) Each time the airway is opened during CPR to provide a rescue breath, look for an object in the victim’s mouth and, if found, remove it. If not found, continue giving the rescue breaths (two total breaths), followed by 30 chest compressions.
 - (3) No studies have evaluated the routine use of the finger sweep to clear an airway in the absence of visible airway obstruction. Case reports have shown some efficacy, but harm has also been demonstrated in patients and rescuers. A finger sweep should not be used in the absence of visible airway obstruction.

- iv. Advanced airways
 - (a) Supraglottic airway devices such as the laryngeal mask airway, the esophageal-tracheal Combitube, and the King airway device are considered within the scope of BLS in some districts.
 - (b) Will be discussed further in ACLS (following).
- v. Naloxone for opioid-related life-threatening emergencies.
 - (a) Should be considered when a pulse is present but the patient has abnormal breathing or gasping (e.g. respiratory arrest).
 - (b) Can consider (in addition to BLS) administration of intramuscular (IM) or intranasal (IN) naloxone.
 - (c) In a scenario in which a patient loses their pulse, provision of CPR should commence with continued consideration of naloxone if opioid intoxication is suspected.
 - (d) Administer 0.4mg IM x 1 or 2mg IN diluted in 3mL of normal saline – may repeat every 4 minutes.
- c. B - Rescue breaths
 - i. Primary purpose is to assist in maintaining oxygenation, with secondary purpose of eliminating carbon dioxide (CO₂).
 - ii. Compressions should always be initiated first as the arterial oxygen content of blood remains unchanged until CPR is initiated.
 - iii. Optimal compression/ventilation ratio, inspired oxygen concentration, tidal volume, and RR yet to be determined.
 - iv. Recommended compression-only CPR for layperson rescuers for out-of-hospital cardiac arrest. For health care provider rescuers, recommendation is 1 breath every 6 seconds (10 breaths/minute), pausing compressions for synchronous rescue breaths (Circulation 2015;132(suppl 2):S315-S367).
 - (a) Low minute ventilation (low tidal volume and low RR) can maintain oxygenation and ventilation because of a reduced cardiac output by around 25%–33% even during chest compressions, resulting in a low oxygen uptake and CO₂ delivery (Circulation 1997; 95:1635-41).
 - (b) Excessive ventilation can increase intrathoracic pressure and decrease venous return as well as cause gastric inflation, which can lead to aspiration and regurgitation and decrease survival (Circulation 2004;109:1960-5; Resuscitation 1998;36:71-3; JAMA 1987; 257:512-5).
 - (c) Continuous chest compressions with asynchronous ventilation compared with chest compressions with interruptions for synchronous ventilation has not resulted in improved outcomes when delivered by emergency medical services (N Engl J Med. 2015; 23: 2203-2214).
 - v. Deliver each rescue breath over 1 second. Mouth-to-mouth, mouth-to-barrier, mouth-to-stoma, and mouth-to-nose variations in initial rescue breathing are all acceptable and can produce oxygenation and ventilation (Chest 1994;106:1806-10; Br J Anaesth 1964;36:542-9).
 - vi. Give sufficient tidal volume to produce visible chest rise (Resuscitation 1996;31:231-4).
 - vii. Positive-pressure ventilation
 - (a) Bag-mask ventilation
 - (1) Components include a nonjam inlet valve, either no pressure relief valve or a pressure relief valve that can be bypassed, standard 15-mm/22-mm fittings, an oxygen reservoir to allow for high oxygen delivery, and a non-rebreathing outlet valve (Respir Care 1992;37:673-90; discussion 690-4).
 - (2) Should not be used by a single rescuer.

- (3) Should use an adult bag (1 or 2 L) and deliver (two-thirds or one-third of bag volume, respectively) about 600 mL of tidal volume, which can produce chest rise, oxygenation, and normocarbia (Resuscitation 2005;64:321-5; Resuscitation 2000;43:195-9)
- (b) Supraglottic airway devices (e.g., King airway device) are considered an acceptable alternative to bag-mask ventilation during cardiac arrest (assuming proper training is supplied to rescuer) (Circ J 2009;73:490-6; Prehosp Emerg Care 1997;1:1-10).

Patient Case

2. L.S. is a 66-year-old woman visiting her husband at the hospital on the hospice unit. She is buying lunch in the cafeteria, and while in line to check out, she collapses. The emergency response team of which you are part is summoned. L.S. does not respond to voice or tapping of the shoulder, and a brief look at her chest shows no chest movement. Chest compressions are initiated while the crash cart and defibrillator are retrieved. Of note, a bag-mask ventilator is available at the scene because it is carried with the emergency response team. Which is most accurate about L.S.'s airway and breathing management?
- A. A compression/ventilation ratio of 60:1 should be used because cardiac arrest patients have minimal blood flow and lower oxygenation/ventilation requirements.
 - B. Because it is a multiple-rescuer scene, bag-mask ventilation should not be used because it is recommended only in single-rescuer resuscitations.
 - C. Rescue breaths should be given every 6 seconds (10 breaths/minute), avoiding excessive ventilation and continuing chest compressions.
 - D. Bag-mask ventilation should not be used in any patient because advanced airways are preferred to supply oxygen and eliminate CO₂.
3. Rapid defibrillation with a manual or automated external defibrillator (AED) (chain of survival)
- a. Defibrillation shock = unsynchronized shock.
 - b. Successful defibrillation is defined as 5 seconds or greater of termination of arrhythmia after a shock is delivered.
 - c. Early defibrillation of VF is crucial because it is the most common rhythm in witnessed out-of-hospital SCA, survival diminishes rapidly over time, and VF often progresses to asystole over time (Resuscitation 2000;44:7-17; Circulation 1997;96:3308-13).
 - d. Three key actions must occur within moments of VF SCA to increase the likelihood of survival: (1) activation of the emergency medical services system (e.g., emergency response team), (2) provision of CPR, and (3) shock delivery (Ann Emerg Med 1993;22:1652-8).
 - e. Performing chest compressions while a defibrillator is obtained significantly improves the probability of survival (Circulation 2009;120:1241-7). When VF is present for more than a few minutes, the myocardium becomes deplete of oxygen and energy substrates.
 - i. CPR can provide the oxygen and energy needed until the shock is delivered.
 - ii. Increased likelihood of termination of VF from shock delivery and ROSC if CPR given first (Circulation 2004;110:10-5).
 - iii. If CPR is initiated immediately, survival can double or triple at most time intervals until defibrillation occurs (Resuscitation 2000;44:7-17; Ann Emerg Med 1995;25:780-4; Ann Emerg Med 1993;22:1652-8).
 - f. Early defibrillation is a powerful predictor of ROSC after VF.
 - i. Survival rates are highest for VF when CPR and defibrillation occur within 3–5 minutes of the event (Circ Cardiovasc Qual Outcomes 2010;3:63-81; Resuscitation 2009;80:1253-8).

- (a) For every minute that passes after collapse, survival from VF decreases 7%–10% (Ann Emerg Med 1993;22:1652-8).
 - (b) CPR prolongs VF and delays the progression to asystole (Resuscitation 2000;47:59-70; Am J Emerg Med 1985;3:114-9).
- ii. There is conflicting evidence to recommend delaying shock delivery in order to provide CPR first in VF and pulseless VT; subsequently, CPR should be initiated immediately, with shock delivery as soon as possible.
- iii. One-shock biphasic (bidirectional) shock protocols are better than or equivalent to three-shock monophasic (one-directional) stacked protocols in terminating VF.
 - (a) Almost all AEDs manufactured currently are biphasic.
 - (b) Polyphasic waveform defibrillators are currently under investigation.
- iv. With any shock delivery, chest compressions should resume immediately, and pulse check should be delayed until the end of the next cycle of CPR because this can increase successful defibrillation with ROSC (Circulation 2004;110:10-5; Circulation 2002;105:2270-3).
- v. The optimal shock energy for biphasic first shock has yet to be determined.
 - (a) Low-energy dosages (200 J or less) are safe and have equivalent or higher efficacy of termination of VF than monophasic waveform shocks at the same or higher energy (Circulation 2007;115:1511-7; Prehosp Emerg Care 2000;4:305-13).
 - (b) The energy dosage used should be according to the manufacturer's recommendation (e.g., 120 or 200 J).
- vi. If additional shocks are needed, it is recommended that at least equivalent and potentially higher energy be used.
- vii. Electrode placement
 - (a) Pad positioning is equally effective in terminating ventricular arrhythmias in four positions: anterolateral, anteroposterior, anterior-left infrascapular, and anterior-right infrascapular (Medicina (Kaunas) 2006;42:994-8; Physiol Meas 2006;27:1009-22).
 - (b) Lateral pads should be placed under breast tissue, and hirsute men should be shaved before the placement of pads.
 - (c) In patients with an implantable cardioverter-defibrillator or a pacemaker, it may be beneficial to avoid placing the pads or paddles over the device.
 - (d) Do not place the pads on top of a medication patch because this can cause current impedance or burning of the skin (Am J Emerg Med 1992;10:128-9).
- viii. In-hospital AED use should be considered in ambulatory and unmonitored areas.
- g. Pulseless VT is treated like VF.
- h. Pacing is not recommended for unstable VF or pulseless VT (Circulation 2010;122:S685-705).

Patient Case

3. T.V. is a 72-year-old man with a history of chronic liver disease, hypoglycemia, and atrial fibrillation. He was admitted to the medical intensive care unit (MICU) 2 days ago for severe sepsis requiring aggressive fluid resuscitation and intravenous antibiotics. T.V. did not require vasopressors to treat his severe sepsis. On ICU day 3, T.V. develops VF on telemetry, loses consciousness, and becomes pulseless; the MICU team is summoned for a presumed VF cardiac arrest. Pads are placed on T.V. by the time the team arrives, and the rhythm is confirmed to be VF. Which is the most accurate statement regarding defibrillation for T.V.?
- A. Three vital actions with VF can lead to increased survival if they occur rapidly: activate emergency response system, provide CPR, and deliver shock.
 - B. T.V. should not be defibrillated but should be paced out of the VF, if possible, because pacing is more effective for pulseless VF.
 - C. Chest compressions should be delayed until the defibrillator is charged because defibrillation is the definitive treatment of VF.
 - D. Alternative treatments such as antiarrhythmics, vasopressors, and magnesium should be tried first because there is no time-sensitive nature of VF to predict the success of defibrillation.

C. ACLS (chain of survival)**1. Airway control and ventilation****a. Background**

- i. During CPR, oxygen delivery to the heart and brain becomes more flow-dependent than arterial oxygen saturation-dependent (Ann Emerg Med 1990;19:1104-6).
- ii. Placement of an advanced airway in cardiac arrest should not delay CPR or defibrillation.
- iii. No studies address the optimal timing of advanced airway placement. The guiding general concept is to place the advanced airway while minimizing interruptions to chest compressions.
- iv. Conflicting evidence exists for the urgent placement of an advanced airway.
 - (a) Study of in-hospital cardiac arrest has shown an increased 24-hour survival in patients with an advanced airway placed within 5 minutes but no difference in ROSC (Resuscitation 2010;81:182-6); however, another study has shown a worse overall survival rate in cardiac arrest patients who required intubation (Arch Intern Med 2001;161:1751-8).
 - (b) Out-of-hospital cardiac arrest studies have shown that intubation in the rural and urban setting and, more specifically intubation within 13 minutes, is associated with better survival (Med J Aust 2006;185:135-9; Prehosp Emerg Care 2004;8:394-9).

b. Oxygen during CPR

- i. Unclear what the optimal concentration of inspired oxygen content should be during CPR, but it is currently recommended that maximum (e.g., 100%) inspired oxygen be used to optimize arterial oxyhemoglobin content and, subsequently, oxygen delivery (Circulation 2015;132(suppl 2):S315-S367).
- ii. Patients with a higher Pao₂ were associated with higher survival to hospital admission but not neurologically intact survival, which is likely a function of underlying pathophysiology (Resuscitation 2013;84:770-5).
- iii. Extended exposure to high oxygen concentrations carries the risk of toxicity, but this toxicity has not been shown in the short-term setting of adult CPR (Resuscitation 1999;42:221-9).
- iv. During chest compressions, air is forcefully expelled from the chest, and oxygen is drawn into the chest by passive recoil. Because the ventilation requirements are lower than normal, passive oxygen delivery is theorized to be sufficient for several minutes of initial CPR (Circulation 1994;90:3070-5), but recommendations to remove ventilation cannot be made.

- c. Bag-mask ventilation: Viable option for oxygenation and ventilation during CPR but should be provided only when there is more than one rescuer and/or trained personnel (for more details, see earlier discussion) (Circulation 2010;122:S729-767).
- d. Airway adjuncts
 - i. *Cricoid pressure* should be used only in special circumstances to help visualize the vocal cords and should be relaxed, released, or adjusted if it impedes ventilation or advanced airway placement.
 - ii. *Oropharyngeal airways* can be considered to help facilitate bag-mask ventilation in the unresponsive patient with no cough or gag reflex.
 - iii. *Nasopharyngeal airways* can be considered in patients with airway obstruction and clenched jaw but should be used cautiously in craniofacial injury and avoided in known coagulopathy because of an increased risk of bleeding (J Trauma 2000;49:967-8; Anaesthesia 1993; 48:575-80).
- e. Advanced airways
 - i. Endotracheal intubation
 - (a) Attempted placement by unskilled providers leads to unacceptably large periods of chest compression interruption and hypoxemia.
 - (b) Benefits include keeping the airway patent, allowing for suctioning of airway, ensuring high oxygen concentration delivery, providing medication administration, allowing for specific tidal volume delivery, and providing protection from aspiration.
 - ii. Supraglottic airways
 - (a) Do not require visualization of glottis, which allow for continuous chest compressions.
 - (b) Types studied during cardiac arrest include laryngeal mask airway, esophageal-tracheal tube (Combitube), and laryngeal tube (laryngeal tube or King LT).
 - (1) Laryngeal mask airway: Compared with bag-mask ventilation, is more secure and reliable and has a lower incidence of aspiration. Easier to place than endotracheal tubes, which would allow placement when access to the patient is limited or positioning constraints are in place.
 - (2) Combitube: Compared with bag-mask ventilation, allows isolation of airway, more reliable ventilation, and protection from aspiration. Compared with endotracheal tubes, may be easier to train personnel, and all levels of experience can use (Prehosp Emerg Care 1997;1:1-10).
 - (3) Laryngeal tube or King LT: Potentially easier to insert than the Combitube but not as vigorously evaluated in the cardiac arrest population.
 - (4) No difference in successful prehospital ventilation, ROSC, or 1-month neurologic outcome between laryngeal mask airway and laryngeal tube for out-of-hospital cardiac arrest (Am J Emerg Med 2015;33:1360-3).
 - (c) When used by trained providers, they allow as effective oxygenation and ventilation as bag-mask ventilation and endotracheal intubation.
 - iii. After advanced airways are secured, proper placement should be confirmed with clinical assessment and objective measures without interruptions to chest compressions.
 - (a) Physical assessments include visually inspecting chest rise bilaterally and listening to the epigastrium (breath sounds should be absent) and lung fields (should be equal and adequate).
 - (b) Exhaled CO₂ or esophageal detector devices are a reasonable and objective means of confirmation if continuous waveform capnography is not readily available.
 - (c) Continuous waveform capnography is the most reliable and objective way to ensure, confirm, and monitor correct endotracheal tube placement. Although not specifically studied with supraglottic airways, readings should be similar to endotracheal readings.

- (d) False-positive CO₂ detection (CO₂ detected not from ventilation) is rare, whereas false-negative CO₂ detection (no CO₂ detection when ventilation is occurring) is more common. Most common cause of false-negative CO₂ detection is a reduction in blood flow or CO₂ delivery to lungs (e.g., lack of quality chest compressions, pulmonary embolism, severe airway obstruction). Partial pressure of end-tidal CO₂ (PETCO₂) less than 10 mm Hg during CPR suggests ROSC is unlikely, and maneuvers such as improving quality of chest compressions, adding vasopressor therapy, and so forth, should be considered.
- iv. Post-intubation airway management
 - (a) Airway should be marked (from front of teeth/gums) and secured (with tape or commercial device), avoiding compression around the neck, which could impair venous return from brain.
 - (b) Chest radiography is suggested for confirmation of location of end of endotracheal tube in relation to the carina.
 - (c) Slower ventilator rates (6–12 breaths/minute) have been shown to improve hemodynamic values and short-term survival in animal models of cardiac arrest (Crit Care Med 2006;34:1444-9; Circulation 2004;109:1960-5; Resuscitation 2004;61:75-82).
- v. After placement, continuous chest compressions should be given at a rate of 100-120 compressions per minute. A breath should be delivered every 6–8 seconds (8–10 breaths/minute), making sure to avoid over-ventilation, which could decrease venous return and cardiac output.

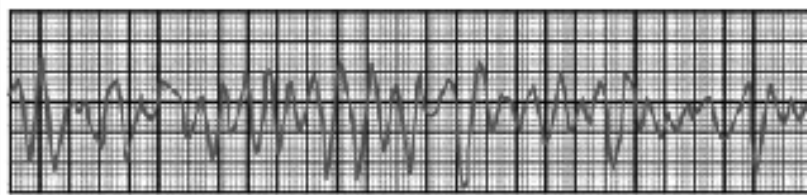
Patient Case

4. F.V. is a 63-year-old woman with a history of diabetes, heart failure with preserved ejection fraction, hypertension, and obstructive sleep apnea who presents to the ED with chest tightness and “feeling funny.” In the ED, F.V. loses consciousness and develops pulseless VT. Chest compressions are initiated immediately, pads are placed, and bag-mask ventilation is given at a compression/ventilation ratio of 30:2. The monitor confirms the rhythm of pulseless VT. The defibrillator is charged, the patient is cleared, and the first shock is delivered. Chest compressions resume, and during the next pulse check, the patient is intubated. F.V. still has no pulse, and chest compressions are continued. Which is the most accurate statement about F.V.’s resuscitation after advanced airway placement?
- A. The compression/ventilation ratio should remain 30:2 to avoid excessive ventilation.
 - B. The advanced airway should have been placed before defibrillation and CPR for pulseless VT.
 - C. The patient should be placed on room air (21% FiO₂ [fraction of inspired oxygen]).
 - D. Proper airway placement should be confirmed with clinical assessment and objective measures.

2. Management of cardiac arrest

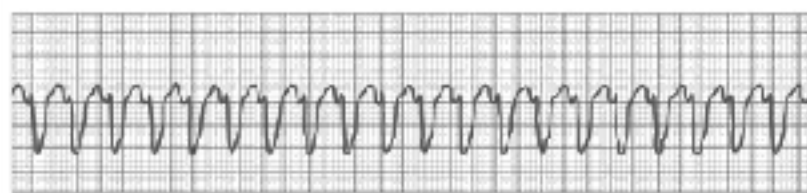
a. Background

- i. Cardiac arrest can be caused by four primary rhythms: VF, pulseless VT, PEA, and asystole.
- ii. These rhythms can also be classified as shockable (VF and pulseless VT) and non-shockable (PEA and asystole).
 - (a) Ventricular fibrillation
 - (1) Wide complex
 - (2) Polymorphic
 - (3) Disorganized
 - (4) Coarse or fine
 - (5) No/minimal forward flow



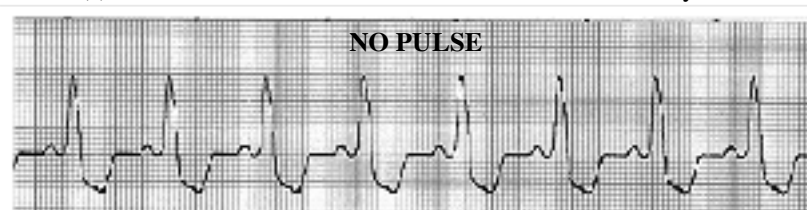
(b) Pulseless VT

- (1) Wide complex
- (2) Monomorphic or polymorphic
- (3) Generally organized
- (4) No/minimal forward flow



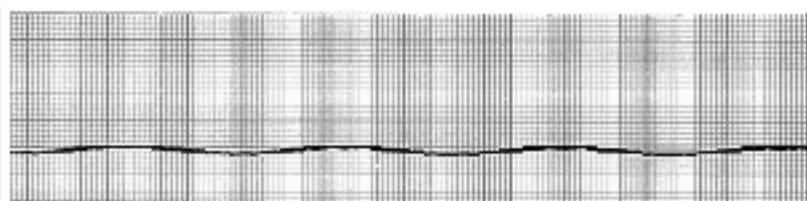
(c) Pulseless electrical activity

- (1) Not a rhythm itself but defined as an organized rhythm that would be expected to produce mechanical activity but does not
- (2) Absent or insufficient mechanical ventricular activity



(d) Asystole (ventricular asystole)

- (1) Absence of detectable ventricular electrical activity
- (2) Accompanied by absence of ventricular mechanical activity



- iii. Survival requires both BLS and ACLS. Foundation of ACLS is high-quality BLS. In addition to CPR, the only proven rhythm-specific therapy that increases survival at hospital discharge is defibrillation of VF/pulseless VT.
- iv. Medications and advanced airways have not been shown to increase survival of cardiac arrest but have been shown to increase the rate of ROSC or survival to hospital admission (Resuscitation 2010;81:182-6; Med J Aust 2006;185:135-9; Resuscitation 2000;45:161-6; N Engl J Med 1999;341:871-8).
 - (a) Vascular access and medication delivery should never interrupt CPR and/or defibrillation. All other therapies are “considerations” and should never compromise chest compressions.

- (b) If interruptions in chest compressions are necessary (e.g., rhythm assessment, delivery of defibrillation shocking in VF/VT), recommendation is to minimize duration (less than 5–10 seconds).
- v. During cardiac arrest treatment, it is imperative to evaluate, treat, and/or reverse any treatable causes of cardiac arrest (Table 2).
- vi. Post–cardiac care should begin immediately after ROSC is obtained to avoid re-arrest.

Table 2. Treatable Causes of Cardiac Arrest

H's	T's
Hypoxia	Toxins
Hypovolemia	Tamponade (cardiac)
Hydrogen ion (acidosis)	Thrombosis
Hypoglycemia	• Pulmonary embolism
	• Coronary thrombosis
Hypo/hyperkalemia	Tension pneumothorax
Hypothermia	

Patient Case

5. V.B., a 62-year-old man with an unknown medical history, comes to your ED altered and incoherent. He is admitted to the ED for observation, where he suddenly becomes unconscious and pulseless. The ED staff immediately initiates CPR for V.B. Which statement best describes appropriate cardiac arrest treatment?
- A. Survival from cardiac arrest is solely dependent on medications and advanced airways, so airway intubation and line placement take priority over CPR.
 - B. The treatable causes of cardiac arrest should be reviewed and addressed while CPR and laboratory tests are sent as able.
 - C. If the patient is in PEA or asystole, pads should be placed, the patient cleared, and shock delivered immediately.
 - D. No strategies exist for post-arrest care to avoid re-arrest or improve outcomes from the cardiac arrest.

- b. Medication background (rhythm independent)
 - i. Goal: Increase myocardial blood flow during CPR and help achieve ROSC
 - ii. Drug delivery
 - (a) Central intravenous administration is recommended, if available. Central line placement should not interrupt CPR. The advantage of central administration is higher peak concentration and shorter drug circulation times than with peripheral routes (Crit Care Med 1988;16:1138-41; Ann Emerg Med 1981;10:73-8; Ann Emerg Med 1981;10:417-9).
 - (b) If peripheral administration of medications is necessitated, the bolus injection should be followed by a 20-mL bolus of an intravenous fluid (e.g., 0.9% sodium chloride) to facilitate drug flow from the extremity to the central circulation (Am J Emerg Med 1990;8:190-3).
 - (c) If proximal humerus intraosseous (IO) access is used, administration and drug delivery are similar to central venous access. If proximal or distal tibial intraosseous access is used, administration and drug delivery are similar to peripheral venous access. In a randomized cadaver study, tibial IO access has been shown to be easier to obtain, which allows for faster medication administration (Medicine 2016; 95: e3724).

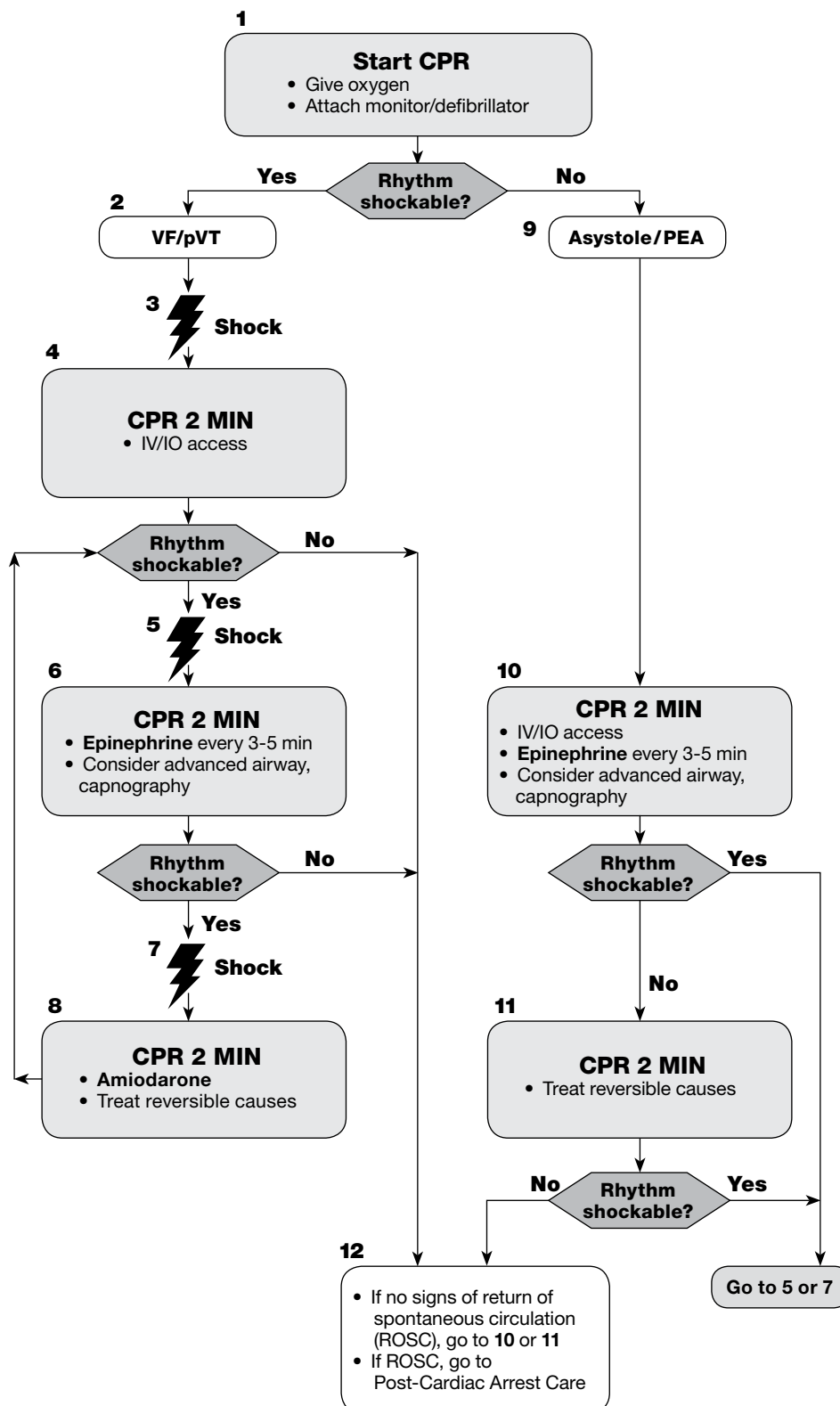
- (d) Endotracheal (ET) delivery
 - (1) NAVEL acronym summarizes medications that have been studied and shown to have tracheal absorption by ET tube delivery. N – naloxone, A – atropine, V – vasopressin, E – epinephrine, L – lidocaine.
 - (2) Serum concentrations of medications are lower when given by ET delivery.
 - (3) Optimal ET doses unknown; typically, they are 2–2.5 times intravenous doses but may be higher (e.g., up to 3–10 higher for epinephrine) (Crit Care Med 1987;15:1037-9).
 - (4) Should be diluted with either 5–10 mL of 0.9% sodium chloride or sterile water and injected directly into the ET tube (Crit Care Med 1994;22:1174-80)
- (e) Peak effect of intravenous or intraosseous medication delayed 1–2 minutes during CPR
- (f) Theoretical concern that giving high-dose bolus vasopressors after ROSC following defibrillation may precipitate cardiac instability and re-arrest. May be avoided by using physiologic monitoring such as quantitative waveform capnography, intra-arterial pressure monitoring, or continuous central venous oxygen saturation monitoring and avoiding administration of vasopressors if ROSC occurs (J Emerg Med 2009;38:614-21; Ann Emerg Med 1992;21:1094-101; Ann Emerg Med 1990;19:1104-6).

Patient Case

6. M.G., a 58-year-old woman with a history of chronic osteoarthritis and peptic ulcer disease, is admitted to the MICU with hypovolemic shock caused by a suspected bleeding gastric ulcer. Endoscopy is performed, confirming the gastric ulceration. The ulcer is cauterized, and M.G. is stabilized. On ICU day 2, M.G. becomes lethargic, hypoxic, and subsequently pulseless. The MICU team is summoned, and the monitor reveals VF. Which general principles are most accurate regarding the medication management of M.G.'s VF arrest?
 - A. Endotracheal delivery is preferred because all cardiac arrest medications can be delivered by the endotracheal route.
 - B. Peripheral administration is preferred because the peak concentrations are higher and the circulation time is shorter than with other routes.
 - C. Intraosseous administration is preferred because administration and dosing are similar to that for the endotracheal route.
 - D. Central intravenous administration is preferred because the peak concentration and circulation time is shorter than with other routes.
- c. Management of VF/pulseless VT (Figure 1): Defibrillation (summary, details available previously in the chain of survival: Defibrillation section)
 - i. When VF/pulseless VT detected, CPR should continue until defibrillator (either manual or automatic) charging period is over.
 - ii. It is strongly recommended that CPR be performed while the defibrillator is readied because chest compressions can deliver oxygen and potentially unload the ventricles, increasing the likelihood that a perfusing rhythm will return after shock is delivered.
 - iii. Because intentionally delaying defibrillation for CPR has mixed results, it cannot currently be recommended.
 - iv. Once defibrillator is charged, patient is “cleared.”
 - v. Shock is delivered, and CPR is immediately resumed, beginning with chest compressions.
 - (a) Pulse check is delayed until 2 minutes of CPR is given.
 - (b) Pause for rhythm and pulse check; continue CPR, if necessary.

- vi. If biphasic defibrillator is available:
 - (a) Provider should use manufacturer's recommended energy dose (e.g., 120–200 J).
 - (b) If information unavailable, the maximum dosing can be considered.
 - (c) Second and subsequent defibrillator energy dosages should be equivalent, and consideration should be made for escalating energy doses, if possible.
- vii. If monophasic defibrillator is available:
 - (a) Initial energy dose should be 360 J.
 - (b) Second and subsequent defibrillator energy dosages should be 360 J.
- viii. If VF/pulseless VT is terminated by defibrillation and reoccurs, resulting in an arrest, the successful energy dosage used previously should be considered.
- ix. Change of multimodal defibrillator from automatic to manual mode may result in fewer interruptions of CPR but also an increased frequency of inappropriate shocks (Resuscitation 2007;73:131-6; Resuscitation 2007;73:212-20).
- d. Medication therapy for VF/pulseless VT
 - i. Previous guidelines suggested medication consideration after one shock and 2 minutes of CPR (one cycle). Recent data from witnessed out-of-hospital cardiac arrest suggest that early administration of epinephrine is associated with improved survival in shockable rhythms (Resuscitation 2015;96:180-5) and that every minute beyond 5 minutes significantly increases the odds of death. With in-hospital arrests, for shockable rhythms, patients receiving epinephrine within 2 minutes of initial shock was associated with a decreased odds of survival, ROSC, and good functional outcome (BMJ 2016; 353: i1577 <http://dx.doi.org/10.1136/bmj.i1577>).
 - ii. Vasopressors:
 - (a) First-line medication is epinephrine. Vasopressin was removed from current guidelines because of equivalence of effect with epinephrine and a drive to simplify treatment (Figure 1; Table 3).
 - (b) No other vasopressors (e.g., phenylephrine or norepinephrine) have shown any benefit compared with epinephrine (JAMA 1992;268:2667-72; Acta Anaesthesiol Scand 1985;29:610-3).
 - (c) Adding methylprednisolone and vasopressin to epinephrine during ACLS plus stress dose hydrocortisone for post-ROSC shock compared with placebo may aid in ROSC during cardiac arrest and improve discharge neurologic function in patients who survive. Role of steroids may be debated, given the addition of vasopressin in the study arm (JAMA 2013;310:270-9). Guidelines suggest this treatment bundle can be considered, but further confirmatory data are needed (Circulation 2015;132(suppl 2):S315-S367).
 - iii. Antiarrhythmics:
 - (a) No evidence that, in cardiac arrest, any antiarrhythmics increase survival to discharge.
 - (b) Conflicting evidence on benefit of amiodarone (Table 3) in the pre-hospital arrest situation:
 - (1) Early evidence suggests an increase in survival to hospital admission with out-of-hospital arrest compared with placebo and lidocaine (N Engl J Med 2002;346:884-90; N Engl J Med 1999;341:871-8). Recent randomized, double-blind data suggests no benefit compared with lidocaine or placebo in one-shock-refractory VF/pulseless VT population (N Engl J Med 2016; 374: 1711-1722).
 - (2) Can be considered for "refractory" (unresponsive to shock x 3, CPR, and a vasopressor) VF/pulseless VT.
 - (3) Administered as intravenous/intraosseous push if pulseless. If pulse is obtained, must be given as slow intravenous piggyback over at least 15 minutes.
 - (4) Hemodynamic effects of bradycardia and hypotension may be partly related to vasoactive solvents (polysorbate 80 and benzyl alcohol) (Am J Cardiol 2002;90:853-9).

- (c) Lidocaine has no proven short- or long-term efficacy in cardiac arrest, but it can be considered if amiodarone is unavailable (Table 3).
- (d) Magnesium sulfate (Table 3) is effective for cardiac arrest caused by torsades de pointes (i.e., caused by early afterdepolarizations during phase 2 of the action potential).
 - (1) Not effective when VF/pulseless VT is not associated with torsades de pointes
 - (2) May consider for emergency magnesium replacement in patients who sustain cardiac arrest and are hypomagnesemic.
 - (3) Optimal dosing has not been established.

Adult Cardiac Arrest Algorithm—2015 Update**Figure 1.** Adult cardiac arrest algorithm**CPR Quality**

- Push hard (at least 2 inches [5 cm]) and fast (100–120/min) and allow complete chest recoil.
- Minimize interruptions in compressions.
- Avoid excessive ventilation.
- Rotate compressor every 2 minutes.
- If no advanced airway, 30:2 compression-ventilation ratio.
- Quantitative waveform capnography
 - If PETCO₂ <10 mm Hg, attempt to improve CPR quality
- Intra-arterial pressure
 - If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality.

Shock Energy

- **Biphasic:** Manufacturer recommendation (eg, initial dose of 120-200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- **Monophasic:** 360 J

Drug Therapy

- **Epinephrine IV/IO Dose:** 1 mg every 3-5 minutes
- **Amiodarone IV/IO Dose:** First dose: 300 mg bolus. Second dose: 150 mg.

Advanced Airway

- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place, give 1 breath every 6 seconds (10 breaths/min) with continuous chest compressions

Return of Spontaneous Circulation (ROSC)

- Pulse and blood pressure
- Abrupt sustained increase in PETCO₂ (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible Causes

- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypo-/hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary

Table 3. Medications Used During Sudden Cardiac Arrest

Medication	Primary Mechanism of Action in Cardiac Arrest	Dosage, Route, Frequency	Clinical Benefits
Epinephrine (N Engl J Med 1992;327:1045-50; Circulation 1984;69: 822-35; Crit Care Med 1979;7:293-6)	α -Adrenergic agonist effects leading to vasoconstriction	1 mg IV/IO q3–5 min 2–2.5 mg ET q3–5 min	Increases coronary and cerebral perfusion pressure during CPR Increases ROSC Increase survival to hospital admission
Amiodarone (N Engl J Med 2002;346:884-90; N Engl J Med 1999;341:871-8; N Engl J Med 2016; 374: 1711-1722)	Na ⁺ /K ⁺ /Ca ²⁺ channel and β -receptor antagonist (Class III antiarrhythmic)	First dose: 300 mg or 5 mg/kg IV/IO x 1 Second dose: 150 mg IV/IO x 1 Max: 2.2 g/day	Conflicting data on clinical outcomes compared with lidocaine or placebo for out-of-hospital arrests
Lidocaine (Resuscitation 1997;33:199-205; N Engl J Med 2016; 374: 1711-1722)	Na ⁺ channel antagonist (Class IB antiarrhythmic)	First dose: 1–1.5 mg/kg IV/IO x 1 Subsequent dosing: 0.5–0.75 mg/kg q5–10 min Max 3-mg/kg cumulative dose	Conflicting data on clinical outcomes for out-of-hospital cardiac arrest.; no improvement in overall or discharge survival Insufficient evidence to recommend for refractory VF/pulseless VT unless amiodarone unavailable
Magnesium (Clin Cardiol 1993;16:768-74; New Trends Arrhythmias 1991;7:437-42; Circulation 1988;77:392-7)	Stops EAD in torsades de pointes by inhibiting Ca ²⁺ channel influx	1–2 g diluted in 10 mL of 5% dextrose or sterile water IV/IO x 1	Can aid in stopping torsades de pointes in patients with prolonged QT interval

EAD = early afterdepolarization; ET = endotracheal; IO = intraosseously; IV = intravenously; q = every.

- e. Management of PEA/asystole
 - i. CPR and treatment of reversible causes are vital to treatment of PEA/asystole.
 - ii. Medication therapy
 - (a) Vasopressors (e.g., epinephrine) can be given as soon as feasible (Table 3).
 - (1) Stepwise increased mortality if first epinephrine dose withheld for more than 4 minutes after in-hospital non-shockable cardiac arrest (BMJ 2014;348:1-9)
 - (2) Recommended for all non-shockable rhythms to administer epinephrine as soon as feasible (Circulation 2015;132(suppl 2):S315-S367)
 - (b) Atropine has been removed from the algorithm because of its lack of therapeutic benefit.
- f. Role in treating reversible causes
 - i. Echocardiography may be helpful, if available, in the management of PEA to help differentiate the following (Am J Cardiol 1992;70:1056-60):
 - (a) Intravascular volume status (ventricular volume)

- (b) Cardiac tamponade
- (c) Massive pulmonary embolism (right ventricular size, function)
- (d) Mass lesions (tumor, clot)
- (e) Coronary thrombosis (right and left ventricular function, regional wall motion abnormalities)
- ii. Because hypoxia is often a cause of PEA arrest, more focused attention may be given to placement of airway and oxygen delivery.
- iii. Please see the specific chapters for pulmonary disorders (massive pulmonary embolism and tension pneumothorax), cardiology (acute myocardial infarction and cardiac tamponade), shock (hypovolemic shock and oxygen delivery), acid-base disorders (acidemia), endocrinologic disorders (hypoglycemia), and electrolytes (hypo/hyperkalemia).
- g. Controversial interventions in cardiac arrest
 - i. Sodium bicarbonate
 - (a) Tissue acidosis and acidemia result during cardiac arrest for several reasons, including inadequate or absent blood flow, arterial hypoxia, or underlying pathophysiology.
 - (b) Mainstays of restoring acid-base status include high-quality chest compressions and appropriate ventilation/oxygenation.
 - (c) Conflicting evidence exists for the use of sodium bicarbonate, with most data showing no benefit or poor outcome with use (Ann Emerg Med 1998;32:544-53; Resuscitation 1995;29:89-95; Am J Emerg Med 1992;10:4-7; Chest 1990;97:413-9; Resuscitation 1989;17(suppl):S161-172; discussion S199-206).
 - (d) Recent data in patients with prolonged CPR efforts (> 20 mins) primarily from VF (~80%) demonstrated an association with increased rate of ROSC (Am J Emerg Med 2016; 34:225-229) after complex retrospective analysis. Caution should be used extrapolating results because significant limitations exist in the study design and all patients included likely were in the metabolic phase of VF (JAMA 2002;288:3035-8) and had pH values < 7.1.
 - (e) Detrimental effects may be associated with sodium bicarbonate in cardiac arrest, including:
 - (1) Compromised coronary perfusion pressure by reducing systemic vascular resistance (JAMA 1991;266:2121-6)
 - (2) Shifting the oxyhemoglobin dissociation curve to the left by creating an extracellular alkalosis and decreased release of oxygen
 - (3) Causing hypernatremia and subsequent hyperosmolarity
 - (4) Producing excess CO₂ through rapid dissociation, which can freely diffuse intracellularly (e.g., myocardial and cerebral cells) and cause intracellular acidosis (Science 1985;227:754-6)
 - (5) Inactivation of concurrently administered catecholamines (e.g., epinephrine) (Hosp Pharm 1969;4:14-22)
 - (f) Certain circumstances may warrant sodium bicarbonate use such as tricyclic antidepressant overdose, bicarbonate (HCO₃⁻)-wasting causes of metabolic acidosis, and hyperkalemia. In addition, it should be noted that endogenous catecholamines have a blunted response during acidosis which may improve if the acidosis is corrected. Initial dosage should usually be 1 mEq/kg intravenous push with monitoring of clinical status, HCO₃⁻ concentration, laboratory values, and blood gas analysis.
 - ii. Calcium
 - (a) No trial has established any impact on survival in either in- or out-of-hospital cardiac arrest (Ann Emerg Med 1985;14:626-9; Ann Emerg Med 1985;14:630-2).
 - (b) Consider in patients with preexisting hypocalcemia and signs and symptoms of acute hypocalcemia (e.g., severe tetany or seizures).

- iii. Atropine
 - (a) No prospective studies have evaluated atropine for bradycardic PEA or asystolic cardiac arrest.
 - (b) Conflicting results exist from retrospective analyses and case reports (*Acta Anaesthesiol Scand* 2000;44:48-52; *Ann Emerg Med* 1984;13:815-7; *Ann Emerg Med* 1981;10:462-7).
 - (c) Atropine has not been associated with harm in treating bradycardic PEA or asystolic cardiac arrest, but because of the lack of convincing evidence of benefit, it is no longer recommended for cardiac arrest.
 - iv. Intravenous fluids
 - (a) Normothermic, hypertonic, and chilled fluids have been evaluated in animal models and small human studies, with no survival benefit.
 - (b) If hypovolemic shock is the suspected cause of the cardiac arrest, fluid resuscitation should be initiated immediately.
 - v. For indications of fibrinolysis for cardiac arrest, please see the Pulmonary chapter for treatment of pulmonary embolism and the Cardiology chapter for treatment of acute myocardial infarction.
 - vi. Pacing
 - (a) Transcutaneous, transvenous, and transmyocardial pacing is not beneficial in cardiac arrest and does not improve ROSC or survival.
 - (b) Not recommended for routine use in cardiac arrest.
 - vii. Dextrose
 - (a) Animal data has demonstrated that dextrose administration before, during, or after cardiac arrest leads to higher rates of mortality and worse neurological outcomes (*J Crit Care* 1987;2:4-14; *Surgery* 1990;72:1005-11; *Acta Anaesthesiol* 1986;100:505-11).
 - (b) Human retrospective data from in-hospital arrests demonstrated that dextrose administration during resuscitation was associated with a significantly decreased chance of survival to discharge and good neurological outcome (*Critical Care* 2015;19:160[1-8]).
 - h. For information on acute symptomatic arrhythmias (bradycardias and tachycardias), see the Cardiology chapter.
- D. Post-Cardiac Arrest Care (chain of survival): Objectives of post-cardiac arrest care can be divided into initial and subsequent (*Circulation* 2010;122:S768-786; *Circulation* 2008;118:2452-83).
- 1. Initial
 - a. Optimize hemodynamics: Target MAP 65-100 mm Hg central venous pressure 8-12 mm Hg, central venous oxygen saturation greater than 70%, urine output greater than 1 mL/kg/hour, and normal serum lactate.
 - i. Consider the patient's normal BP, cause of arrest, and severity of myocardial dysfunction for all values above.
 - ii. Use intravenous crystalloids and colloids, continuous vasopressors and inotropes, transfusions, and renal replacement as needed to meet target goals.
 - iii. In a randomized study of vasopressor dependent shock post-cardiac arrest, the provision of corticosteroids (hydrocortisone 100mg IV q8hr x 7days or until shock reversal) did not improve time to shock reversal, rate of shock reversal, or clinical outcomes (*Critical Care* 2016;20:821-8) and thus should be avoided unless otherwise indicated.
 - b. Transfer patient (out-of-hospital arrest) to a system or unit (in-hospital arrest) that can provide advanced post-cardiac arrest care, including continuous electrocardiographic (ECG) monitoring with immediate 12-lead ECG, central intravenous access if possible, coronary reperfusion, and/or targeted temperature management.
 - c. Try to identify and treat the reversible causes of cardiac arrest (Table 2). Laboratory and diagnostic tests should be performed to aid in identifying a potential underlying cause.

2. Subsequent

- a. Consider therapeutic hypothermia and body temperature regulation (“targeted temperature management” [TTM]). Should be considered for any patient with ROSC who does not follow commands (i.e., comatose) after cardiac arrest.
 - i. Early evidence suggested significant benefit for out-of-hospital primarily shockable rhythm (VF/pulseless VT) cardiac arrest (N Engl J Med 2002;346:549-56; N Engl J Med 2002;346:557-63; Circulation 2010;122:S768-786). Recent meta-analysis demonstrated a similar nonsignificant reduction in mortality and poor neurological outcome (Am J Med 2016;129:522-527) when including all randomized studies. After exclusion of one trial that allowed for TTM in the control arm, there was a significant reduction in poor neurological outcome when implementing TTM.
 - ii. Evidence for nonshockable rhythms (in- and out-of-hospital arrests) has conferred a similar result demonstrating increased survival and better neurological outcomes (Circulation 2015; 132: 2146-2151).
 - iii. Optimal targets, timing, duration, and other variables still unclear:
 - (a) Goal target body temperature 32°C–36°C given recent data showing that targeting 36°C instead of 33°C may be equivocal (Circulation 2015;132(suppl 2):S315-S367; N Engl J Med 2013;369:2197-206; N Engl J Med 2002;346:549-56; N Engl J Med 2002;346:557-63)
 - (b) Duration of at least 12 hours; optimally, a minimum of 24 hours. Ongoing study evaluating 48-hour duration compared with the recommended 24 hours (Trials 2016; 17: 228 (1-9).
 - (c) Initiate therapeutic hypothermia as soon as possible (within 2 hours, if possible), with goal temperature attainment within 6–8 hours; however, several retrospective studies have not confirmed the timing of initiation or the timing of temperature attainment as predictors of neurologic outcome (Acta Anaesthesiol Scand 2009;53:962-34; Int J Cardiol 2009; 133:223-8).
 - (d) Modality for cooling includes feedback-controlled endovascular systems, surface-cooling devices, ice packs/bags, cooling blankets, and/or iced isotonic fluids.
 - (e) Axillary or oral temperature monitoring is inadequate for therapeutic hypothermia (Acta Anaesthesiol Scand 1998;42:1222-6; J Cardiothorac Vasc Anesth 1996;10:336-41) and requires central/core temperatures by esophageal, bladder (avoid in anuric patients), or pulmonary artery temperature monitoring. Ideally, the monitoring modality chosen will be used for other indications as well.
 - (f) Prehospital infusion of cold intravenous fluids for out-of-hospital cardiac arrest in several randomized controlled studies conferred no benefit and may increase the number of complications; thus it is not recommended (Circulation 2015;132(suppl 2):S315-S367).
 - iv. Major complications of therapeutic hypothermia include those related to the cooling and rewarming process and those found in patients undergoing targeted temperature management (Table 4). The adverse events of sepsis, myoclonus, seizures, and hypoglycemia within 72 hours of targeted temperature management have been associated with poor neurologic outcome (Crit Care 2015;19:283-96).

Table 4. Major Organ-Specific Complications of Therapeutic Hypothermia

Musculoskeletal (Crit Care Med 2015;43:2228-38; N Engl J Med 2013;369:2197-206; Anesthesiology 2009;111:110-5; Br J Anaesth 2005;94:756-62; N Engl J Med 2002;346:549-56; N Engl J Med 2002;346:557-63; JAMA 1997;277:1127-34; Am J Physiol 1960;198:481-6)	Shivering: Body's natural response to hypothermia, preceded by arteriovenous vasoconstriction; most common complication of hypothermia; can increase metabolic heat production by 600%, thereby slowing the induction of hypothermia Typically slows or stops at core temperatures < 33.5°C 1. Agents that decrease the shivering threshold (i.e., decreases the temperature at which shivering will occur): a) Scheduled acetaminophen 650 mg q4–6 hr or buspirone 30 mg q12 hr confer modest (0.2°C–0.4°C) reductions in shivering threshold b) Magnesium sulfate reduces the shivering threshold (~0.3°C); can be considered during the induction phase of hypothermia c) Meperidine decreases the shivering threshold (up to 2°C) but should be avoided because of decreased effective glomerular filtration rate (GFR) during hypothermia and subsequent increased risk of seizures when meperidine is used in patients with decreased GFR d) Dexmedetomidine and clonidine decrease the shivering threshold (~0.8°C), but extreme caution should be used because of the hypotensive and bradycardic effects of both agents e) Propofol decreases the shivering threshold by ~0.6°C and has a linear relationship between serum concentrations and reduction in body temperature; Caution should be used given the hypotensive and bradycardic effects 2. Options to stop shivering include: a) Continuous or as-needed paralytics can be used for prevention and treatment of shivering (see the chapter on management of paralytics for appropriate selection and dosing of agent[s]) —Hypothermia decreases clearance and prolongs the duration of neuromuscular blockade (see Table 5 for examples) —Train of four is not a reliable method of monitoring during hypothermia; clinical monitoring or continuous EEG (electroencephalography) may be warranted b) Surface warming if using internal cooling devices c) Chilled fluids to promote faster core temperature reduction

Table 4. Major Organ-Specific Complications of Therapeutic Hypothermia (*continued*)

Neurologic (Circulation 2010;122:S729-767; Circulation 2008;118:2452-83; Pharmacotherapy 2008;28:102-11; Ther Hypo and Temp Manag 2016 DOI: 10.1089/ther.2016.0009)	Sedation and Analgesia: Adequate pain control and sedation must be used Target Richmond Agitation and Sedation Scale score of -3 to -5 (see chapter on sedation for agent selection and dosing) during hypothermia Accumulation of parent and active metabolites can be expected for each analgesic and sedative, which lead to prolonged sedation and potentially untoward adverse effects (see Table 5 for examples) Seizures: Possible complication of cardiac arrest and therapeutic hypothermia Consider benzodiazepines as first line to abort seizure Phenytoin, barbiturates, valproic acid, and propofol can all be used, with vigilant monitoring of adverse effects because of decreased clearance (see Table 5 for examples; for dosing and monitoring values, see the Status Epilepticus chapter) Intracranial Pressure: Increases post-cardiac arrest likely because of ischemic injury and cytotoxic edema and is partially attenuated by TTM Major increase appears to occur during rewarming phase of TTM Uncertain if targeted therapy would impact outcomes
Cardiac (Heart Lung 2001;30:161-3; Int Anesthesiol Clin 1964;2:803-27)	Arrhythmias: Include VT, VF, and atrial fibrillation If life threatening, should consider discontinuing therapeutic hypothermia and active rewarming Sinus bradycardia is common and, in isolation, should not be treated unless it leads to hemodynamic instability (hypotension or organ dysfunction) ECG observations: Prolonged PR, QRS, and QT intervals Caution should be exercised when using medications that prolong the QT interval Hemodynamics: Decreased cardiac output Fluid shifts away from central compartment
Hepatobiliary (Pharmacotherapy 2008;28:102-11; Ther Drug Monit 2001;23:192-7; Anesthesiology 2000;92:84-93; Clin Pharmacol Ther 1979;25:1-7)	Elevated transaminases Reduced activity of non-cytochrome and cytochrome P450-mediated metabolism See Table 5 for examples of metabolic changes in selected medications during hypothermia
Endocrinologic (N Engl J Med 2002;346:557-63; Endocrinology 1970;87:750-5)	Hyperglycemia caused by a decreased insulin production and effect in periphery, increased gluconeogenesis, and glycogenolysis Continuous insulin infusions may be necessary for glucose control. Goal should be < 180 mg/dL without inducing hypoglycemia

Table 4. Major Organ-Specific Complications of Therapeutic Hypothermia (*continued*)

Renal (Resuscitation 2004;60:253-61; J Neurosurg 2001;94:697-705)	Decreased effective glomerular filtration (urine output may increase because of cold diuresis, but not effective) Electrolyte shifts (K ⁺ , PO ₄ ³⁻ , Na ⁺ , Ca ²⁺) during cooling phase; reverse upon rewarming, thus caution should be exerted with replacement
Hematologic (Pharmacotherapy 2008;28:102-11; Br J Haematol 1999;104:64-8; Crit Care Med 1992;20:1402-5)	Coagulopathy caused by thrombocytopenia, impaired activation and activity of clotting factors, impaired platelet function Actively bleeding patients should not be cooled

Table 5. Pharmacokinetic and Pharmacodynamic Changes of Selected Medications During Hypothermia

Fentanyl	Plasma concentration increases by 25% with a 3.7-fold decrease in clearance
Morphine	Receptor affinity (μ) decreases as temperature decreases
Propofol	Plasma concentration increases by 28%; decreased clearance
Midazolam	Clearance decreases by about 11% per degree Celsius below 36.5°C
Rocuronium	Clearance decreases by 50%, increases duration of action 2-fold
Vecuronium	Clearance decreases by 11% per degree Celsius; increases duration of action 2-fold
Cisatracurium	Eliminated by Hofmann elimination, which is a temperature-dependent enzymatic process; anticipate prolonged activity
Phenytoin	AUC (area under the concentration-time curve) increases by 180%; clearance and elimination rate constant decrease by 50%

Information from: Pharmacotherapy 2008;28:102-11; Ther Drug Monit 2001;23:192-7; Anesthesiology 2000;92:84-93; Br J Haematol 1999;104:68-8; Eur J Anaesthesiol Suppl 1995;1:95-106; Clin Pharmacol Ther 1979;25:1-7)

- v. Rewarming should be a passive process over 8 hours (around 0.33°C–0.5°C per hour) (Acta Anaesthesiol Scand 2009;53:926-34; N Engl J Med 2002;346:557-63; N Engl J Med 2002;346:549-56).
- b. Identify and treat acute coronary syndromes.
 - i. Cardiovascular disease and acute coronary ischemia are the most common causes of cardiac arrest (Am Heart J 2009;157:312-8; N Engl J Med 1997;336:1629-33).
 - ii. Consideration of treatment of acute coronary syndromes should not be deferred in patients who are comatose or when therapeutic hypothermia is used.
 - iii. Increased emphasis on early angiography, particularly in out-of-hospital arrests because of the high prevalence of acute coronary occlusion as the cause for the cardiac arrest (Circulation 2015;132(suppl 2):S315-S367).
 - iv. Effects of antiplatelet and antithrombotic drugs augmented by derangements in normal platelet activation/coagulation pathways caused by hypothermia.
 - iv. See the Cardiology chapter for the workup and treatment of acute coronary syndromes.
- c. Optimize mechanical ventilation.
 - i. Goal arterial oxygen saturation is 94% or greater.
 - ii. Avoid hyperventilation or over-bagging to avoid increase in intrathoracic pressure and decrease in cardiac output.
 - iii. Goal PaCO₂ is 40–45 mm Hg or PETCO₂ 35–40 mm Hg.
- d. Support organ systems
 - i. Vasopressor/inotropes to support end-organ perfusion (see Table 6)
 - (a) Adrenergic medications should not be administered with alkaline solutions or sodium bicarbonate because they are inactivated (Hosp Pharm 1969;4:14-22).

- (b) Central line is recommended because any agent with α -agonist properties can lead to extravasation and tissue necrosis.

Table 6. Common Vasoactive Agents Used After Cardiac Arresta

Medication	Typical Dosing Range (mcg/kg/min)	Clinical Pearls
Epinephrine	0.03–0.3	Mixed α and $\beta_{(1>2)}$ activity Used to treat severe hypotension (e.g., SBP < 70 mm Hg) Used for symptomatic bradycardia Used for hemodynamically unstable anaphylactic reactions Higher doses associated with increased α_1 activity
Norepinephrine	0.03–0.3	$\alpha > \beta_{(1>2)}$ receptor activity Used to treat severe hypotension (e.g., SBP < 70 mm Hg) Should be used in volume-resuscitated patients Currently first line for septic shock Higher doses associated with increased α_1 activity
Phenylephrine	0.3–3	Pure α -agonist Used to treat severe hypotension (e.g., SBP < 70 mm Hg) Should be used in volume-resuscitated patients Avoid in patients with low cardiac output
Dopamine	2–20	Dose-related receptor activity: 2–5 mcg/kg/min dopamine receptor, 5–10 mcg/kg/min β_1 -receptor, > 10 mcg/kg/min α_1 -receptor Does not provide exclusive receptor activity across dosing ranges and, thus, can be arrhythmogenic at any dose Use cautiously in patients with a history of heart disease or arrhythmias Useful for patients with bradycardia and hypotension
Dobutamine	2–20	Predominance of inotropic properties but with activity on $\beta_1 > \beta_2 > \alpha_1$ -receptor Used to treat low cardiac output α_1 -agonist and β_2 -agonist counterbalance, leading to little change in systemic vascular resistance Can lead to vasodilation in select patients Less systemic or pulmonary vasodilation than milrinone More tachycardia than milrinone but similar risk of ventricular arrhythmias Use cautiously in patients with a history of arrhythmias
Milrinone	0.25–0.75	Phosphodiesterase type 3 inhibitor leading to increased intracellular cAMP leading to influx of calcium and subsequently inotropy and chronotropy Used to treat low cardiac output Loading dose rarely used because of significant systemic hypotension Longer duration of activity than dobutamine Accumulates in renal dysfunction More systemic and pulmonary vasodilation than dobutamine Less tachycardia than dobutamine but similar risk of ventricular arrhythmias Use cautiously in patients with a history of arrhythmias

^aSee chapter on shock for a detailed discussion regarding selection of agent, dosing, pharmacology, and clinical considerations.

SBP = systolic blood pressure

- ii. Glucose management (Circulation 2010;122:S768-786; Circulation 2008;118:2452-83)
 - (a) Avoidance of severe hypoglycemia (40 mg/dL or less)
 - (b) Target moderate glucose control: 144–180 mg/dL
 - (c) May require continuous insulin infusion to maintain above goals
- iii. Seizure control/prevention (Neurology 1988;38:401-5; JAMA 1985;253:1420-6): Seizures, myoclonus, or both occur in 5%–15% of adult patients who achieve ROSC and are more common in those who remain comatose.
 - (a) Clonazepam, valproic acid, and levetiracetam are all effective for myoclonus, but clonazepam should be considered first line.
 - (b) Benzodiazepines, phenytoin, valproic acid, propofol, and barbiturates are all effective for post–cardiac arrest seizures.
 - (c) For dosing and monitoring guidelines, see the Status Epilepticus chapter.
- iv. Renal dysfunction: The indications for initiating renal replacement therapy in cardiac arrest survivors are the same as in critically ill patients in general (Lancet 2005;365:417-30).
- v. Infectious disease: Association has been shown between the use of prophylactic antibiotics and decreased incidence of pneumonia and sepsis (Resuscitation 2015;92:154-159) in patients who underwent TTM to goal 32-34°C. Impact on length of stay or neurological outcome was not demonstrated and no information is available regarding impact of higher temperature goals on above outcomes.
- e. Assess prognosis.
 - i. Brain injury and cardiovascular instability are the main determinants of survival after cardiac arrest (Intensive Care Med 2004;30:2126-8).
 - ii. If therapeutic hypothermia is considered, a delay of 72 hours after rewarming should be implemented for prognostication.
 - iii. If therapeutic hypothermia is not considered:
 - (a) Prognostication should wait until 72 hours after ROSC.
 - (b) No clinical neurologic sign has shown to be predictive of neurologic prognosis less than 24 hours after arrest (Neurology 2006;66:62-8; Crit Care Med 1987;15:820-5).
 - iv. Prudent to perform any prognostication after removal of opioids, sedatives, paralytics, and so forth.
 - v. Using several modalities of testing including clinical examination, neurophysiological testing, and imaging is recommended.
- f. Assist survivors with rehabilitation needs.

Patient Case

7. K.G., a 71-year-old woman with a history of atrial fibrillation, coronary artery disease status post three-vessel coronary bypass artery grafting 6 years ago, diabetes, and osteoarthritis, is being admitted to your MICU for therapeutic hypothermia after PEA arrest and subsequent ROSC. K.G., who remained comatose after the ROSC, was intubated and is now hemodynamically stable (BP 94/72 mm Hg and HR 86 beats/minute). Which is the most accurate statement regarding targeted temperature management (therapeutic hypothermia)?
- Hypoglycemia is a common complication of hypothermia and may require continuous dextrose infusions.
 - Because of reduced enzymatic activity, dose modifications or avoidance of cytochrome P450 (CYP)–metabolized medications should occur during hypothermia.
 - The optimal duration of therapeutic hypothermia should be at least 72 hours to affect survival.
 - Temperature targets should be 28°C–30°C to improve the neurologic recovery.

II. HYPERTENSIVE CRISIS

- Definitions (Cardiol Clin 2012;30:533-43; Chest 2007;131:1949-62; Cardiol Clin 2006;24:135-46):
 - Hypertensive urgency: A systolic blood pressure (SBP) of 180 mm Hg or greater and/or a diastolic blood pressure (DBP) of 110 mm Hg or greater without evidence of target organ damage
 - Hypertensive emergency: Presence of an abrupt significantly elevated BP (often defined as SBP greater than 200 mm Hg and/or DBP greater than 120 mm Hg) with concurrent target organ dysfunction (e.g., acute kidney injury/failure, heart failure exacerbation, obtundation). Table 7 lists example conditions that, when accompanied by high BP, define hypertensive emergency.
 - MAP: Average pressure in the arteries experienced during one cardiac cycle. Calculated by $MAP = 1/3 SBP + 2/3 DBP$.

Table 7. Examples of Acute Target Organ Damage and Clinical Presentations

Eclampsia, preeclampsia	Hypertensive encephalopathy
Acute kidney injury/failure	Acute shortness of breath, flash pulmonary edema, or acute left ventricular dysfunction
Acute aortic dissection (type A or B)	Acute intracranial bleeding (nontraumatic)
Seizures	Acute myocardial ischemia/infarction
Retinopathy	Cerebral infarction

- Less than 1% of patients with hypertension will experience a hypertensive crisis (Acta Med Scand Suppl 1981;650:1-62).
- 10-year survival approaches 70% (Q J Med 1993;96:485-93), with 1-year survival greater than 90%.
- Common Causes (Cardiol Clin 2012;30:533-43; Cardiol Clin 2006;24:135-46):
 - Intoxications – Cocaine, amphetamines, phencyclidine hydrochloride, stimulant diet pills
 - Nonadherence to antihypertensive regimen
 - Withdrawal syndromes – Clonidine or β -antagonists

4. Drug-drug/drug-food interactions (e.g., monoamine oxidase inhibitors and tricyclic antidepressants, antihistamines, or tyramine)
5. Spinal cord disorders
6. Pheochromocytoma
7. Pregnancy

E. Management:

1. Hypertensive urgency: Lower BP slowly during the first 24–48 hours using oral medications (often home regimen reinitiation). Does not require an ICU admission for treatment.
2. Hypertensive emergency: Requires ICU monitoring and intravenous medications. See goals listed in Table 8.

Table 8. Time Interval for BP Lowering with Hypertensive Emergency^a

Goal Time	BP Target
< 60 min	↓ DBP by 10%–15% or MAP by 25% with goal DBP ≥ 100 mm Hg
2–6 hr	SBP 160 mm Hg and/or DBP 100–110 mm Hg
6–24 hr	Keep above BP goals (hours 2–6) during first 24 hr
24–48 hr	Outpatient BP targets

^aSee exceptions to these goals in the text that follows.

- a. A 25% reduction in MAP during the first hour is targeted to maintain cerebral perfusion (blood flow autoregulation) and to not precipitate ischemia, which has been found with >50% reductions (Stroke 1984;15:413-6).
- b. If neurologic function deteriorates during the initial 25% decrease (or during subsequent lowering), therapy should be discontinued (N Engl J Med 1990;323:1177-83).
- c. Exceptions exist regarding the timing and BP goals listed earlier:
 - i. Acute aortic dissection
 - (a) Propagation of acute aortic dissection is dependent on arterial BP and shear stress (force of left ventricular contraction as a function of time).
 - (b) HR and contractility control can minimize shear stress and, together with BP, become a target of management.
 - (c) Goal HR less than 60 beats/minute and SBP less than 100 mm Hg as soon as possible (within 5–10 minutes).
 - ii. Acute ischemic stroke
 - (a) Hypertension with ischemic stroke is an adaptive response to maintain cerebral perfusion pressure to the brain.
 - (b) Cerebral perfusion pressure (CPP) equals mean arterial pressure minus intracranial pressure (ICP): $CPP = MAP - ICP$.
 - (c) Treatment should occur only if thrombolytic therapy is required (goal SBP less than 185 mm Hg and DBP less than 110 mm Hg to decrease risk of bleeding), other target organ damage occurs, or SBP is greater than 220 mm Hg and/or DBP is greater than 120 mm Hg (Stroke 2013; 44: 870-947).
 - (d) If treatment is indicated (outside of thrombolytic goal stated above): goal 10%–20% MAP reduction over 24 hours (Cardiol Clin 2012;30:533-43; CNS Drugs 2015; 29: 17-28).

- iii. Intracerebral hemorrhage
 - (a) BP reduction goals will be based on individual factors, including medical history; ICP, if known; demographics such as age; presumed cause of hemorrhage (e.g., arteriovenous malformation); and interval since onset.
 - (b) High BP is associated with worse outcomes, including hematoma expansion, neurological deterioration, death, and inability to perform activities of daily living after intracranial hemorrhage (Eur J Neurol 2013;20:1277-83; Stroke 2013;44:1846-51; J Hypertens 2008;26:1446-52).
 - (c) BP reductions in patients without ICP elevations to goal SBP targets of less than 140 mm Hg and/or less than 160 mm Hg have been shown to be safe and may confer benefit regarding functional recovery (Stroke 2013;44:1846-51; Stroke 2012;43:2236-8; Arch Neurol 2010;67:570-6; Hypertension 2010;56:852-8; Lancet Neurol 2008;7:391-9; N Engl J Med 2013; 368: 2355-2365).
 - (d) It is unclear in patients with extreme elevations in BP (e.g., SBP greater than 220 mm Hg), patients with large hematomas, or those with elevations in ICP whether aggressive targets are safe. Aggressive therapy can be considered with a titratable intravenous option with continual clinical and BP monitoring (Stroke 2015;46:2032-60).
3. Agents for BP management of hypertensive emergency
 - a. The drug of choice for hypertensive emergency is intravenous nitroprusside.
 - i. Intravenous nitroprusside works rapidly and is safe in the presence of renal and/or hepatic impairment for short-term use (24 hours or less).
 - ii. Continuous BP monitoring (e.g., arterial line) is recommended with use because rapid changes can occur.
 - iii. Nitroprusside can increase ICP and may result in coronary steal; caution or avoidance should be considered in patients with elevated ICP and acute myocardial ischemia/infarction.
 - b. Table 9 summarizes available agents, dosing, onset, duration, and hemodynamic considerations. Table 10 summarizes possible indications and special considerations.

Table 9. Medications Used in Hypertensive Emergencies

Medication	Usual Dosing Range	Onset	Duration	Preload	Afterload	Cardiac Output
Nitroprusside	IV 0.25–10 mcg/kg/min Titrate by 0.1–0.2 mcg/kg/min q5 min	Seconds	1–2 min	↓	↓↓	↑
Hydralazine	IV bolus: 10–20 mg IM: 10–40 mg q30 min PRN	IV: 10 min IM: 20 min	IV: 1–4 hr IM: 2–6 hr	↔	↓	↑
Nicardipine	IV 5–15 mg/hr Titrate by 2.5 mg/hr q5–10 min	5–10 min	2–6 hr	↔	↓	↑
Clevidipine	IV 1–6 mg/hr Titrate by 1–2 mg/hr q90s. Max 32 mg/hr	1–4 min	5–15 min	↔	↓	↑

Table 9. Medications Used in Hypertensive Emergencies (*continued*)

Medication	Usual Dosing Range	Onset	Duration	Preload	Afterload	Cardiac Output
Nitroglycerin	IV 5–200 mcg/min Titrate by 5–25 mcg/min q5–10 min	2–5 min	5–10 min	↓↓	↓↔	↔↑
Esmolol	IV 25–300 mcg/kg/min (bolus of 500 mcg/kg, not often required given short onset) Titrate by 25 mcg/kg/min q3–5 min	1–2 min	10–20 min	↔	↔	↓
Metoprolol	IV bolus: 5–15 mg q5–15 min PRN	5–20 min	2–6 hr	↔	↔	↓
Labetalol	IV bolus: 20 mg, may repeat escalating doses of 20–80 mg q5–10 min PRN IV 1–2 mg/min Titrate by 1–2 mg/min q2 hr given longer half-life	2–5 min, peak 5–15 min	2–6 hr	↔	↓	↓
Enalaprilat	IV bolus: 1.25 mg q6 hr Titrate no more than q12–24 hr; max dose 5 mg q6 hr	15–30 min	12–24 hr	↓	↓	↑
Phentolamine	IV bolus: 1–5 mg PRN; max 15 mg	Seconds	15 min	↔	↓	↑
Fenoldopam	IV 0.03–1.6 mcg/kg/min Titrate by 0.05–1 mcg/kg/min q15 min	10–15 min	10–15 min	↔↓	↓	↑

IM = intramuscular; IV = intravenous; PRN = as needed.

Table 10. Indications and Special Considerations for Medications Used for Hypertensive Emergencies

Medication	Indication	Special Consideration
Nitroprusside	Most indications (exclusions: ICP elevation, coronary infarction/ischemia)	Liver failure – cyanide accumulation Renal failure – thiocyanate accumulation Can draw serum cyanide and thiocyanate concentrations to monitor Toxicity associated with prolonged infusions (> 72 hr) or high doses (> 3 mcg/kg/min) May result in coronary steal Increases ICP
Hydralazine	Pregnancy	Can result in prolonged hypotension (less predictable dose response) Risk of reflex tachycardia Headaches, lupus-like syndrome (with long-term use)
Nicardipine	Acute ischemic or hemorrhagic stroke	Risk of reflex tachycardia Infusion can lead to large fluid volumes administered

Table 10. Indications and Special Considerations for Medications Used for Hypertensive Emergencies (*continued*)

Medication	Indication	Special Consideration
Clevidipine	Acute ischemic or hemorrhagic stroke	Formulated in oil-in-water formulation providing 2 kcal/mL of lipid calories Caution for patients allergic to soy or eggs
Nitroglycerin	Coronary ischemia/infarction Acute left ventricular failure Pulmonary edema	Tachyphylaxis occurs rapidly, requiring dose titrations Adverse effects: Flushing, headache, erythema; often dose-limiting adverse effects Veno > arterial vasodilator
Esmolol	Aortic dissection Coronary ischemia/infarction	Contraindicated in acute decompensated heart failure Should be used in conjunction with an arterial vasodilator for BP management in aortic dissection (initiate esmolol first because of the delayed onset relative to vasodilators such as nitroprusside) Metabolism is organ-independent (hydrolyzed by esterases in blood) Useful in tachyarrhythmias
Metoprolol	Aortic dissection Coronary ischemia/infarction	Contraindicated in acute decompensated heart failure Should be used in conjunction with an arterial vasodilator for BP management in aortic dissection (initiate metoprolol first because of the delayed onset relative to vasodilators such as nitroprusside) Useful in tachyarrhythmias
Labetalol	Acute ischemic or hemorrhagic stroke Aortic dissection Coronary ischemia/infarction Pregnancy	May be used as monotherapy in acute aortic dissection Contraindicated in acute decompensated heart failure Prolonged hypotension and/or bradycardia may be experienced with over-treatment; dose cautiously
Enalaprilat	Acute left ventricular failure	Contraindicated in pregnancy Caution in dose adjustments given prolonged duration of action
Phentolamine	Catecholamine excess (e.g., pheochromocytoma)	Use in catecholamine-induced hypertensive emergency
Fenoldopam	Most indications	Risk of reflex tachycardia Caution with glaucoma Can cause hypokalemia, flushing May increase ICP

ICP = intracranial pressure.

- c. Certain populations require specific medication therapy approaches:
 - i. Pregnancy
 - (a) Severe preeclampsia can only be managed by delivery of the baby.
 - (b) Magnesium can be considered as an adjunctive therapy to decrease seizure risk or if seizures develop.
 - (c) Intravenous medications should only be considered for persistently elevated BPs (SBP greater than 160 mm Hg and/or DBP greater than 110 mm Hg).

- (d) Hydralazine and labetalol are feasible first-line options, and labetalol may have fewer adverse effects (Am J Health Syst Pharm 2009;66:337-44).
- ii. Catecholamine-induced hypertensive emergency
 - (a) Phentolamine is the drug of choice because it competitively inhibits α -adrenergic receptors.
 - (b) β -Antagonists are contraindicated unless the patient is fully α -blocked.
- iii. Cocaine-induced hypertensive emergency (Ann Emerg Med 2008;52:S18-20; Chest 2007;131:1949-62)
 - (a) Benzodiazepines are used to target the central effects of cocaine as first-line therapy and often will result in control of tachycardia and hypertension. Diazepam 5–10 mg intravenously or lorazepam 2–4 mg intravenously titrated to effect.
 - (b) If central control of cocaine-induced hypertension fails, consider direct α -antagonism with phentolamine.
 - (1) Phentolamine 1 mg intravenously; repeat every 5 minutes as needed
 - (2) If direct α -antagonism does not gain control, consider additional antihypertensives:
 - (A) Nitroglycerin, nicardipine, nitroprusside, or fenoldopam titrated to effect are viable options (see Tables 9 and 10 for dosing and considerations).
 - (B) Verapamil and diltiazem decrease coronary vasospasm associated with acute cocaine intoxication (Am J Cardiol 1994;73:510-3).
 - (C) Controversy exists regarding the use of β -blockers.
 - Labetalol has shown conflicting results regarding ability to control MAP but not alleviate cocaine-induced coronary vasoconstriction.
 - Consensus opinion recommends β -blockers only if full α -antagonism is used first.
- iv. Blood pressure variability (BPV)
 - (a) Concept of BPV emerging as a key therapeutic target in various populations (Stroke 2014; 45: 2275-2279; Euro J of Neuro 2013;20:1277-1283; J of CT and Vasc Anesth 2014;28: 579-585)
 - (b) BPV is often expressed as the standard deviation of SBP, MAP, DBP, or the area under the curve of time spent outside of blood pressure target.
 - (c) In the intracerebral hemorrhage population, decreased BPV has been correlated with improved early neurological function (Euro J of Neuro 2013;20:1277-1283), favorable outcome (Stroke 2014;45:2275-2279), and death or major disability (Lancet Neurol 2014;13:364–73).
 - (d) Agent selection can influence BPV
 - (1) Compared with labetalol, nicardipine has demonstrated superior results regarding BPV (Neurocrit Care 2013;19:41-47; Neurocrit Care 2008;9:167-176), but impact on clinical outcomes has not been demonstrated.
 - (2) In the cardiac surgery population, clevidipine demonstrated better perioperative BPV compared with nitroglycerin or sodium nitroprusside but not compared with nicardipine (Anesth Analg 2008;107:1110-1121) and was associated with decreased time to extubation and postoperative length-of-stay (J of CT and Vasc Anesth 2014;28:579-585).
 - (e) Unclear what the future clinical impact will be on other populations, how agent selection will influence BPV, but should be an area of future research.
- d. All intravenous medications should be transitioned to oral medications as soon as possible.
 - i. Oral antihypertensives should be initiated within 24 hours.
 - ii. Medication history and reconciliation can assist in resuming home regimens.
 - iii. Additional or new agents should be selected according to disease-specific indications.

Patient Case

8. B.B. is a 44-year-old man with no significant medical history who presents to the ED with a ripping sensation in his chest. His social history includes cigarette smoking, 1.5 packs/day for the past 20 years. Chest radiography in the ED reveals mediastinal widening. Cardiac enzymes are within normal limits. Laboratory values include sodium 135 mEq/L, potassium 4.3 mEq/L, HCO_3^- 24 mEq/L, SCr 0.55 mg/dL, glucose 110 mg/dL, DBil 0.2 mg/dL, and AST 39 U/L. B.B. is rushed for a chest CT and angiography, which reveal an acute type A and B aortic dissection. His vital signs include BP 208/140 mm Hg and HR 120 beats/minute. Which is the most appropriate management for B.B.?
- A. Use esmolol to achieve goal of 25% reduction in MAP during the first 60 minutes.
 - B. Use lisinopril and hydrochlorothiazide to achieve BP reduction goal to 160/100 mm Hg during the first 24 hours.
 - C. Use labetalol to achieve 25% reduction in MAP and HR less than 60 beats/minute in the first 60 minutes.
 - D. Use esmolol with or without nitroprusside to achieve SBP less than 100 mm Hg and HR less than 60 beats/minute as soon as possible.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Because rescuer fatigue is common and may lead to inadequate compression quality, it is recommended to change rescuers every 2 minutes, with no more than 5 seconds between changes (Answer A is incorrect). Compressions are vital because they increase intrathoracic pressure and directly compress the heart, leading to oxygen delivery to the vital organs (Answer B is correct). Specific aspects of chest compression quality are necessary. These include a rate of 100–120 compressions per minute at a depth of 2–2.4 inches in adults, allowing for recoil after each compression; placement of the patient on a hard surface (e.g., backboard); and minimization of interruptions (Answer C is incorrect). Outcomes, including neurologically intact survival, ROSC, and possibly overall survival, are linked to minimizing interruptions in chest compressions. Because of this, it is recommended that interruptions (e.g., pulse checks and intubation) be less than 10 seconds and that chest compressions be resumed immediately (Answer D is incorrect).

2. Answer: C

Cardiac arrest patients have minimal blood flow, and oxygenation/ventilation requirements are lower; the new recommendation is to provide 1 breath every 6 seconds (10 breaths/minute) during continuous chest compressions (Answer C is correct). Although the optimal ratio is unclear and chest compressions appear to be more vital to resuscitation, other ratios cannot currently be recommended (Answer A is incorrect). It is clear, however, that excessive ventilation can lead to decreased venous return and gastric inflation, which can lead to aspiration, regurgitation, and impacts on outcomes. In this case, a bag-mask ventilator is available, and more than one rescuers are involved, so the bag-mask ventilator should be used (Answer B is incorrect). In single health care provider rescuer situations, the bag-mask ventilator should never be used, and mouth-to-mouth or mouth-to-barrier resuscitation is recommended. In a single layperson rescuer situation, hands-only CPR is recommended. Advanced airways can be considered but should be placed only by experienced and trained personnel. Bag-mask ventilation can provide adequate oxygenation/ventilation until an airway can be secured (Answer D is incorrect).

3. Answer: A

Three vital actions with VF aid in survival: call emergency response team (already accomplished in case), begin CPR (must be initiated in case), and deliver shock (must occur in case) (Answer A is correct). Pacing can be effective in overriding stable VT but should not be used in the cardiac arrest or hemodynamically unstable patient (Answer B is incorrect). It is currently unclear whether postponing defibrillation for the provision of chest compressions first is of benefit, but it is clear that chest compressions should be initiated until the defibrillator is ready, charged, and set to deliver the shock because this increases the likelihood of success with defibrillation (Answer C is incorrect). Because time in VF predicts survival, and the longer patients are in VF the more difficult it is to terminate the arrhythmia, alternative treatments such as medications should not impede the provision of defibrillation (Answer D is incorrect).

4. Answer: D

After the advanced airway is in place, it is crucial to confirm placement in order to provide the intended oxygenation/ventilation. The confirmation should occur with both clinical and objective measurements (Answer D is correct). These include a physical assessment of the chest and epigastrium, end-tidal CO₂ monitoring, and/or continuous waveform capnography. In most cardiac arrests (particularly in this patient's pulseless VT), airway management should not impede the provision of CPR and/or defibrillation (when defibrillation is indicated) (Answer B is incorrect). After the advanced airway is in place, 100% oxygen should be delivered to optimize the arterial oxygen saturation (Answer C is incorrect). In the cardiac arrest population, this has not been shown to carry the same toxicity as in other populations. Furthermore, after advanced airway is placed, compressions should be administered at a rate of 100–120 compressions per minute continuously, with breaths every 6 seconds (Answer A is incorrect).

5. Answer: B

In all cardiac arrests, the treatable causes (i.e., H's and T's) should be reviewed and addressed, if possible (Answer B is correct). In patients for whom the laboratory and diagnostic data are known, the information should be reviewed while CPR is being provided. In

patients for whom the information is unknown, clinical evaluation and attainment of information should occur, when possible. This retrieval of information, together with the administration of medications and advanced airway placement, should never impede on the provision of CPR or defibrillation, if indicated, because defibrillation (for VF and pulseless VT) and CPR are the only strategies that have been shown to affect survival from cardiac arrest (Answer A is incorrect). Pulseless electrical activity and asystole are not wide complex rhythms, and defibrillation would not be indicated if either were detected (Answer C is incorrect). Post-cardiac arrest care is crucial in the prevention of re-arrest and, in therapeutic hypothermia, can significantly affect neurologic outcomes (Answer D is incorrect).

6. Answer: D

In general, it is important to remember that medication administration benefits only myocardial blood flow, ROSC, and possibly survival to hospital admission in cardiac arrest. Medication administration should never impede the provision of CPR and/or defibrillation. Central administration, if already available, is preferred for several reasons. These include higher peak concentrations, shorter circulation time, more standard dosing, and the lack of additional administration techniques needed (Answer D is correct). Endotracheal administration is an option, but only NALOXONE (naloxone, atropine, vasopressin, epinephrine, and lidocaine) medications can be administered, the optimal doses are unknown, and medications must be diluted before administered (Answer A is incorrect). Given that this patient is in VF arrest, amiodarone, for example, could not be administered by endotracheal administration if it were indicated. Peripheral administration can be used and is the most common route of administration given that most hospitalized patients have it already, but it requires an additional bolus of fluid afterward and has a longer circulating time than does central administration (Answer B is incorrect). Intraosseous can also be used, with the caveat that tibial intraosseous administration is similar to peripheral administration and requires training to master the technique for placement (Answer C is incorrect).

7. Answer: B

Targeted temperature management (therapeutic hypothermia) improves neurologic recovery when initiated, optimally within 2 hours but in up to 6–8 hours for

VF cardiac arrest (application to all forms), and used for 12–24 hours. The goal temperature is 32°C–36°C. Newer data suggest there is no benefit of 33°C versus 36°C in improvement of survival or neurologic outcomes (Answer D is incorrect). If targeted temperature management will be used, close monitoring of complications should occur. These complications include hyperglycemia caused by decreased insulin production and peripheral activity, bradycardias, enzymatic slowing (including CYP system), increased incidence of sepsis and infections, coagulopathies, decreased glomerular filtration, and shivering (Answer B is correct; Answers A and C are incorrect).

8. Answer: D

This patient is experiencing a hypertensive emergency with his target organ damage being an acute aortic dissection. Aortic dissection is one of the individual hypertensive emergencies that has a specific mechanism of worsening (propagation) from BP and shear stress, which require both rapid BP and HR control. Given the gravity of propagation, goals for aortic dissection are HR less than 60 beats/minute and SBP less than 100 mm Hg within minutes, if possible (Answer A is incorrect). This can be accomplished with a single agent like labetalol, which will control HR with its β -antagonist properties and decrease BP (afterload) with its α -antagonist properties (Answers B and C are incorrect). Esmolol can also be used as first line but will likely require an additional afterload-reducing agent such as nitroprusside (Answer D is correct).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: C**

The largest portion of adult cardiac arrests are caused by cardiovascular, not respiratory, events (Answer A is incorrect). In addition, this patient was on room air and nasal cannula immediately before the event, which could suggest his respiratory status was stable and unlikely to lead to cardiac arrest. Advanced airways and medications have only been shown to facilitate ROSC in cardiac arrest in contrast to chest compressions and defibrillation (if indicated), which can improve survival. Because of this, CPR should begin immediately for this patient before line placement to facilitate medication delivery (Answer B is incorrect), starting with chest compressions in accordance with the BLS guidelines with pads placed simultaneously to facilitate rapid defibrillation if the patient's rhythm reveals a shockable rhythm (Answer C is correct; Answer D is incorrect).

2. Answer: A

The cornerstone of therapy for VF cardiac arrest is rapid defibrillation (Answer A is correct). The recommended dosage of voltage for biphasic defibrillators is 200 J or the manufacturer's recommendation (often the same dosage). Although amiodarone is in the treatment algorithm for VF cardiac arrest, it is reserved and recommended for refractory VF cardiac arrest, which is defined as defibrillation refractory (Answer B is incorrect). Therefore, defibrillation should occur first. Atropine has been removed from the cardiac arrest algorithms for PEA and asystole because of a lack of benefit on outcomes and should be not be considered for VF cardiac arrest (Answer C is incorrect). Pacing has not shown benefit in cardiac arrest and should not be used (Answer D is incorrect).

3. Answer: B

Because the rhythm detected is PEA and no longer VF, the cornerstone of therapy changes from giving defibrillation (Answer A is incorrect) to giving high-quality chest compressions and addressing the treatable causes of cardiac arrest (H's and T's) (Answer B is correct). Lidocaine is reserved for refractory VF/pulseless VT (defined as defibrillator refractory) when amiodarone is unavailable (Answer C is incorrect). Atropine was previously recommended for PEA/asystole, but in the 2010 ACLS guidelines it was removed because of a lack of data supporting any beneficial outcomes (Answer D is

incorrect). Therefore, the correct answer for this patient would be targeting high-quality chest compressions and reversing any treatable causes.

4. Answer: C

Targeted temperature management is a consideration, according to the international guidelines for all patients with ROSC who remain comatose after a cardiac arrest (Answer A is incorrect). Although most well-designed and executed studies primarily enrolled patients with VF cardiac arrest, application is recommended for all patients with a cardiac arrest independent of rhythm. Although worsening transaminitis and hepatic enzymatic function slowing is likely to occur during hypothermia, neither of these principles would be considered a contraindication for hypothermia (Answer B is incorrect). Furthermore, renal function with respect to glomerular filtration worsens, which requires vigilant monitoring of renal function and close attention to renal dose modifications and serum concentration monitoring of medications when applicable (Answer C is correct). An additional complication of therapeutic hypothermia is an induced coagulopathy, which leads patients to be at risk of bleeding. Thrombolytics may carry specific indications for cardiac arrest (e.g., pulmonary embolism or acute coronary syndromes), but they would not be recommended empirically (Answer D is incorrect).

5. Answer: B

Therapeutic hypothermia improves neurologic recovery in patients after a cardiac arrest (Answer B is correct). Most patients included in randomized clinical trials have VF as the causative rhythm (Answers A and D are incorrect). Because of its impact on neurologic recovery, guideline recommendations have applied this literature to cardiac arrests of all rhythms, and many institutions have adopted this same recommendation. Recent studies targeting mild hypothermia (36°C vs. 33°C) have shown no difference regarding outcomes between the two modalities, and because of this, some question the utility of hypothermia at all in an era of potentially more advanced cardiac arrest care (Answer C is incorrect).

6. Answer: D

By definition, this patient is having a hypertensive emergency because she has an abrupt, severe increase in

BP with target organ damage (Answer D is correct and Answer C is incorrect)—in this case, potentially shock liver and vision changes. Hypertensive urgency would be defined as an SBP greater than 180 mm Hg and/or a DBP greater than 110 mm Hg without evidence of target organ damage (Answers A and B are incorrect). But given the patient's presentation, she would be classified as having a hypertensive emergency.

7. Answer: C

The patient should be initiated on nitroprusside for BP management (Answer C is correct). Although she has transaminitis, nitroprusside can be used safely in the first 24 hours in these patients. Cyanide accumulation would be a concern with extended use, but for the first 24 hours, the patient will be at minimal risk, and the benefit of rapid BP control outweighs any potential risk. Phentolamine would be reserved for hypertensive crisis that presents from a catecholamine crisis (Answer A is incorrect). Oral metoprolol might be an appropriate option to transition to after the emergency is resolved, but because of the target organ damage, more rapid reduction is needed using an intravenous agent such as nitroprusside (Answer B is incorrect). Enalaprilat is an option, but 10 mg every 6 hours would not be an appropriate starting dose because it would put the patient at risk of overshooting and, given the long duration of activity, could lead to unwanted consequences (Answer D is incorrect).

8. Answer: A

The initial goal reduction for this patient's BP, given that she is experiencing a hypertensive emergency, is a 25% reduction in MAP within the first 60 minutes (Answer A is correct). More rapid BP reductions may result in a lack of cerebral perfusion; therefore, they are not recommended (Answer B is incorrect). The patient is not experiencing any of the specific hypertensive emergencies (e.g., aortic dissection) that would call for a more rapid BP reduction. In addition, she is not experiencing a hypertensive emergency that would require a slower BP reduction (e.g., stroke) (Answers C and D are incorrect).

INFECTIOUS DISEASES I

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Learning Objectives

1. Develop risk factor–based empiric antibiotic regimens for patients with suspected ventilator-associated pneumonia.
2. Identify a definitive management strategy for central line–associated bloodstream infections.
3. Describe definitive and supportive care pharmacotherapeutic interventions for patients with severe influenza.
4. Develop empiric and definitive antimicrobial therapy plans for patients with catheter-related urinary tract infection.
5. Differentiate between location of intra-abdominal infection and respective empiric antimicrobial therapy.
6. Describe the role of antibiotic therapy in patients with acute pancreatitis.
7. Develop a definitive management strategy for critically ill patients with severe *Clostridium difficile* infection.
8. Recommend definitive antibiotic therapy for patients with postoperative wound infection.
9. Describe the role of pharmacotherapy in the management of severe cutaneous reactions.

Abbreviations in This Chapter

ARDS	Acute respiratory distress syndrome
BAL	Bronchoalveolar lavage
CAUTI	Catheter-associated urinary tract infection
CDI	<i>Clostridium difficile</i> infection
CLABSI	Central line–associated bloodstream infection
CVC	Central venous catheter
ED	Emergency department
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IVIG	Intravenous immunoglobulin
MDRO	Multidrug-resistant organism
MICU	Medical intensive care unit
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MRSE	Methicillin-resistant <i>Staphylococcus epidermatitis</i>
MSSA	Methicillin-sensitive <i>Staphylococcus aureus</i>
NHSN	National Healthcare Safety Network
SICU	Surgical intensive care unit

SIRS	Systemic inflammatory response syndrome
SJS	Stevens-Johnson syndrome
TBSA	Total body surface area
TEN	Toxic epidermal necrolysis
UTI	Urinary tract infection
VAP	Ventilator-associated pneumonia

Self-Assessment Questions

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

Questions 1 and 2 pertain to the following case.

K.P., a 38-year-old otherwise healthy woman, was involved in a motor vehicle collision, sustaining a traumatic brain injury and severe chest injuries requiring endotracheal intubation and mechanical ventilation. After being in the trauma intensive care unit (ICU) for 96 hours, a new infiltrate is noted on her chest radiograph, as well as a temperature of 101.9°F (38.8°C), a white blood cell count (WBC) of 15×10^3 cells/mm³, and macroscopically purulent sputum. K.P. is hemodynamically stable. Accordingly, your team decides to obtain a bronchoscopic bronchoalveolar lavage (BAL) of the affected lung field to assess for ventilator-associated pneumonia (VAP).

1. Which is the most likely causative pathogen of K.P.'s suspected VAP?
 - A. *Acinetobacter* spp.
 - B. Methicillin-resistant *Staphylococcus aureus* (MRSA)
 - C. Multidrug-resistant *Pseudomonas aeruginosa*
 - D. *Streptococcus pneumoniae*
2. Based on the 2016 IDSA guidelines, which empiric antibiotic regimen is best for the likely causative pathogen(s) of K.P.'s suspected VAP?
 - A. Azithromycin plus moxifloxacin
 - B. Cefepime
 - C. Ceftriaxone
 - D. Ceftriaxone plus vancomycin
3. T.D. is a 57-year-old man admitted to the medical intensive care unit (MICU) with severe hyperosmolar hyperglycemic syndrome. A subclavian central venous catheter (CVC) is placed on his arrival at the MICU. On ICU day 4, T.D. has a temperature of

- 102.7°F (39.2°C) and a WBC of 17×10^3 cells/mm³. The nurse notes new-onset erythema at the catheter site. After an appropriate diagnostic workup, it is decided to initiate empiric antibiotic therapy for a suspected central line-associated bloodstream infection (CLABSI). Which agent is best for empiric therapy?
- A. Cefazolin
 - B. Linezolid
 - C. Piperacillin/tazobactam
 - D. Vancomycin
4. D.G., a 31-year-old woman, presents to the MICU with severe respiratory failure and acute respiratory distress syndrome (ARDS) requiring intubation after 48 hours of malaise, fever, and myalgias. The nasal washing sent by the emergency department (ED) for rapid diagnostic testing is positive for influenza A. The local prevalence of subtype 2009 H1N1 is high. Which agent would be most appropriate for initial treatment of D.G.'s severe influenza?
- A. Amantadine
 - B. Inhaled zanamivir
 - C. Intravenous zanamivir
 - D. Oseltamivir
5. T.S. is a 79-year-old woman admitted to the MICU for respiratory failure and severe community-acquired pneumonia. T.S. has had a urethral catheter in place for 6 days while mechanically ventilated on fentanyl infusion and intermittent haloperidol as needed for pain and delirium, respectively. This morning, T.S. had a temperature of 101.6°F (38.7°C) and an elevation in WBC to 16×10^3 cells/mm³; she is hemodynamically stable. Blood and urine cultures are sent. Urinalysis reveals significant pyuria. Which pathogen is most likely to cause a catheter-associated urinary tract infection (CAUTI) in T.S.?
- A. *Enterococcus faecalis*
 - B. *Escherichia coli*
 - C. *P. aeruginosa*
 - D. *S. aureus*
6. K.D. is a 59-year-old man admitted to the surgical intensive care unit (SICU) after an emergency operation and partial bowel resection with primary anastomosis for mid-small bowel necrosis and perforation likely secondary to severe peripheral vascular disease. During the operation, significant peritoneal contamination with evidence of gross peritonitis was noted together with persistent hypotension and need for vasopressors. K.D. received perioperative cefazolin and metronidazole. Which empiric antibiotic regimen would be most appropriate for K.D.?
- A. Ceftriaxone and vancomycin
 - B. Ciprofloxacin and metronidazole
 - C. Ertapenem
 - D. Piperacillin/tazobactam
7. T.M. is a 42-year-old man with chronic alcoholism who presents to the ED with severe epigastric pain and serum lipase greater than 10 times the upper limit of normal. The resident orders a computed tomography (CT) scan, which reveals necrosis affecting almost 40% of the pancreas but no abnormal fluid collections or evidence of abscess. T.M. is febrile and tachycardic, and his WBC is elevated. T.M.'s urine output is less than 0.5 mL/kg/hour, suggestive of hypovolemia. Which best describes the role of antibiotic therapy for T.M. at this time?
- A. Antibiotic therapy is not indicated.
 - B. Initiate empiric antibiotic therapy for presumed sepsis and likely pancreatic infection.
 - C. Initiate perioperative antibiotic therapy in preparation for pancreatic debridement.
 - D. Initiate prophylactic antibiotic therapy to prevent infection of necrotic tissue.
8. J.E. is a 67-year-old woman admitted to the MICU for severe metabolic acidosis secondary to unintentional metformin overdose. Her ICU stay has been complicated by a femoral vein CLABSI and related severe sepsis caused by pan-sensitive *E. coli*. J.E. received a 3-day course of empiric piperacillin/tazobactam, removal of her central line, and 11 days of ceftriaxone as definitive therapy with resolution of sepsis. Starting yesterday, it was noted that J.E. had nine loose bowel movements and new leukocytosis of $14,500$ cells/mm³, which suggests *Clostridium difficile* infection (CDI). J.E. continues to tolerate enteral nutrition. Which is the most appropriate regimen for J.E.'s suspected CDI?
- A. Fidaxomicin 200 mg per feeding tube every 12 hours
 - B. Metronidazole 500 mg per feeding tube every 8 hours

- C. Metronidazole 500 mg intravenously every 8 hours
 - D. Vancomycin 125 mg per feeding tube every 6 hours
9. J.S. is a 42-year-old man admitted to the SICU after an open total colectomy with ileostomy for ischemic colitis. On postoperative day 4, the surgery resident on your interdisciplinary ICU team notes moderate erythema (3 cm) and purulent drainage from the wound. The resident subsequently opens the skin portion of the wound and finds infected material just above the unaffected fascia. No systemic signs and symptoms are noted. Which intervention is most appropriate?
- A. Continue dressing changes and patient assessment.
 - B. Initiate empiric vancomycin for postoperative wound infection.
 - C. Initiate empiric antibiotic therapy targeted against skin and colonic flora.
 - D. Initiate broad-spectrum antibiotic therapy for suspected necrotizing fasciitis.
10. A.C. is a 27-year-old man with human immunodeficiency virus (HIV) on active antiretroviral therapy who presents to the burn ICU from an outside hospital with 30% total body surface area (TBSA) epidermolysis of his back and upper arms suggestive of toxic epidermal necrolysis (TEN), likely from sulfamethoxazole/trimethoprim. Reportedly, A.C. arrived at the outside hospital about 6 hours ago with less than 10% TBSA involvement. Vital signs include heart rate 142 beats/minute, respiratory rate 30 breaths/minute, and blood pressure 100/50 mm Hg. Which would be the best initial pharmacotherapeutic intervention?
- A. Administer high-dose corticosteroids to halt the progression of TEN.
 - B. Initiate crystalloid resuscitation for hypovolemia.
 - C. Place a nasogastric tube to administer antiretroviral medications.
 - D. Initiate broad-spectrum antibiotic prophylaxis for wound infection.

I. VENTILATOR-ASSOCIATED PNEUMONIA

A. Epidemiology

1. About 90% of hospital-acquired pneumonia episodes in critically ill patients occur during mechanical ventilation. Mechanical ventilation is an independent risk factor for pneumonia.
2. The incidence of pneumonia increases with the duration of mechanical ventilation. From 9% to 27% of mechanically ventilated patients develop pneumonia. In 2012, the National Healthcare Safety Network (NHSN) reported mean VAP rates across the adult critically ill populations as 0.7–4.4 episodes per 1000 mechanical ventilator-days.
3. The risk of developing VAP is highest during the first 5 days of mechanical ventilation. Individual risk factors for VAP include underlying chronic lung disease, acute lung injury, aspiration, coma, trauma (e.g., chest trauma; traumatic brain injury), burns, reintubation, and overall severity of illness.
4. VAP accounts for more than 50% of antibiotic use in critically ill patients and has an attributable cost of more than \$40,000 per episode.
5. VAP has an estimated attributable mortality of 10%–50%, which varies among critically ill populations.

B. Classification and Etiology

1. VAP is defined as hospital-acquired pneumonia arising more than 48 hours after endotracheal intubation. VAP is further classified by the Centers for Disease Control and Prevention (CDC) as a ventilator-associated event and infection-related ventilator-associated complication. Updated guidelines from the IDSA for the diagnosis and management of VAP were published in 2016. Please see Table 2 at the end of this section for summary and comparison with 2005 guidelines.
2. VAP is usually caused by bacterial pathogens; may be monomicrobial or polymicrobial, but is rarely caused by viral or fungal pathogens.
3. The prevalence of specific bacterial pathogens varies between critically ill patient populations, geographic region, and local antibiotic usage patterns. Risk factors for multidrug-resistant organisms (MDROs) are summarized in Box 1.
4. Classification of VAP as early onset (within the first 2–4 days of hospitalization) or late onset (after 5 days or more of hospitalization) to differentiate between suspected pathogens is no longer recommended. However, longer duration (e.g., 5 days) of hospitalization before the onset of VAP is associated with nosocomial and MDRO pathogens.

Box 1. Risk Factors for MDROs Causing VAP

Prior intravenous antibiotic therapy in preceding 90 days
Acute renal replacement therapy before VAP onset
5 or more days of hospitalization before to the occurrence of VAP
Septic shock at the time of VAP
ARDS preceding VAP

MDRO = multidrug-resistant organism.

C. Prevention

1. VAP is considered a reportable and preventable complication of endotracheal intubation and mechanical ventilation.
2. Data are emerging on effective prevention strategies.
3. Recommended best practices for preventing VAP include:
 - a. Avoid or limit the duration of endotracheal intubation.
 - b. Minimize duration and deep levels of sedation to promote assessment of readiness to extubate.

- c. Maintain and improve physical conditioning while mechanically ventilated.
- d. Minimize pooling of secretions above the endotracheal tube cuff.
- e. Elevate head of bed at least 30 degrees.
- f. Maintain integrity of mechanical ventilator circuit.

D. Diagnosis

1. The diagnostic approach for VAP includes (1) determining whether clinical signs and symptoms are caused by pneumonia and (2) if pneumonia is present, identifying the causative pathogen(s), preferably using lower respiratory tract culture.
2. About half of mechanically ventilated patients with a clinical suggestion of pneumonia will have bacteriologically confirmed pneumonia.
3. Clinical signs and symptoms of pneumonia include new or changing infiltrate on chest radiograph and at least two of the following:
 - a. a. Elevated WBC
 - b. b. Fever (e.g., temperature greater than 100.4°F [38°C])
 - c. c. Macroscopically purulent sputum production
 - d. d. Impaired or worsening oxygenation
4. Lower respiratory tract cultures can be obtained through noninvasive or invasive techniques and reported as qualitative, semiquantitative, or quantitative.
 - a. Quantitative (expressed as colony-forming units per milliliter) and semiquantitative (expressed as rare/few to many) cultures using recommended diagnostic growth thresholds are more specific than qualitative cultures for identifying the causative pathogen.
 - b. Noninvasive techniques: Tracheal aspirate from endotracheal or tracheostomy tube – proximal to distal sampling (depending on depth of sample) of upper airway secretions; usually semiquantitative
 - c. Invasive techniques
 - i. Blind, catheter-directed, or bronchoscopic BAL – Distal sampling of lung lobe/segment using saline lavage; significant quantitative growth threshold above 10,000 or 100,000 CFU/mL
 - ii. Bronchoscopic protected specimen brush – Distal sampling of specific bronchial segment; significant quantitative growth threshold above 1000 CFU/mL
5. The suggested diagnostic strategy for VAP includes clinical suspicion and use of noninvasive sampling with semiquantitative cultures to diagnose VAP, rather than invasive sampling or noninvasive sampling with quantitative cultures.
 - a. If an invasive strategy with quantitative cultures is used, it is suggested that antibiotics be withheld rather than continued if quantitative culture results are below the diagnostic threshold for VAP (i.e., PSB < 1,000 cfu/mL; BAL < 10,000 cfu/mL).

E. Treatment

1. Antibiotic therapy for VAP is empiric or definitive.
2. Antibiotic selections should include intravenous agents able to achieve relevant lung concentrations related to pathogen minimum inhibitory concentration (MIC) dosed optimally using evidence-based pharmacokinetic and pharmacodynamic principles.
3. Empiric antibiotic therapy should be initiated in patients with clinical suspicion for VAP (Table 1). Patients with septic shock should receive antibiotics within 1 hour from onset of hypotension (see Sepsis chapter).
 - a. Inappropriate empiric antibiotic therapy for VAP (delay in or absence of antibiotics active against identified causative pathogen[s]) is associated with increased mortality.

- b. To decrease the likelihood of inappropriate therapy, empiric antibiotic selections should be based on:
 - i. Presence of MDRO risk factor
 - ii. Local VAP pathogen prevalence, particularly MRSA
 - iii. Local antibiotic susceptibility patterns (i.e., ICU-specific antibiogram)
- c. All patients with suspected VAP should receive an antibiotic active against MSSA and *P. aeruginosa*.
 - i. Suggest prescribing two antipseudomonal antibiotics from different classes in patients with any of the following:
 - (a) MDRO risk factor
 - (b) ICU antibiogram with greater than 10% of gram-negative isolates are resistant to an agent being considered for monotherapy (i.e., multidrug-resistant [MDR] *P. aeruginosa*)
 - (c) ICU where local antimicrobial susceptibility rates unavailable
- d. Suggest including an agent active against MRSA in patients with any of the following:
 - i. MDRO risk factor
 - ii. ICU MRSA prevalence greater than 10%–20% of *S. aureus*
 - iii. Prevalence of MRSA is not known
- e. Combination antibiotic therapy using agents with similar bacterial spectra but different mechanisms of action may be necessary to increase the likelihood of appropriate empiric antibiotic therapy for other gram-negative pathogens.

Table 1. VAP Classifications, Associated Pathogens, and Recommended Empiric Antibiotic Therapy Based on 2016 IDSA VAP Guidelines

Likely Pathogens	Recommended Empiric Antibiotic(s) ^a
Patients without MDRO risk factor: Single antipseudomonal agent with 90% or greater empiric activity on local ICU antibiogram, and local MRSA prevalence is less than 10-20%	
<i>P. aeruginosa</i> <i>S. pneumoniae</i> <i>Haemophilus influenzae</i> α - and β -hemolytic <i>Streptococcus</i> spp. Methicillin-sensitive <i>S. aureus</i> (MSSA) Antibiotic-sensitive enteric gram-negative bacilli (GNB) (e.g., <i>E. coli</i> <i>Klebsiella</i> spp.; <i>Enterobacter</i> spp.; <i>Proteus</i> spp.; <i>Serratia</i> spp.)	Cefepime, imipenem, levofloxacin, meropenem, piperacillin/tazobactam
Patient without MDRO risk factor: Single antipseudomonal agent with less than 90% empiric activity on local ICU antibiogram and/or local MRSA prevalence greater than 10-20%^b	
<i>P. aeruginosa</i> Methicillin-resistant <i>S. aureus</i> (MRSA) <i>S. pneumoniae</i> <i>Haemophilus influenzae</i> α - and β -hemolytic <i>Streptococcus</i> spp. Methicillin-sensitive <i>S. aureus</i> (MSSA) Antibiotic-sensitive enteric gram-negative bacilli (GNB) (e.g., <i>E. coli</i> <i>Klebsiella</i> spp.; <i>Enterobacter</i> spp.; <i>Proteus</i> spp.; <i>Serratia</i> spp.)	<u><i>P. aeruginosa</i></u> Antipseudomonal β-lactam^c (aztreonam, cefepime, ceftazidime, imipenem, meropenem, piperacillin/tazobactam) + Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR aminoglycoside^d (amikacin, gentamicin, or tobramycin) <u>MRSA</u> Linezolid or vancomycin

Table 1. VAP Classifications, Associated Pathogens, and Recommended Empiric Antibiotic Therapy Based on 2016 IDSA VAP Guidelines (*continued*)

Likely Pathogens	Recommended Empiric Antibiotic(s) ^a
Patients with MDRO risk factor	
<i>P. aeruginosa</i> Methicillin-resistant <i>S. aureus</i> (MRSA) <i>Acinetobacter</i> spp. Antibiotic-resistant enteric GNB (e.g., extended-spectrum β -lactamase [ESBL]-producing organisms) <i>Stenotrophomonas maltophilia</i>	Antipseudomonal β -lactam ^c (aztreonam, cefepime, ceftazidime, imipenem, meropenem, piperacillin/tazobactam) + Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR aminoglycoside ^d (amikacin, gentamicin, or tobramycin) AND Linezolid or vancomycin

^aAgents/classes are listed in alphabetic order.

^bThere may be situations in which a patient has no MDRO risk factors but may meet the recommendation to receive dual antipseudomonal therapy and/or MRSA coverage.

^cDoripenem has a U.S. Food and Drug Administration (FDA) warning against use for treatment of ventilator-associated bacterial pneumonia.

^dGuidelines suggest avoiding empiric aminoglycoside if alternative agents with activity are available.

- f. Lower respiratory tract cultures should be obtained before initiation of antibiotic therapy to increase the likelihood of identifying causative pathogen(s). Inappropriate delays in initiation of antibiotic therapy should be avoided in unstable patients (e.g., patients with septic shock).
- g. Empiric antibiotic therapy should be de-escalated to definitive therapy, depending on identified pathogen(s) and antibiotic susceptibilities.
4. Definitive antibiotic therapy should be focused on the causative pathogen(s) identified on lower respiratory tract culture.
 - a. Pathogen-specific definitive antibiotic choices should be based on antibiotic susceptibilities and, if possible, available evidence supporting efficacy and safety in patients with VAP.
 - i. MRSA: Vancomycin or linezolid; daptomycin is not indicated for pneumonia because of direct inhibition by pulmonary surfactant.
 - ii. *P. aeruginosa*
 - (a) Monotherapy with a β -lactam listed below and found to be susceptible on final culture results is recommended in immunocompetent patients not in septic shock and not at a high risk of dying. Concomitant aminoglycoside or antipseudomonal fluoroquinolone is recommended in immunocompromised patients and those in septic shock or at a high risk of dying. Combination therapy can be de-escalated to monotherapy β -lactam once septic shock resolves.
 - (b) β -Lactams: Cefepime, ceftazidime, piperacillin/tazobactam, imipenem, or meropenem
 - (c) Aminoglycosides: Amikacin, gentamicin, or tobramycin
 - (d) Fluoroquinolones: Ciprofloxacin or levofloxacin
 - iii. *Acinetobacter* spp.: Imipenem or meropenem; ampicillin/sulbactam (sulbactam is active agent) as alternative option
 - iv. *Stenotrophomonas maltophilia*: Sulfamethoxazole/trimethoprim
 - v. Extended-spectrum β -lactamase (ESBL)-producing organisms: Carbapenem (e.g., ertapenem; imipenem; meropenem)

- b. Duration of definitive antibiotic therapy is recommended to be 7 days for all patients rather than longer durations. Pathogen-based recommendations for duration of definitive antibiotic are no longer indicated in VAP guidelines.
 - i. The PneumA trial was a pivotal noninferiority study that evaluated 8 days (7 full treatment days) versus 15 days (14 full treatment days) for duration of definitive antibiotic therapy in patients with bacteriologically diagnosed VAP. The primary noninferiority outcome was VAP recurrence. All patients included in the study received appropriate empiric antibiotic therapy (JAMA 2003;290:2588-98). Major study findings were:
 - (a) Definitive antibiotic therapy for 8 days was noninferior to 15 days in patients with VAP not caused by non-lactose-fermenting gram-negative bacilli (e.g., *P. aeruginosa*).
 - (b) Patients with VAP caused by non-lactose-fermenting gram-negative bacilli in the 8-day group more often had VAP recurrence.
 - (c) The rate of MDR pathogens during a recurrent VAP episode was higher in patients in the 15-day group.
 - ii. Two meta-analyses that included the results of the PneumA trial suggest limited benefit of prolonged duration of definitive antibiotic therapy for treating VAP. Synopsis includes:
 - (a) Any increase in VAP recurrence rate is small;
 - (b) Mortality and clinical cure do not appear to be affected by shorter durations;
 - (c) Evidence for recurrence from subgroup analyses has important limitations.
 - iii. Guidelines acknowledge that situations may exist in which shorter or longer durations of definitive antibiotic therapy may be indicated, depending on the rate of clinical and radiologic improvement.
5. Response to antibiotic therapy should be assessed serially using clinical signs and symptoms of infection and status of VAP-related organ dysfunction.
 - a. Lack of response in signs and symptoms of VAP beyond treatment day 3 necessitates reassessment of diagnosis, causative pathogen(s), antibiotic regimen, and presence of pneumonia-related complications (e.g., ARDS).
 - b. Patients thought to have persistent VAP should undergo repeat lower respiratory tract culture and receive empiric antibiotic therapy considering previous pathogen(s) and antibiotic exposure.

Table 2. Summary of Key Changes in 2016 IDS VAP Guidelines

Characteristic	2005 Guidelines	2016 Guidelines
Methodology	Expert opinion based on level of evidence ranging from Level I (high) to III (low)	GRADE criteria to identify “recommended” (strong) or “suggested” (weak) guidance based on level of evidence categories “very low,” “low,” “moderate,” and “high quality”
Diagnosis	Clinical strategy or bacteriologic strategy	Suggest clinical suspicion with noninvasive sampling and semiquantitative cultures If invasive sampling is used, suggest that antibiotics be withheld rather than continued if quantitative culture results are below the diagnostic threshold for VAP
Classification	Early onset or late onset	No longer differentiate VAP episodes based on time from hospital admission Emphasis on local risk assessment for <i>P. aeruginosa</i> and MRSA occurring early in hospitalization

Table 2. Summary of Key Changes in 2016 IDS VAP Guidelines (*continued*)

Characteristic	2005 Guidelines	2016 Guidelines
MDRO Risk Factors	• Antibiotic therapy in preceding 90 days • Chronic dialysis within 30 days • Current hospitalization of 5 days or more • Home chronic wound care • Home infusion therapy • Hospitalization in the preceding 90 days • Immunosuppressive disease and/or therapy • Known contact or colonization with MDROs • Residence in a nursing home or extended-care facility	• Prior intravenous antibiotic therapy in preceding 90 days • Acute renal replacement therapy before VAP onset • 5 or more days of hospitalization before the occurrence of VAP • Septic shock at the time of VAP • ARDS preceding VAP
Empiric Therapy	Categorized based on early onset or late onset and presence of MDRO risk factor • Early onset without MDRO risk factor: no antipseudomonal or MRSA coverage • Late onset or early onset with MDRO risk factor: dual antipseudomonal and MRSA coverage	Recommend coverage for MSSA, <i>P. aeruginosa</i>, and other gram-negative bacilli in all empiric regimens. Suggest including an agent active against MRSA if any of the following: • MDRO risk factor for antimicrobial resistance • ICU MRSA prevalence greater than 10%-20% of all <i>S. aureus</i> • Prevalence of MRSA is not known Suggest prescribing dual antipseudomonal antibiotics from different classes if any of the following: • MDRO risk factor for antimicrobial resistance • ICUs with greater than 10% of gram-negative isolates are resistant to an agent being considered for monotherapy • ICU where local antimicrobial susceptibility rates unavailable
Aminoglycosides	No specific recommendation	Suggest avoiding if alternative agents with adequate gram-negative activity are available
Colistin	No specific recommendation	Suggest avoiding if alternative agents with adequate gram-negative activity are available
Duration of Definitive Therapy	In patients who received appropriate empiric antibiotic therapy: • Non-lactose-fermenting Gram negative bacilli: 14 days • All other pathogens: 7 days	Recommend 7 days rather than longer durations regardless of pathogen Suggest using procalcitonin plus clinical criteria to guide discontinuation of antibiotic therapy, rather than clinical criteria alone

Patient Cases

1. C.T. is a 48-year-old man sustaining a 40% TBSA burn to his left side with likely inhalational injury requiring mechanical ventilation. C.T. has been in the ICU for 7 days. Overnight, C.T. had a temperature of 102.1°F (38.9°C), a WBC of 18×10^3 cells/mm³, and an increase in macroscopically purulent sputum production; C.T. is hemodynamically stable with no signs of new-onset organ dysfunction. C.T.'s chest radiograph is difficult to assess, given his inhalational injury. The respiratory therapist was asked by the fellow to do a catheter-directed BAL for suspected VAP. The culture was sent to the microbiology laboratory. Which would be best to do at this point?
 - A. Initiate broad-spectrum empiric antibiotic therapy for suspected MDR VAP.
 - B. Use Gram stain results to determine empiric antibiotic regimen.
 - C. Await preliminary quantitative culture results before initiating empiric antibiotic therapy.
 - D. Send blood and urine cultures, and await their results before initiating empiric antibiotic therapy.
2. C.P. is a 67-year-old woman with a medical history significant for chronic obstructive pulmonary disease (COPD), type 2 diabetes, and coronary artery disease. She is readmitted to the ICU with respiratory failure requiring intubation secondary to severe COPD. C.P. had a 10-day hospitalization 12 days ago, during which time she received intravenous azithromycin for a COPD exacerbation. On day 4 of this readmission, a worsening infiltrate is in the left lower lung base with increased sputum production from admission, maximum temperature is 101.9°F (38.8°C), and there is worsening oxygenation, despite previous improvement in initial COPD exacerbation. The patient is thought to have clinical VAP, and a semiquantitative tracheal aspirate is sent to identify causative pathogen(s). The local ICU prevalence of MRSA is 30%, and the most active β -lactam antibiotic against *P. aeruginosa* on the antibiogram has 80% activity. Which empiric antibiotic regimen is best for this patient?
 - A. Azithromycin plus moxifloxacin
 - B. Cefepime plus tobramycin, and vancomycin
 - C. Ceftriaxone plus azithromycin
 - D. Linezolid plus tobramycin
3. K.L., a 37-year-old man who presents after a motorcycle collision, has sustained several orthopedic and chest injuries. K.L. has been mechanically ventilated for 8 days, during which time he was given a diagnosis of VAP caused by *Klebsiella pneumoniae*. K.L. received appropriate empiric antibiotic therapy and has improved oxygenation, decreased WBC temperature curve. Which would be the best duration of definitive antibiotic therapy for K.L.'s VAP?
 - A. 48 hours after resolution of clinical signs and symptoms
 - B. 7 days
 - C. 10 days
 - D. 14 days

II. CENTRAL LINE–ASSOCIATED BLOODSTREAM INFECTIONS

A. Epidemiology

1. Critically ill patients commonly require short-term (less than 14 days per catheter) or temporary (non-tunneled or non-implanted) placement of a CVC or central line for medication administration and hemodynamic support and monitoring.
2. More than 40,000 bloodstream infections a year are associated with central catheter placement.
3. In 2012, the NHSN reported rates of CLABSI across adult critically ill populations of 0.8–3.4 episodes per 1000 central line–days. Although specific rates vary, all central line types and locations of insertion have an attributable risk of bloodstream infection.
4. Established risk factors for CLABSI include:
 - a. Excessive manipulation of the catheter during and after insertion
 - b. Internal jugular or femoral insertion site
 - c. Microbial colonization at the insertion site or catheter hub
 - d. Neutropenia
 - e. Prolonged duration of catheterization
 - f. Prolonged hospitalization before catheterization
 - g. Total parenteral nutrition
5. The attributable cost of a CLABSI is up to \$40,000 per episode.

B. Definitions

1. Central or peripheral venous catheters are defined by the location at which the distal tip of the catheter terminates. CVCs terminating in a great vessel are considered part of the central blood circulation. The distal tip of a CVC usually resides in the inferior, superior, or distal vena cava, right atrium, or pulmonary artery (e.g., pulmonary artery catheter).
2. CVCs are usually inserted into the central venous system using the internal or external jugular, subclavian, femoral, or iliac veins. There are several types of short-term CVCs:
 - a. Single- and multiple-lumen (e.g., triple lumen) catheters: Most commonly used CVC
 - b. Catheter introducer: Used for massive resuscitation or facilitation of pulmonary artery catheter insertion
 - c. Peripherally inserted central catheter (PICC): Short- or medium-term central catheter inserted in a peripheral vein (e.g., cephalic, basilic, or brachial veins)
 - d. Pulmonary artery catheter: A central catheter of around 100 cm used for invasive hemodynamic monitoring
3. Primarily for surveillance, the CDC defines CLABSI as a primary laboratory-confirmed bloodstream infection occurring no sooner than 2 calendar days from catheter placement and no later than the day after catheter removal. Laboratory-confirmed bloodstream infection is defined as either:
 - a. A recognized pathogen (i.e., not a common commensal organism) cultured from one or more blood cultures, and the organism cultured from blood is not related to an infection at another site, or
 - b. A common commensal organism (e.g., diphtheroids, *Bacillus spp.*, *coagulase-negative staphylococci*, *viridans streptococci*) cultured from two or more blood cultures drawn on separate occasions, and the organism cultured from blood is not related to an infection at another site, and patient has at least one of the following signs or symptoms: fever (temperature greater than 100.4°F [38°C]), chills, or hypotension

4. The Infectious Diseases Society of America (IDSA) defines a catheter-related bloodstream infection as minimally bacteremia or fungemia in a patient who has an intravascular device and:
 - a. More than one positive blood culture obtained from a peripheral vein. A definitive diagnosis requires that the same organism(s) grow from at least one percutaneous blood culture and from the CVC tip or that two blood cultures, one from a catheter hub and one from a peripheral vein, are positive for the same organism(s).
 - b. Clinical manifestations of infection (e.g., fever, chills, and/or hypotension), and
 - c. No apparent source for bloodstream infection other than the catheter
- C. Etiology
1. CLABSIs are usually monomicrobial. Pathogen prevalence is based on patient-specific risk factors and underlying illness.
 2. Common organisms responsible for CLABSIs include coagulase-negative staphylococci (e.g., *Staphylococcus epidermidis*), *S. aureus*, *Candida* spp., and enteric gram-negative bacilli (e.g., *E. coli*, *Klebsiella* spp., *Enterobacter* spp.).
 3. Risk factors for MDROs include critical illness, femoral catheter placement, immunosuppression, and previous antibiotic exposure.
 4. *Candida* spp. are more common in patients with the following risk factors: total parenteral nutrition, prolonged exposure to broad-spectrum antibiotics, hematologic malignancy, stem cell or solid-organ transplantation, femoral site of catheterization, or colonization owing to *Candida* spp. at several sites.
- D. Prevention
1. CLABSI is considered a preventable complication. The NHSN, using CDC definitions, provides population-specific event rates for institution surveillance and performance benchmarks.
 2. The foundation for preventing CLABSI includes training and education, proper aseptic insertion techniques, and active surveillance and performance improvement systems.
 3. Recommended best practices for preventing CLABSI have been proposed and endorsed by the IDSA, the Society for Healthcare Epidemiology of America (SHEA), and the Joint Commission. These evidence-based recommendations are categorized as basic practices for all acute care hospitals or special practices wherein basic practices are less than effective at reducing CLABSI rates. The entire document is available (Infect Control Hosp Epidemiol 2014;35:753-71). Major recommendations include:
 - a. Basic practices
 - i. Minimize central venous line insertions and durations of insertion.
 - ii. Provide comprehensive education to and ensure competency for all involved with insertion, care, and maintenance of CVC.
 - iii. Daily chlorhexidine baths for patients to reduce colonization
 - iv. Use of a systematic process or checklist at the time of insertion to ensure adherence to proper insertion technique
 - v. Alcohol-based chlorhexidine skin cleanser for the site during insertion
 - vi. Handwashing during insertion, care, and maintenance of the catheter
 - vii. Cleanse catheter hubs before accessing.
 - viii. Routine post-insertion site care
 - ix. Limit prolonged use of intravenous tubing sets.
 - b. Special practices
 - i. Use antiseptic or antimicrobial-impregnated catheters.
 - ii. Chlorhexidine-containing site/catheter dressings
 - iii. Use antiseptic hub cover or port protector.
 - iv. Antimicrobial lock therapy

E. Diagnosis

1. Clinical signs and symptoms of infection have poor sensitivity and specificity. Fever is the most sensitive clinical finding, whereas inflammation or purulence at the insertion site is the most specific.
2. If a CLABSI is suspected, paired blood cultures drawn from the catheter (at least one hub/port) and from a peripheral vein should be obtained. The individual bottles should be appropriately marked through the culture-reporting period.
 - a. If a blood culture cannot be drawn from a peripheral vein, it is recommended that at least two blood cultures be obtained through different catheter hubs/ports.
 - b. Blood cultures positive for *S. aureus*, coagulase-negative staphylococci, or *Candida* spp. that are not attributable to another source should increase the suggestion of CLABSI.
 - c. Blood cultures should be obtained before initiation of antimicrobial therapy, as appropriate.
3. A definitive diagnosis of CLABSI requires positive percutaneous blood culture results with positive culture of same pathogen from the catheter tip or catheter-drawn cultures.

F. Treatment

1. Catheter removal should be considered in all patients with a confirmed CLABSI. If a CVC is still necessary, a different anatomic site should be used. Changing to a new catheter at the same site using a guidewire or catheter introducer should be avoided.
2. Antimicrobial therapy for CLABSI is empiric or definitive.
3. Inappropriate empiric antimicrobial therapy is associated with increased mortality, including bacterial and fungal etiologies.
 - a. Empiric antimicrobial therapy should minimally include an agent active against methicillin-resistant coagulase-negative (e.g., methicillin-resistant *S. epidermidis* [MRSE]) or coagulase-positive (e.g., MRSA) staphylococci. Vancomycin or daptomycin are preferred; linezolid should not be used for empiric management of CLABSI.
 - b. Pathogen-specific risk factors, documented colonization, and previous antimicrobial exposure should be considered when choosing empiric antimicrobial therapy.
 - i. Patients at risk of MDROs should receive combination therapy against gram-negative bacilli using agents from separate antibiotic classes.
 - ii. Use of an echinocandin (e.g., anidulafungin, caspofungin, or micafungin) should be considered for patients at risk of candidemia. Fluconazole is reasonable in patients without recent exposure to and low prevalence of nonsusceptible species.
 - c. Local antimicrobial activity should be considered to increase the probability of appropriate therapy.
 - d. Empiric antimicrobial therapy should be de-escalated, depending on the identified pathogen(s) and related antimicrobial susceptibility. Antimicrobial therapy should be discontinued if a CLABSI is not evident and there are no other sources of infection.
4. Definitive management and antimicrobial therapy should be based on whether the CLABSI is complicated or uncomplicated and the identified pathogen(s). Ongoing clinical trials may provide guidance to the optimal duration of antibiotic therapy for CLABSI and non-central line-associated bacteremia (e.g., BALANCE Trial. *Trials* 2015;16:173.).
 - a. The duration of antimicrobial therapy should be based on the first day of negative blood culture.
 - b. Complicated CLABSI
 - i. Endocarditis; immunosuppression (*S. aureus* only); diabetes (*S. aureus* only); chronic intravascular hardware; osteomyelitis; positive blood cultures greater than 72 hours from initiation of appropriate therapy; septic thrombus; thrombophlebitis
 - ii. Remove catheter.
 - iii. Treat with pathogen-targeted antimicrobial therapy for 4–6 weeks; 6–8 weeks for osteomyelitis.

- c. Uncomplicated CLABSI
 - i. Coagulase-negative staphylococci
 - (a) Consider catheter removal. If catheter is retained, consider antibiotic lock therapy in addition to systemic antibiotic therapy.
 - (b) Treat with systemic antibiotic therapy for 5–7 days.
 - ii. *S. aureus*
 - (a) Remove catheter.
 - (b) Treat with systemic antibiotic therapy for a minimum of 14 days.
 - (1) Methicillin-sensitive *S. aureus* (MSSA) – Penicillinase-resistant penicillin (e.g., nafcillin); first-generation cephalosporin (e.g., cefazolin)
 - (2) MRSA – Vancomycin; daptomycin or linezolid; sulfamethoxazole/trimethoprim
 - (c) Patients with catheter tip bacterial growth but negative blood cultures should receive antibiotic therapy for 5–7 days with close monitoring for signs and symptoms of ongoing infection and consideration for repeat blood cultures.
 - iii. *Enterococcus* spp.
 - (a) Remove catheter.
 - (b) Treat with systemic antibiotic therapy for 7–14 days.
 - iv. Gram-negative bacilli
 - (a) Remove catheter.
 - (b) Treat with systemic antibiotic therapy for 7–14 days.
 - v. *Candida* spp.
 - (a) Remove catheter.
 - (b) Treat with systemic antifungal therapy for at least 14 days.

Patient Cases

4. T.W. is a 47-year-old woman admitted to the MICU with respiratory failure secondary to severe 2009 H1N1 influenza infection. T.W., who requires intubation and mechanical ventilation, is given a diagnosis of septic shock associated with influenza and a secondary MSSA pneumonia. An internal jugular vein CVC was placed in the ED during acute resuscitation. T.W. continues to require a CVC. Although her hypotension and fever resolved 72 hours post-admission, she has a new temperature of 101.7°F (38.7°C) with worsening leukocytosis on ICU day 5; there is no change on her chest radiograph. Which action would be best to take next?
- A. Initiate broad-spectrum antibiotic therapy for a new sepsis episode.
 - B. Perform bronchoscopic BAL for suspected VAP.
 - C. Remove CVC.
 - D. Send two sets of blood cultures, one from the catheter and one from a peripheral blood sample.

Patient Cases (continued)

Questions 5 and 6 pertain to the following case.

F.P. is a 29-year-old man admitted to the MICU from another hospital with severe, alcohol-induced, sterile acute pancreatitis. During his 5-day stay at the outside hospital, he had multiple organ failure, including respiratory failure requiring tracheostomy. A right internal jugular CVC was placed on the patient's admission to the outside hospital. On MICU day 3, F.P. has a maximum temperature of 102°F (38.9°C). Two sets of blood cultures are obtained; the right internal jugular catheter is removed and the tip sent for culture.

5. Which regimen would be best to consider for empiric management of a suspected CLABSI?
 - A. Daptomycin and ceftriaxone
 - B. Fluconazole
 - C. Linezolid and cefepime
 - D. Vancomycin, cefepime, and tobramycin
6. F.P. is found to have *K. pneumoniae* CLABSI and receives appropriate empiric antibiotic therapy. He has had a good clinical response with no persistence of bacteremia. Which represents the best duration of F.P.'s definitive antibiotic therapy for CLABSI?
 - A. 5 days
 - B. 14 days
 - C. 21 days
 - D. 4 weeks

III. INFLUENZA**A. Epidemiology**

1. Influenza is a seasonal viral illness affecting all ages and associated with significant morbidity and mortality. Seasonal patterns in the United States vary from year to year. The 2008–2009 influenza season started in November 2008 and waned by April 2009, but then, because of influenza A H1N1 (2009 H1N1), it resurged in May 2009, peaking in mid-October 2009 and persisting to April 2010. The 2014–2015 season spanned late November 2014 through late June 2015.
2. Up to 400,000 patients a year in the United States are hospitalized with influenza-related illness. During the 2014–2015 season, the reported overall rate (per 100,000 population) of hospitalization for laboratory-confirmed influenza was 31.2, ranging from 16.6 for adults 18–49 years of age to 84.9 for those 65 years or older. More than 19% of hospitalizations required ICU admission.
3. Risk factors for severe influenza requiring hospitalization include chronic respiratory or metabolic illness, immunosuppression (disease or pharmacotherapy), pregnancy, and age older than 65 years. In 2009, reemergence of the high-virulence strain influenza A H1N1 (pandemic 2009 H1N1) caused significant morbidity and mortality in young adults and other groups considered at a lower risk of severe influenza. The pandemic 2009 H1N1 strain continues to be tracked. Although this strain persisted through the 2013–2014 season, causing up to 70% of cases, it was associated with fewer than 2% of cases in 2014–2015.

4. The most common complications of severe influenza include hypoxemic respiratory failure, bacterial pneumonia, and ARDS. Concomitant sepsis, septic shock, multiple organ failure, encephalopathy, and rhabdomyolysis also are associated with severe influenza.
5. Among all causes of deaths in the United States, pneumonia and influenza have surpassed the epidemic threshold since 2009, with rates close to 10% during the peak of influenza seasons. Severe influenza caused by the 2009 H1N1 strain has been associated with crude mortality rates of 15%–53%.

B. Etiology

1. Influenza is caused by the RNA viruses influenza A, B, or C, which usually spread through droplet transmission. Influenza A and B viruses are the predominant causes of clinically significant illness. Influenza virus subtypes are described by surface proteins hemagglutinin (H) and neuraminidase (N).
2. Influenza A has been the most prevalent cause of influenza since 2009, with 2009 H1N1 and H3 being the most prevalent influenza A subtypes. Influenza B prevalence has varied during the same period, but it remains an important cause of illness. Although overall cases of influenza began to decline, influenza B became the predominant strain past the midway point of the 2013–2014 and 2014–2015 seasons. Strain prevalence during the 2015–2016 season (as of June 2016) has been 55% for influenza A 2009 H1N1, 13% for influenza A H3, and 30% for influenza B subtypes.
3. Influenza viruses can cause a broad range of respiratory tract infections, ranging from mild to moderate upper respiratory tract infections to severe pneumonia. Influenza infection has been associated with acute viremia.

C. Prevention

1. Annual vaccination remains the primary tool for influenza prevention.
2. In-hospital and ICU outbreaks of influenza can contribute to viral transmission and associated sequelae.
3. Institutions should begin implementing influenza screening and infection control measures when influenza viruses are confirmed to be in the local community.
4. The CDC recommends the implementation of droplet precautions for hospitalized patients with suspected or confirmed influenza; further, these precautions are recommended for 7 days after illness onset or until 24 hours after the resolution of fever and respiratory symptoms, whichever is longer.

D. Diagnosis

1. Patients with influenza may present with fever, myalgias, headache, malaise, dry cough, pharyngitis, and rhinorrhea. Fever and myalgias generally last 3–5 days, whereas malaise and respiratory symptoms may last 2 weeks or more. Patients with severe influenza may present with hypoxemic respiratory failure and sepsis.
2. Clinical signs and symptoms of influenza are nonspecific. To confirm the diagnosis of influenza, sampling of the upper respiratory tract using nasal washing or nasopharyngeal swab or lower respiratory tract within 5 days of illness is preferred. Diagnostic tests obtained beyond 5 days may have false-negative results.
3. Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, polymerase chain reaction (PCR), and immunofluorescence assays.
 - a. Viral culture and reverse transcription polymerase chain reaction (RT-PCR) are the most sensitive and are the only tests able to identify individual influenza subtypes. These tests can be performed using nasopharyngeal swab or respiratory tract culture (e.g., sputum, BAL).
 - b. Rapid diagnostic tests of nasopharyngeal swab or nasal wash have high specificity (90%–95%) (i.e., low false-positive rate and rapid turnaround), promoting these tests as first line for general diagnosis. Depending on the rapid diagnostic assay used, differentiation between influenza A and influenza B is possible, although further subtype identification is not available with these tests. Because of poor sensitivity, negative rapid diagnostic tests should be followed up with viral culture or RT-PCR.

4. Case definitions for influenza surveillance are suspected, probable, or confirmed based on patient presentation and laboratory assessment.
 - a. Suspected – Mild to severe influenzalike illness within reasonable seasonal threshold.
 - b. Probable – Mild to severe influenzalike illness within reasonable seasonal threshold or after recent contact with person with probable or confirmed influenza infection and not otherwise explained.
 - c. Confirmed – Mild to severe influenzalike illness with confirmatory laboratory tests indicating presence of influenza A or B.

E. Management and Treatment

1. Management of critically ill patients with influenza includes treatment of primary influenza infection, secondary bacterial infection(s), and related noninfectious complications (e.g., respiratory failure, ARDS, prolonged mechanical ventilation, multiple organ failure). Management of common bacterial infections and noninfectious complications is described in other chapters.
 - a. Diagnostic tests for influenza should be obtained and empiric antiviral treatment of influenza initiated during seasonal outbreaks in critically ill patients presenting with acute febrile and respiratory illness consistent with influenza. Severely ill patients with influenza may present with hypothermia similar to other populations with sepsis. Accompanying severe hypoxemic respiratory failure should heighten the concern for influenza.
 - b. Antiviral treatment (Table 3) should be initiated within 48 hours from onset of symptoms. Hospitalized patients receiving antiviral therapy after 48 hours from symptom onset may benefit.
 - c. Neuraminidase inhibitors have emerged as the mainstay of antiviral therapy for recent influenza A and B strains. These agents inhibit viral neuraminidase, decreasing the release of post-replication viral particles (virions) from infected cells, limiting spread to additional tissues. Neuraminidase inhibition may also suppress the initiation of infection after acute inoculation.
 - i. Oseltamivir phosphate is an oral (capsule, powder for suspension) ethyl ester prodrug converted through hepatic ester hydrolysis to the active form oseltamivir carboxylate. Oseltamivir can be administered to critically ill patients by orogastric or nasogastric tube. An intravenous formulation of oseltamivir has been tested in early clinical trials.
 - ii. Zanamivir is available on the market as an orally inhaled drug delivered by a Diskhaler device. Intravenous zanamivir is available for patients with severe influenza through clinical trial participation or emergency investigational new drug through the manufacturer. Use of intravenous zanamivir should be considered in patients who cannot tolerate or absorb oseltamivir because of suspected or known gastric stasis, malabsorption, or GI bleeding.
 - iii. Peramivir is an intravenous neuraminidase inhibitor with activity against influenza A and B. Peramivir was approved in December 2014 for use in patients 18 years or older with acute uncomplicated influenza. Peramivir is administered as a single 15-minute intravenous infusion.
 - d. Adamantanes inhibit the replication of influenza A viruses by preventing viral assembly. Adamantanes also interfere with the function of the transmembrane domain of the viral M2 protein, preventing release of viral particles into host cells.
 - e. Susceptibility of influenza to available antiviral agents varies from year to year and between strains and subtypes. Local surveillance of susceptibility patterns at the beginning and throughout a respective season is imperative to provide appropriate therapy.
 - i. In the 2015–2016 season, 99.3% of tested 2009 H1N1 viruses were susceptible to oseltamivir and peramivir, and 100% were susceptible to zanamivir; 100% of influenza A (H3N2) and influenza B were susceptible to all three agents.
 - ii. High levels of resistance to the adamantanes (amantadine and rimantadine) persisted among circulating influenza A viruses. The adamantanes are not effective against influenza B viruses.

Table 3. Influenza-Specific Pharmacotherapy

Agent	Influenza Activity	Bioavailability	Half-life (hr)	Treatment Dosage	Adverse Effects	Comments
Oseltamivir carboxylate	A and B	Orally or OG/NG tube: > 75%	6–10	75 mg twice a day for 5 days ^a ; up to 150 mg twice a day has been used in patients with severe influenza	Nausea, vomiting, delirium	Dosage adjustment for renal impairment may be necessary; patients requiring continuous renal replacement therapy should receive normal dosing
Peramivir	A and B; limited clinical trial experience for Influenza B strains	IV: 100%	20	600 mg once for 15 minutes	Diarrhea, hypersensitivity reactions, delirium	Dosage adjustment recommended in patients with creatinine clearance below 50 mL/min; should be administered after dialysis in patients receiving hemodialysis
Zanamivir	A and B	Inhaled: Up to 17% IV: 100%	2.5–5	10 mg twice a day for 5 days ^a	Allergic reactions, diarrhea, nausea, headache, dizziness	Not recommended in patients with chronic lung disease or severe influenza; not available for delivery through mechanical ventilator circuit
Amantadine	A only	70%–100%	15–17	100 mg twice a day	Nausea, dizziness, insomnia, lower seizure threshold, anticholinergic effects	High resistance to current influenza A strains
Rimantadine	A only	> 90%	24–35	100 mg twice a day	Dizziness, nausea, vomiting; anticholinergic effects	High resistance to current influenza A strains; limited market availability

^aLonger durations of up to 14 days may be needed for severely ill patients.

IV = intravenous(ly); NG = nasogastric; OG = orogastric.

2. Response to antiviral therapy should be assessed throughout treatment using clinical signs and symptoms of infection. Development of oseltamivir resistance during therapy has been reported, but this is rare. If suggested through local surveillance, therapy should be switched to zanamivir by the appropriate administration route. Improvement in infectious and noninfectious complications may be delayed, despite resolution of primary influenza infection. ARDS, in particular, may persist for days beyond primary influenza.

Patient Case

7. T.Y., a 32-year-old woman who has had flulike symptoms for the past 72 hours, presents to the ED from home with severe fatigue, shortness of breath, and rigors. T.Y. has a heart rate of 120 beats/minute, mean arterial pressure 70 mm Hg, respiratory rate 24 breaths/minute, temperature 102.7°F (39.3°C), and arterial oxygen saturation (Sao₂) of 85% on room air. Because it is in the middle of influenza season (high prevalence of influenza A and B), a nasal swab is done and sent for rapid diagnostic testing for suspected influenza infection. Shortly thereafter, T.Y. is intubated for severe respiratory failure and admitted to the MICU. In addition to antibiotic therapy for CAP, which would best be considered next?
 - A. None; the patient is outside the time window to effectively treat influenza.
 - B. Await rapid diagnostic test results before initiating influenza-specific therapy.
 - C. Give amantadine.
 - D. Give oseltamivir.

IV. CATHETER-ASSOCIATED URINARY TRACT INFECTIONS**A. Epidemiology**

1. Urinary catheters are commonly used in critically ill patients, with documented use of 50%–80% of adult critically ill patient-days. Urinary catheters most often used are short term (less than 30 days) temporary indwelling or intermittent urethral catheters. Other catheters include suprapubic catheters or external collection catheters (e.g., condom catheters). Presence of an indwelling urinary catheter is an independent risk factor for urinary tract infection (UTI).
2. CAUTIs are the most common cause of infection in critically ill patients. In 2012, the incidence (cases per 1000 catheter-days) of CAUTIs varied among acute care critically ill populations and ranged from 1.2 for medical/surgical patients to 4.7 for burn patients.
3. CAUTIs account for 15%–21% of hospital-acquired bacteremias.
4. The attributable mortality for CAUTI is 0%–15%.

B. Definitions

1. CDC adult surveillance definitions
 - a. UTI – At least one of the following signs or symptoms: Fever (temperature greater than 100.4°F [38°C]); suprapubic tenderness; or costovertebral angle pain or tenderness and one of the following:
 - i. A positive urine culture of 10⁵ CFU/mL or more of no more than two species of microorganisms

- ii. At least one of the following findings: Positive dipstick for leukocyte esterase and/or nitrite, pyuria (urine specimen with at least 10 white blood cells/mm³ of unspun urine or greater than 5 white blood cells/high-power field of spun urine), or microorganisms seen on Gram stain of unspun urine and a positive urine culture of 10³–10⁵ CFU/mL of no more than two species of microorganisms
 - b. CAUTI – A UTI in which an indwelling urinary catheter was in place for greater than 2 days and attributable to the catheter removed no more than 1 day before infection
2. IDSA adult definitions
- a. Catheter-associated asymptomatic bacteruria – Patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization (or condom catheter in a man) is defined by the presence of 10⁵ CFU/mL or greater of one or more bacterial species in a single catheter urine specimen in a patient without symptoms compatible with UTI
 - b. CAUTI – In patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization, CAUTI is defined by the presence of symptoms or signs compatible with a UTI with no other identified source of infection, together with 10³ CFU/mL or more of one bacterial species in a single catheter urine specimen or in a midstream-voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hours. Lower colony counts are more likely to represent significant bacteriuria in a symptomatic person than in an asymptomatic person.
- C. Etiology
- 1. Most pathogens causing CAUTIs are acquired from the external environment, including the urethra, the catheter collection system, and local skin flora. Most short-term catheter CAUTIs are monomicrobial. Longer duration of an indwelling catheter is associated with the formation of biofilms within the catheter and related system, which can promote polymicrobial infections.
 - 2. *E. coli* is the most prevalent pathogen causing CAUTIs; however, because of a wider distribution of pathogens compared with non-catheter-associated UTIs, *E. coli* accounts for only about one-third of CAUTIs. Additional bacterial pathogens include other enteric gram-negative bacilli (e.g., *Klebsiella* spp.; *Proteus* spp.; *Enterobacter* spp.), non-lactose-fermenting gram-negative bacilli (e.g., *P. aeruginosa*), and gram-positive cocci (e.g., *Enterococcus* spp.; MSSA; MRSA; MRSE). *Candida* spp. may be involved in up to one-third of CAUTIs.
 - 3. Similar to other health care-associated infections, causative pathogens are associated with local pathogen patterns, pathogen-specific risk factors, and patient severity of illness.
- D. Prevention
- 1. CAUTI is considered a preventable complication. The NHSN, using CDC definitions, provides population-specific event rates for institution surveillance and performance benchmarks.
 - 2. The most effective way to reduce the incidence of catheter-associated asymptomatic bacteruria and catheter-associated UTI is to reduce the use of urinary catheterization by restricting its use to patients who have clear indications and by removing the catheter as soon as it is no longer needed.
 - 3. The foundation for preventing CAUTIs includes training and education, proper aseptic insertion techniques, and active surveillance and performance improvement systems.
 - 4. Recommended best practices for preventing CAUTIs have been proposed and endorsed by IDSA, SHEA, and the Joint Commission. These evidence-based recommendations are categorized as basic practices for all acute care hospitals or special practices wherein basic practices are less than effective at reducing CAUTI rates. The entire document is available (Infect Control Hosp Epidemiol 2014;35:464-79). Major recommendations include:
 - a. Basic practices
 - i. Minimize use and duration of indwelling catheters.

- ii. Provide comprehensive education to and ensure competency for all involved with insertion, care, and maintenance of urinary catheters.
 - iii. Use of a systematic process or checklist at the time of insertion to ensure adherence to proper insertion technique
 - iv. Handwashing during insertion, care, and maintenance of the catheter
 - v. Proper care and maintenance of indwelling catheter and collection system
 - b. Special practices
 - i. Daily systematic assessment of continued need for indwelling catheter
 - ii. Development and implementation of a protocol to manage postoperative urinary retention
- E. Diagnosis
1. Although clinical signs and symptoms are the mainstay for differentiating CAUTIs from catheter-associated asymptomatic bacteruria, they are not specific for CAUTI. These include fever, rigors, altered mental status, malaise, or lethargy with no other identified cause. Presence of flank pain, costovertebral angle tenderness, acute hematuria, and pelvic discomfort may be more specific, but these are difficult to assess in many critically ill patients.
 2. Urine culture should be obtained in all critically ill patients with signs and symptoms of CAUTI. Sampling should be done through the catheter port using aseptic technique. Catheters in place for longer than 2 weeks should be replaced and a urine sample obtained from the port of the newly placed catheter. Samples from the catheter collection system (e.g., catheter bag) should be avoided because of the potential for colonization.
 3. Urinalysis should be obtained in patients with a suspected CAUTI. Pyuria without signs and symptoms does not indicate CAUTI; however, the absence of pyuria in a symptomatic patient suggests a diagnosis other than CAUTI.
- F. Treatment
1. A urinary culture should be obtained before initiation of antimicrobial therapy.
 2. If an indwelling catheter has been in place for longer than 2 weeks, the catheter should be removed or, if still indicated, replaced to hasten resolution of symptoms.
 3. Similar to other health care-acquired infections, empiric antimicrobial therapy should be based on local pathogen prevalence, pathogen-specific risk factors (e.g., MDRO risk factors), previously identified pathogens, previous antimicrobial exposure, and local antibiotic susceptibility.
 4. Empiric antimicrobial therapy should be de-escalated according to the identified pathogen(s) and respective antimicrobial susceptibility on final urine culture results. Empiric antimicrobial therapy should be discontinued in patients without CAUTI or other sources of infection.
 5. Definitive antimicrobial therapy should be based on final antimicrobial susceptibility results and presence of concomitant infection(s). Catheter irrigation (i.e., bladder washings) is not recommended.
 6. Shorter duration of antimicrobial therapy should be considered depending on clinical response. Regardless of catheter removal, duration of antimicrobial therapy should be 7 days for patients with resolution of signs and symptoms within 72 hours of appropriate antimicrobial therapy and up to 14 days in patients with resolution after 72 hours.
 7. Patients with persistent signs and symptoms of CAUTI should receive a urologic workup to assess for abscess or other causes of relapse.

V. COMPLICATED INTRA-ABDOMINAL INFECTION

A. Epidemiology

1. Complicated intra-abdominal infection spans prehospital and in-hospital dispositions and a variety of pathogenic processes involving several organ systems.
2. The incidence of complicated intra-abdominal infection is difficult to estimate, given the breadth of illness. Appendicitis is the most prevalent cause of complicated intra-abdominal infection. Recent controlled trials and large international observational sepsis studies report abdominal infection as the second or third most common source of sepsis, accounting for 21% of sepsis and 30% of septic shock cases.
3. Complicated intra-abdominal infection is the second most common cause of mortality in critically ill patients. Crude mortality for primary intra-abdominal infection is almost 30%, whereas rates exceed 50% in patients with secondary intra-abdominal infection. Those presenting with sepsis caused by intra-abdominal infection have crude mortality above 40%.

B. Definitions

1. A complicated intra-abdominal infection is defined by the IDSA as infection that extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis. These infections usually arise from spillage of viscus-related fluid and flora into the peritoneal cavity, causing inflammation and injury to the peritoneal membrane. Retroperitoneal infections also are possible, but these are related to the individual retroperitoneal organ rather than the peritoneum.
2. Peritonitis is described as primary, secondary, and tertiary.
 - a. Primary peritonitis, or spontaneous bacterial peritonitis, is peritonitis related to bacterial translocation of proximal small bowel overgrowth and not peritoneal disruption or organ perforation. Primary peritonitis is generally diffuse in nature.
 - b. Secondary peritonitis is caused by leakage of intraluminal fluid and microorganisms secondary to macro- or microperforation of the GI tract. Secondary peritonitis can be diffuse or localized to an organ, depending on the extent of peritoneal involvement. Causes of secondary peritonitis include direct trauma, ischemia, thrombosis, ulceration, malignancy, and anastomotic leak.
 - c. Tertiary peritonitis is peritonitis that persists or recurs at least 48 hours after the management of primary or secondary peritonitis. Tertiary peritonitis can represent a new intra-abdominal process or host, anatomic, or therapeutic failure of treatment of primary or secondary peritonitis.

C. Etiology

1. Pathogens associated with complicated intra-abdominal infections and peritonitis are influenced by type/cause of peritonitis, MDRO risk factors, previous antibiotic exposure, and patient-specific colonization. Patients having health care–associated intra-abdominal infections more often tend to have antibiotic-resistant, nosocomial pathogens compared with patients having community-acquired infection.
2. Primary peritonitis is usually monomicrobial and associated with translocation of organisms across the diaphragm or proximal small bowel. The most prevalent organisms include *S. pneumoniae*, *E. coli*, and *Klebsiella* spp.
3. Secondary peritonitis is typically polymicrobial related to the origin of GI tract leakage.
 - a. Gastric and duodenal secretions are usually sterile or with limited inocula of gram-positive bacteria and *Candida* spp.
 - b. Proximal small bowel is densely populated with aerobic gram-negative bacilli including *E. coli*, *Klebsiella* spp., *Proteus* spp., and *Enterobacter* spp., as well as populations of aerobic gram-positive bacteria such as *S. aureus*, streptococci, and enterococci.

- c. The distal small bowel and the large bowel are populated with proximal small bowel flora in addition to anaerobic gram-negative and gram-positive organisms, including *Bacteroides fragilis* and *Clostridium* spp. (usually non-*C. difficile*).
4. Tertiary peritonitis includes core organisms of primary and secondary peritonitis further compounded by the influence of management strategies, including malnutrition, anatomic disruption, and antimicrobial therapy.

D. Diagnosis

1. The diagnosis of complicated intra-abdominal infection relies on assessment of clinical signs and symptoms, differentiation from other causes of infection, and radiographic evaluation.
2. Rapid-onset abdominal pain and tenderness with signs of peritoneal irritation on physical examination are the most common presenting signs and symptoms. Additional symptoms of anorexia, abdominal distention, nausea, or vomiting, with or without fever, tachycardia, or tachypnea. These are often difficult to assess in critically ill patients; therefore, intra-abdominal infection should be considered in patients with unexplained new-onset organ dysfunction and sepsis.
3. Radiographic evaluation is commonly performed using abdominal radiographs, ultrasonography, and CT, including contrast CT to assess for vascular thrombosis. Contrast studies of postoperative drains or fistulae may also help assess anastomotic integrity.
4. Culture of intra-abdominal fluid associated with the primary source should be obtained in moderately to severely ill patients. Gram stain results should be used to help guide empiric antimicrobial therapy. Pathogens identified on final culture should guide definitive antimicrobial therapy.

E. Management and Treatment

1. Resuscitation for hemodynamic instability should be initiated and managed according to the Surviving Sepsis Campaign guidelines.
2. Achieving primary source control of ongoing peritoneal contamination by operative diversion or resection is recommended for patients with diffuse peritonitis. Patients with focal peritonitis should undergo percutaneous abscess and fluid drainage.
3. Empiric antimicrobial therapy should be initiated in patients thought to have complicated intra-abdominal infections.
 - a. Empiric antimicrobial regimens should be based on the source/location of intra-abdominal infection, community-acquired or health care-associated disposition of infection, severity of infection, local pathogen trends and susceptibilities, MDRO risk factors, and patient-specific colonization patterns.
 - b. Individual antimicrobial agents should be dosed according to available pharmacokinetic and pharmacodynamic principles to optimize efficacy and limit toxicity.
 - c. Community-acquired, mild to moderate severity
 - i. Routine culture is not recommended.
 - ii. Empiric antibiotic therapy should include agents active against aerobic and facultative enteric gram-negative bacilli and enteric streptococci. Obligate anaerobic therapy should be initiated in patients with distal small bowel, appendiceal, or colonic sources. Anti-enterococcal and antipseudomonal therapies are not recommended.
 - (a) Cefazolin plus metronidazole
 - (b) Cefoxitin
 - (c) Ceftriaxone or cefotaxime plus metronidazole
 - (d) Cefuroxime plus metronidazole
 - (e) Ertapenem
 - (f) Moxifloxacin alone; levofloxacin or ciprofloxacin plus metronidazole

- (g) Tigecycline
 - (1) Pooled results from approval trials across all infections suggests increased mortality in patients treated with tigecycline versus active comparator regimens. The cause of this increase has not been established.
 - (2) FDA-approved label warns that the increase in all-cause mortality should be considered when selecting among treatment options.
 - d. Community acquired, high severity defined as severe physiologic disturbance (e.g., septic shock); advanced age; immunocompromised state; delay in, or high likelihood of failure to achieve, primary source control
 - i. Routine culture of intra-abdominal fluid is recommended as available.
 - ii. Empiric antimicrobial therapy should be broadened to include MDROs, enterococci, and obligate anaerobes. Agents active against MRSA are not recommended empirically. Although fluoroquinolones are recommended, emergence of resistant *E. coli* and *P. aeruginosa* is a concern.
 - (a) Broad-spectrum carbapenem (e.g., doripenem, imipenem, meropenem)
 - (b) Cefepime or ceftazidime plus metronidazole (may need additional anti-enterococcal agent)
 - (c) Ciprofloxacin or levofloxacin plus metronidazole (may need additional anti-enterococcal agent)
 - (d) Piperacillin/tazobactam
 - e. Health care associated
 - i. Routine culture of intra-abdominal fluid is recommended as available.
 - ii. Broad-spectrum empiric antimicrobial therapy should include MDROs, enterococci, obligate anaerobes, and MRSA. Depending on empiric antibiotic susceptibility rates (i.e., local antibiogram), combination therapy against aerobic gram-negative bacilli with aminoglycoside, or, if MDROs are prevalent, polymyxin.
 - (a) Broad-spectrum carbapenem (e.g., doripenem, imipenem, meropenem) plus vancomycin
 - (b) Cefepime or ceftazidime plus metronidazole plus vancomycin
 - (c) Piperacillin/tazobactam plus vancomycin
 - f. Antifungal therapy should be added to the regimen of patients with yeast on Gram stain or recent evidence of colonization. Fluconazole is the drug of choice for fluconazole-susceptible strains. Echinocandins should be used first line in critically ill patients until final culture results are available.
 - g. Empiric antimicrobial therapy should be de-escalated to final culture results and related antimicrobial susceptibilities.
4. Definitive antimicrobial therapy for complicated intra-abdominal infection should be continued for 4–7 days, depending on clinical response and success of primary source control. Patients with delayed or incomplete primary source control may require therapy for longer durations.
 5. Considerations for short-term prophylactic courses no longer than 24 hours include:
 - a. Acute gastric or jejunal perforation in absence of malignancy or acid-reducing pharmacotherapy with adequate source control within 24 hours
 - b. Traumatic or iatrogenic bowel injuries repaired within 12 hours of injury
 - c. Acute appendicitis without perforation or abscess
 6. Response to therapy should be evaluated daily using signs of symptoms of intra-abdominal infection and evidence of infection-related organ dysfunction. Patients with persistent or recurrent signs and symptoms after 4–7 days of therapy should be assessed for uncontrolled primary source, secondary/tertiary peritonitis, and extra-abdominal infectious sources. Antimicrobial therapy should be continued during diagnostic assessment.

Patient Case

8. D.L. is a 69-year-old woman admitted from home to the SICU with severe acute abdominal pain in the left lower quadrant. An abdominal CT reveals free air in the peritoneal cavity and evidence of distal ischemic colitis. D.L. is taken urgently to the operating room, where she is noted to have gross contamination from distal colonic perforation with marked peritonitis. After a partial colectomy and abdominal washout, she is admitted to the SICU for continued resuscitation for septic shock. Which empiric antibiotic regimen would be most appropriate for D.L.?
- A. Ceftriaxone and vancomycin
 - B. Ciprofloxacin and metronidazole
 - C. Ertapenem
 - D. Piperacillin/tazobactam

VI. ACUTE PANCREATITIS**A. Epidemiology**

1. Acute pancreatitis is responsible for more than 200,000 acute care admissions annually in the United States.
2. About 20% of acute pancreatitis episodes are severe, have evidence of pancreatic necrosis, and are associated with local and systemic complications. An Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 8 or higher and a Ranson's criteria score of 3 or greater, together with clinical presentation, have been used to categorize patients as severe acute pancreatitis.
3. Between 30% and 78% of patients with necrotizing pancreatitis will have concomitant organ failure, with the highest incidence in patients having infected necrosis. Pancreatitis-associated systemic sequelae and organ failure includes:
 - a. Systemic inflammatory response syndrome (SIRS)
 - b. Hypovolemic shock
 - c. Hypoxemia secondary to ARDS
 - d. Acute kidney injury
 - e. Gastrointestinal (GI) bleeding
 - f. Disseminated intravascular coagulation and severe metabolic disturbances can also occur.
4. Although most pancreatic necrosis is sterile, about one-third of patients with necrotizing pancreatitis will have infected necrosis.
5. Overall, crude mortality for acute pancreatitis is 2%–9%; however, mortality rates for necrotizing and infected necrotic pancreatitis are as high as 44% and 62%, respectively.

B. Pathophysiology

1. Pancreatitis is a result of glandular autodigestion from excessive ductal and tissue exposure to amylase, lipase, and protease caused by trypsin-related hyperstimulation, macro-ductal blockade, or micro-ductal blockade.
2. The pathophysiology of acute pancreatitis can be organized into three phases:
 - a. Excessive activation or decreased inactivation of trypsin leading to activation of pancreatic exocrine enzymes

- b. Local inflammatory and immune response to pancreatic injury
- c. Systemic inflammatory and immune response, including SIRS, hypovolemia, and ARDS
- 3. Common causes of acute pancreatitis include biliary obstruction (e.g., gallstones), direct toxicity (e.g., alcohol), trauma, surgery/biliary procedures, and drugs.

C. Definitions

- 1. Severe pancreatitis is defined as pancreatitis associated with hypovolemia, organ failure, or local complications including necrosis, abscess, or pseudocyst. Hypovolemia may increase the risk of pancreatic necrosis and intestinal ischemia because of tissue hypoperfusion.
- 2. Pancreatic necrosis is evidenced on CT scan as diffuse or focal areas of nonviable pancreatic tissue often associated with peripancreatic fat necrosis. In general, greater than 30% of the pancreas should be affected. Infected necrosis is defined as the presence of pathogenic microorganisms in the necrotic tissue.
- 3. Pancreatic pseudocyst is a non-epithelialized wall containing pancreatic excretions caused by acute or chronic pancreatitis or pancreatic trauma. Pseudocysts are usually sterile.
- 4. Pancreatic abscess is an infected pseudocyst or liquefaction of pancreatic necrosis that becomes infected.

D. Diagnosis

- 1. The diagnosis of acute pancreatitis requires two of the following three features:
 - a. Acute and constant epigastric or right upper quadrant abdominal pain with or without nausea and vomiting;
 - b. Serum amylase and/or lipase greater than 3 times the upper limit of normal; and
 - c. Characteristic findings of acute pancreatitis on CT scan.
- 2. Patients with severe pancreatitis may present with SIRS, hypovolemia, and new-onset organ failure, including hypotension.

E. Management and Treatment

- 1. Management of severe acute pancreatitis includes acute pain management, fluid resuscitation, supportive care of systemic complications and organ failure, and nutrition support. Surgical debridement of infected necrosis or drainage of pancreatic abscess should be considered.
- 2. Antibiotic therapy for acute pancreatitis is considered empiric, definitive, or prophylactic.
 - a. Empiric antibiotic therapy is indicated in patients with suspected or confirmed infected necrosis or pancreatic abscess.
 - i. Patients with suspected infected necrosis or pancreatic abscess should undergo radiographically (e.g., ultrasonography, CT) guided drainage with culture of recovered material/fluid. Common organisms associated with infected necrosis or pancreatic abscess include:
 - (a) *E. coli*
 - (b) *Klebsiella* spp.
 - (c) *Enterobacter* spp.
 - (d) *Proteus* spp.
 - (e) Streptococci
 - ii. The antibiotics of choice include:
 - (a) Broad-spectrum carbapenems (e.g., imipenem; meropenem)
 - (b) Fluoroquinolone plus metronidazole
 - (c) Third-generation cephalosporin plus metronidazole
 - iii. Antifungal therapy should be added to antibiotic therapy if yeast is identified on culture Gram stain. Fluconazole is recommended unless there is a high suspicion for fluconazole-resistant fungi.

- iv. Empiric antibiotics should be discontinued if pancreatic culture is negative. Patients with persistent SIRS should undergo repeat imaging and drainage of identified abscess or fluid.
- v. If infection is confirmed, antibiotic therapy should be de-escalated toward the identified pathogen(s) according to antibiotic susceptibility.
- vi. Definitive antibiotic therapy for confirmed infection should be continued for up to 14 days.
- b. Prophylactic antimicrobial therapy in patients with sterile necrotizing pancreatitis is controversial. Although small pilot investigations suggest benefit, a large, noninferiority, placebo-controlled trial suggested no benefit with prophylactic meropenem. Current recommendations do not support routine use of prophylactic antibiotic or antifungal therapy in patients with sterile necrotizing pancreatitis.
- 3. Ongoing assessment of resolution of SIRS and pancreatitis-associated organ failure is imperative. Serial assessment of serum amylase or lipase has limited value over clinical assessment and physical examination. Elevation of serum amylase or lipase for several weeks, however, should heighten concern for persistent pancreatic/peripancreatic inflammation, blockage of the pancreatic duct, or development of a pseudocyst.

Patient Case

9. T.J. is a 27-year-old man who is admitted to the MICU from an outside hospital with alcohol-induced acute pancreatitis and associated respiratory failure, SIRS, and blood pressure 100/55 mm Hg. Admission abdominal CT shows severe pancreatitis with about 30% necrosis and a large focal fluid collection requiring guided drainage. A fluid sample is sent for a Gram stain, which reveals many gram-negative rods and yeast. Which antimicrobial regimen would best be initiated in T.J.?
- A. None – low suspicion for infected pancreatitis
 - B. Ciprofloxacin and metronidazole
 - C. Imipenem
 - D. Meropenem and fluconazole

VII. CLOSTRIDIUM DIFFICILE INFECTION

A. Epidemiology

- 1. *C. difficile* is a spore-forming, anaerobic, gram-positive bacillus. Stool carriage of *C. difficile* has been found in up to 26% of acute care patients.
- 2. *C. difficile* is transmitted person to person through the fecal-oral route. The capability to become dormant in spores increases the potential for environmental spread.
- 3. *C. difficile* is pathogenic through the production and expression of two primary toxins, *C. difficile* toxin A (TcdA) and *C. difficile* toxin B (TcdB). North America has seen a recent emergence of strains with increased virulence (e.g., BI/NAP1 strain) through increased production of toxins A and B, production of additional toxins, and enhanced sporification.
- 4. CDI is responsible for almost 30% of antibiotic-associated diarrhea and is the most common cause of infectious diarrhea in health care settings. The estimated incidence of CDI is 3–10 cases per 10,000 patient-days. Community-acquired CDI has increased in prevalence.

5. The clinical manifestations of CDI range from symptomless carriage to CDI spanning mild or moderate diarrhea to fulminant and sometimes fatal pseudomembranous colitis, toxic megacolon, or colonic perforation. Post-colectomy small bowel enteritis and rectal pouchitis related to CDI have been reported. Additional complications of severe CDI include:
 - a. SIRS
 - b. Hypovolemia
 - c. Electrolyte disturbances
 - d. Sepsis and septic shock
 - e. Multiple organ failure
6. CDI is associated with medical costs greater than \$3 billion per year.
7. Attributable mortality from CDI is estimated to be below 10%. However, crude mortality is as high as 75% in patients presenting with septic shock, colonic perforation, or toxic megacolon. Subtotal colectomy in patients with a severe CDI is associated with an in-hospital mortality rate of up to 42%.

B. Definitions

1. CDI is defined as the presence of symptoms (e.g., diarrhea) and a stool test result positive for *C. difficile* toxin, toxigenic *C. difficile* (e.g., DNA amplification detecting toxin-coding genes), or pseudomembranous colitis on colonoscopic examination.
2. Severe CDI, according to expert-based guidelines, is defined as above plus one of the following:
 - a. WBC 15×10^3 cells/mm³ or greater
 - b. Serum creatinine (SCr) of 1.5 times or greater the premorbid level
3. A severe, complicated CDI is defined as a severe CDI plus one of the following:
 - a. Hypotension or evidence of shock
 - b. Colonic ileus
 - c. Toxic megacolon
4. Recurrence is defined as the relapse of a recent infection or a reinfection after definitive therapy.
5. Additional categorizations of CDI are used for infection control surveillance and institutional/ICU quality review. These are related to the locations of *C. difficile* acquisition (e.g., community acquired or health care associated) and onset of symptoms (e.g., community onset vs. health care onset).

C. Risk Factors

1. Antibiotic therapy is the most important risk factor.
 - a. All antibiotic classes have been associated with CDI.
 - b. Highest-risk antibiotic classes include fluoroquinolones, cephalosporins, penicillins, and clindamycin.
2. Gastric acid-suppressing pharmacotherapy, including proton pump inhibitors and histamine-2 receptor antagonists
3. Age older than 65 years
4. Duration of hospitalization
5. Cancer chemotherapy
6. GI surgery
7. Previous CDI

D. Prevention – There are two global strategies to prevent CDI:

1. Decrease the risk of acquiring *C. difficile*.
 - a. Staff, patient, family, caregiver education
 - b. Hand hygiene to remove *C. difficile* spores through non-alcohol-based handwashing using soap or chlorhexidine gluconate and water
 - c. Contact isolation, including full-barrier precautions (gown and gloves), single-occupancy room, and the cohorting of patients with a CDI

- d. Limit reuse or between-patient sharing, and terminal clean patient care–related equipment (e.g., digital thermometers, point-of-care blood glucose machines, dietary trays, intravenous infusion pumps).
 - e. Environmental decontamination using bleach-containing cleaning solution
 - 2. Avoid or address reversible risk factors.
 - a. Limit overuse of, and discontinue unnecessary, antibiotic therapy.
 - b. Decrease duration of hospital stay.
 - c. Discontinue unnecessary gastric acid–reducing pharmacotherapy.
- E. Diagnosis
 - 1. Diagnosis of CDI is based on clinical and laboratory findings.
 - 2. Clinical findings include presence of diarrhea, defined as passage of three or more unformed stools within 24 consecutive hours.
 - a. Rarely, a symptomatic patient will present with ileus and colonic distension with minimal or no diarrhea.
 - b. Patients with cecal CDI or right-sided CDI colitis may have formed stools.
 - 3. Laboratory findings include stool sample positive for toxigenic *C. difficile*, *C. difficile* toxin, or colonoscopic or histopathologic findings showing pseudomembranous colitis. Available strategies for detecting toxin-producing *C. difficile* include:
 - a. Testing for *C. difficile* should only be performed on unformed stool unless patients have ileus. Identifying the ideal testing strategy remains difficult. Institution-specific decisions for which test(s) to use should be evidence based and collaborative across interested parties.
 - b. Stool culture with detection of a toxigenic isolate through identification of neutralizable toxin activity is considered the gold standard test. However, this process could take up to 9 days, limiting its clinical utility.
 - c. Enzyme immunoassay (EIA) tests for *C. difficile* toxins A and B are rapid and widely available; however, poor sensitivity may limit their utility. Obtaining serial samples has been used to increase sensitivity. Sensitivity may also be increased using a two-step process with initial EIA to detect the *C. difficile* antigen glutamate dehydrogenase and a follow-up stool culture with detection of the toxigenic isolate.
 - d. PCR testing is rapid, sensitive, and specific. Widespread availability may be limited.
 - e. Emerging evidence supports an illumigene *C. difficile* assay, which uses loop-mediated isothermal DNA amplification to detect a specific genetic region responsible for coding toxins A and B.
 - 4. The same diagnostic criteria are used for recurrent CDI.
- F. Management and Treatment
 - 1. Removal of potential cause(s), as appropriate (e.g., discontinuation of associated antibiotic therapy)
 - 2. Assessment of disease severity (mild or moderate vs. severe) and whether episode is initial or recurrent
 - 3. Evaluation of need for surgical intervention
 - a. Subtotal colectomy with rectal preservation should be considered for severely ill patients.
 - b. Alternative colon-sparing operative surgical strategies have been described.
 - 4. Antibiotic therapy targeted against *C. difficile* (Table 4)
 - a. Samples for diagnostic testing for *C. difficile* should be obtained before empiric antibiotic therapy is initiated. Initiation of empiric antibiotic therapy before final test results should be based on clinical assessment.

- b. Antibiotic choices and respective routes of administration should be based on severity of CDI and ability to achieve relevant intraluminal antibiotic concentrations relative to CDI. Special considerations include:
 - i. For enema volumes in patients requiring rectal instillation of vancomycin, location of CDI-affected area(s) and risk of colonic perforation should be considered. Patients receiving vancomycin enemas may need a cuffed rectal delivery device/tube to facilitate retention.
 - ii. Patients with CDI-related colitis and proximal colonic diversion (i.e., no continuity with oral or gastric route) may require rectal instillation of vancomycin enema.
 - iii. Fidaxomicin, an oral, limited bioavailability macrolide antibiotic, is indicated for treatment of CDI. Evidence supports its noninferiority to oral vancomycin for clinical response with decreased recurrence post-therapy in non-BI/NAP1 strains. Data are limited supporting its use in critically ill patients.
 - iv. Fecal transplantation has improved outcomes compared with oral vancomycin in noncritically ill patients with recurrent CDI.
 - v. There are no definitive recommendations for duration of CDI antibiotic therapy or prevention of recurrence when non-CDI antibiotic therapy is continued concurrently.
- c. Response to therapy should be assessed by evaluating clinical signs and symptoms, including resolution of diarrhea, laboratory abnormalities, sepsis, and related organ failure. Results of stool testing for *C. difficile* in patients with resolution of disease do not predict recurrence.

Table 4. Treatment Options for CDI

Episode and Illness Category	Therapy
Initial episode, mild to moderate CDI	Metronidazole 500 mg orally or by OG/NG/feeding tube three times daily for 10–14 days
Initial episode, severe CDI	Vancomycin 125–250 mg orally or by OG/NG/feeding tube four times daily for 10–14 days
Initial episode, severe, complicated CDI	Vancomycin 500 mg orally or by OG/NG tube four times daily and metronidazole 500 mg intravenously three times daily If concerned for decreased distal delivery (e.g., ileus): Rectal instillation of vancomycin 500 mg in 0.9% sodium chloride for irrigation by enema retained for 1 hour administered every 6 hr; guidelines recommend 100 mL (IDSA) to 500 mL (American College of Gastroenterology) volumes; enema dose volumes up to 1000 mL have been reported
First recurrence	Same as initial episode, qualified by illness severity
Second recurrence	Vancomycin orally, followed by a 28-day dosage taper

NG = nasogastric; OG = orogastric.

Patient Case

10. K.L. is a 57-year-old man admitted to the MICU with diffuse abdominal pain, temperature 101.9°F (38.8°C), WBC 27×10^3 cells/mm³, heart rate 125 beats/minute, and mean arterial pressure 57 mm Hg. An abdominal CT scan reveals a large amount of intestinal air, suggestive of ileus and moderate transverse and sigmoid colonic inflammation. On review of the patient's history, it is learned that K.L. recently completed a 4-week course of broad-spectrum antibiotic therapy for a postoperative osteomyelitis after repair of right comminuted femur fracture, increasing the suggestion of CDI. Which regimen would be best for empiric management of a suspected CDI in K.L.?
- A. Metronidazole 500 mg intravenously every 8 hours.
 - B. Metronidazole 500 mg intravenously every 8 hours and intracolonic vancomycin 500 mg instilled every 8 hours.
 - C. Metronidazole 500 mg orally or by nasogastric tube every 8 hours and vancomycin 250 mg orally or by nasogastric tube every 6 hours.
 - D. Vancomycin 250 mg orally or by nasogastric tube every 6 hours.

VIII. WOUND INFECTION**A. Epidemiology**

1. Postoperative wound infection is the most common health care–associated infection, affecting up to 5% of inpatient surgery patients. There are 150,000–300,000 cases of postoperative wound infections annually in the United States.
2. Most postoperative wound infections are mild or moderate in severity. Major complications associated with severe postoperative wound infections include wound dehiscence, reoperation, sepsis, and necrotizing fasciitis.
3. Patients with postoperative wound infection have more than a 2-fold higher risk of death compared with those without infection. Crude mortality in patients with streptococcal necrotizing fasciitis and shock (e.g., streptococcal toxic shock) is high, ranging from 30% to 70%.

B. Definitions

1. Superficial incisional: Infection involving only the skin or subcutaneous tissue of the incision
2. Deep incisional: Infection involving fascia and/or muscular layers
 - a. Deep incision primary: Wound infection in the primary incision in a patient who has had an operation with one or more incisions
 - b. Deep incision secondary: Wound infection in a secondary incision in a patient who has had an operation with more than one incision
 - c. Necrotizing fasciitis is an aggressive, deep incisional infection tracking along the superficial fascia, which consists of the tissues between the skin and the underlying muscles. Necrotizing fasciitis often results in major tissue destruction. Fournier gangrene is a variant of necrotizing fasciitis involving the scrotum and penis or vulva.
3. Organ or space: Infection involving any space or organ, opened or manipulated during the procedure, excluding skin incision, fascia, or muscle layers.

C. Etiology

1. Pathogens causing postoperative wound infections are often related to local flora present on the skin at the time of incision and flora associated with organs/tissues involved in the operative procedure.
2. Prevalence of drug-resistant strains (e.g., MRSA, multidrug-resistant gram-negative bacilli) depends on local patterns of infection and patient colonization.
 - a. The most common bacterial pathogens causing postoperative wound infection are skin flora, including staphylococci and streptococci.
 - b. Bacterial pathogens related to anatomic location of the operation:
 - i. Upper GI tract (gastric, biliary, proximal small intestine)
 - (a) Biliary: Aerobic and anaerobic gram-negative and gram-positive organisms
 - (b) Non-biliary: Enteric, aerobic gram-negative bacilli
 - ii. Lower GI tract (distal small bowel; colon): Mixed gram-positive and gram-negative flora, facultative and anaerobic
 - iii. Female genitalia: Mixed gram-positive and gram-negative flora, facultative and anaerobic
 - iv. Axilla: Aerobic gram-negative organisms
 - v. Perineum: Aerobic gram-negative and mixed anaerobic organisms
 - vi. Respiratory: Aerobic gram-positive and gram-negative organisms
 - c. Necrotizing fasciitis
 - i. Most infections are monomicrobial, caused predominantly by group A streptococci (*Streptococcus pyogenes*), *S. aureus*, and anaerobic streptococci (e.g., *Peptostreptococcus*). Non-*C. difficile* clostridia (e.g., *Clostridium septicum*) and *Aeromonas hydrophilia* also are associated with monomicrobial infection.
 - ii. Polymicrobial infections usually involve a broad range of pathogens, including aerobic and anaerobic gram-positive and gram-negative organisms. Likelihood of polymicrobial infection is increased if associated with:
 - (a) Decubitus ulcers
 - (b) Injection sites in illicit drug users
 - (c) Intestinal operation
 - (d) Penetrating abdominal trauma
 - (e) Perianal abscess
 - (f) Spread from genitalia (i.e., Fournier gangrene)

D. Prevention

1. Using evidence-based guidelines can prevent up to 60% of postoperative wound infections. Wound infections after elective operation are considered preventable and are reportable health care–associated infections.
2. Many organizations and agencies promote prevention and monitor the prevalence of postoperative wound infection, including the CDC, the Surgical Care Improvement Project (SCIP), the Joint Commission, and the Centers for Medicare & Medicaid Services.
3. Recommended strategies are basic or special approaches.
 - a. Basic approaches include:
 - i. Administer preoperative weight-based antibiotic therapy according to operative site and level of expected operative field contamination. Timing of antibiotic therapy should maximize blood and tissue concentrations at the time of incision. Antibiotics should be redosed every 2 half-lives for prolonged procedures. Antibiotic duration should be limited to 24 hours unless there is evidence of peritonitis or active infection during the operative procedure.
 - ii. Avoid use of hair removal. If necessary, use clippers or depilatory agent.
 - iii. Maintain glycemic control in immediate postoperative period; goal should be to avoid glucose above 180 mg/dL.

- iv. Avoid perioperative hypothermia.
 - v. Optimize tissue oxygenation by maintaining adequate perfusion and oxygen delivery.
 - vi. Interdisciplinary staff education, use of procedural checklists, and infection surveillance
 - b. Special approaches include:
 - i. Preoperative screening for *S. aureus* and consideration of decontamination in patients undergoing orthopedic or cardiothoracic procedures
 - ii. Aseptic, intraoperative wound lavage
- E. Diagnosis
 - 1. Postoperative wound infections most commonly occur 48 hours after the procedure. Fever in the first 48 hours is usually idiopathic or from noninfectious causes.
 - 2. Wounds should be physically examined serially until healed. Purulent material should be collected aseptically and sent for Gram stain and culture. Cultures in patients with suspected deep tissue infections should be obtained from deep tissues with concomitant blood cultures.
 - 3. Signs and symptoms of superficial incisional postoperative wound infection include:
 - a. Purulent incisional drainage
 - b. Local pain or tenderness, swelling, and erythema after the incision is opened
 - c. Positive culture of purulent drainage
 - 4. Necrotizing fasciitis should be suspected if the following are present:
 - a. Severe pain that seems disproportional to the appearance of the wound
 - b. Failure to respond to initial antibiotic therapy
 - c. Hard, wooden feel of the subcutaneous tissue, often extending beyond the area of affected skin
 - d. Crepitus on physical examination or radiographic (radiograph, CT scan) finding, indicating gas in subcutaneous tissues
 - e. Skin necrosis or ecchymoses
 - f. Sepsis, severe sepsis, or septic shock
- F. Management and Treatment
 - 1. Opening of the incision, evacuation of the infected material, and continued dressing changes are the foundation of treatment for confirmed postoperative wound infections.
 - 2. Antibiotic therapy targeted against likely pathogens should be initiated in patients with systemic signs and symptoms or suspected deep tissue infection.
 - 3. Superficial incisional infection
 - a. Erythema and induration less than 5 cm and minimal systemic signs of infection (no fever, no leukocytosis, and tachycardia):
 - i. Serial dressing changes
 - ii. No antibiotic therapy necessary
 - iii. Continue to assess wound for resolution or progression.
 - b. Erythema and induration greater than 5 cm, fever, leukocytosis, and tachycardia:
 - i. Open suture line.
 - ii. Initiate empiric antibiotic therapy targeted against operative site–related suspected pathogens. Examples include:
 - (a) Extremity, head, neck, or trunk site: Cefazolin or vancomycin if MRSA suspected
 - (b) GI, genitalia, or perineum site: Cephalosporin or levofloxacin plus metronidazole; ertapenem
 - iii. Adjust antibiotics according to culture results. Continue for up to 48 hours or until infection is resolved.

- iv. Serial dressing changes
 - v. Continue to assess wound for resolution or progression.
- 4. Necrotizing fasciitis
 - a. Surgical debridement of necrotic tissue serially (i.e., every 24–48 hours) until no further need for debridement
 - b. Antibiotic therapy is empiric or definitive.
 - i. Empiric antibiotic therapy should be initiated as early as possible.
 - ii. Polymicrobial infection should be suspected, with empiric therapy that is active against aerobic and anaerobic gram-positive and gram-negative pathogens
 - (a) Vancomycin, plus:
 - (b) Piperacillin/tazobactam, broad-spectrum carbapenem, or cefepime plus metronidazole
 - (c) Consider clindamycin to decrease pathogenic toxin and cytokine production if *S. pyogenes* is suspected.
 - iii. Empiric antibiotic therapy should be de-escalated according to final culture results.
 - iv. Definitive antibiotic therapy should be based on final culture results and antibiotic susceptibility. Infection caused by *S. pyogenes* should be treated with an active β -lactam or vancomycin (in severe penicillin allergy) plus clindamycin. Use of intravenous immunoglobulin (IVIG) is controversial. Limited evidence suggests a shorter time to no further need for debridement but no effect on mortality.
 - v. Antibiotic therapy should be continued until surgical debridement is no longer necessary and until resolution of infection-related signs and symptoms.
- 5. Organ or space infection: See individual chapters, sections, or guidelines for managing organ/space-specific infection (e.g., pancreatitis, intra-abdominal infection; genitourinary tract).

IX. STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

A. Epidemiology

1. Severe cutaneous reactions and related syndromes are unpredictable and rare. The primary causes of these injuries include drugs, dysregulated immune response, and acute infection. Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug hypersensitivity syndrome, or drug rash with eosinophilia and systemic symptoms (DRESS) are the most common presentations. There is a suggestion of genetic influence on the occurrence of SJS and TEN.
2. SJS and TEN are the most severe of reactions, representing different points on a similar spectrum of cutaneous injury involving epidermolysis or separation of the epidermis from the dermis.
3. Similar to thermal injury, the TBSA affected is used to describe the extent of cutaneous injury. According to contemporary reports from U.S. burn centers, the mean TBSA involvement for patients with TEN is greater than 60%.
4. The incidence of severe cutaneous reactions is difficult to estimate. The highest rates reported approach 20%; however, definitions include mild to moderate reactions. The estimated incidence of SJS and TEN is 1 in 500,000–1,000,000 population. Patients infected with HIV may have a higher incidence.
5. The severity of clinical presentation is associated with the extent of tissue and mucosal injury and necrosis. Most patients have a prodromal fever and malaise preceding cutaneous symptoms. Clinical presentation usually includes fever, SIRS, hypotension from cytokine-mediated vasodilation, and mild to moderate hypovolemia from volume depletion and third spacing. Bleeding may also be present, depending on the extent of mucosal injury.

6. Health care–associated or nosocomial complications, including pneumonia, CAUTIs, CLABSI, and malnutrition, are common in severely injured patients.
7. SJS and TEN are life-threatening reactions. Average crude mortality associated with SJS/TEN is 25%–55% and can be as high as 90%.

B. Definitions

1. SJS and TEN are part of the same disease process, differing in severity. Common features of SJS and TEN include cutaneous erythema, progressive blistering, epidermolysis, and mucosal erosions.
2. The most widely accepted classification system for SJS and TEN was proposed by Bastuji-Garin et al. This system includes five categories:
 - a. Bullous erythema multiforme: Epidermal detachment involving less than 10% TBSA and localized typical targets or raised atypical targets
 - b. SJS: Epidermal detachment involving less than 10% TBSA and widespread erythematous or purpuric macules or flat atypical targets
 - c. SJS/TEN overlap: Epidermal detachment involving 10%–30% TBSA and widespread purpuric macules or flat atypical targets
 - d. TEN with spots: Epidermal detachment involving greater than 30% TBSA and widespread purpuric macules or flat atypical targets
 - e. TEN without spots: Large sheets of epidermal detachment involving greater than 10% TBSA without purpuric macules or target lesions

C. Etiology

1. Drugs are the most common cause of SJS and TEN and are implicated in more than 90%–95% of cases. More than 200 medications have been reported as causing SJS and TEN. The most common agents implicated are sulfonamide antibiotics and aromatic anticonvulsants (phenytoin, phenobarbital, and carbamazepine). Other agents/classes include:
 - a. Abacavir
 - b. Allopurinol
 - c. β -Lactam antibiotics
 - d. Lamotrigine
 - e. Nevirapine
 - f. Nonsteroidal anti-inflammatory drugs, particularly the oxicams
 - g. Quinolones, particularly ciprofloxacin
 - h. Tetracyclines
2. Vaccinations also have been associated with SJS and TEN, including measles, mumps, and rubella (MMR).
3. Exposure to industrial chemicals and fumigants
4. Infection with *Mycoplasma pneumoniae*

D. Diagnosis

1. Primary clinical signs/symptoms associated with SJS and TEN are fever and malaise, followed by cutaneous blisters and erosive mucosal lesions of the mouth, lips, eyes, and genital area. The distribution of cutaneous lesions is predominantly central, with mucosal involvement of usually at least two sites. Lesions consist of widespread, flat atypical targets or purpuric macules. TBSA is used to differentiate SJS from TEN and to categorize the severity of cutaneous and mucosal involvement. TBSA is calculated by the following:
 - a. Arms – 9% each
 - b. Head and neck – 9%

- c. Legs – 18% each
 - d. Perineum – 1%
 - e. Trunk – Anterior 18%; posterior 18%
2. The diagnosis of SJS and TEN is confirmed by histopathologic analysis of lesional tissue and is corroborated with clinical presentation. Early lesions show scattered necrotic keratinocytes in the epidermis, whereas late-stage lesions reveal confluent full-thickness epidermal necrosis, which leads to formation of subepidermal bullae.
- a. SCORTEN is a severity-of-illness system designed to predict mortality for TEN. It is computed within the first 24 hours of presentation and on day 3 using the sum of seven objective clinical variables (each item present is worth 1 point):
 - i. Age older than 40 years
 - ii. Heart rate greater than 120 beats/minute
 - iii. Presence of cancer or hematologic malignancy
 - iv. Epidermal detachment greater than 10% TBSA on day 1
 - v. Blood urea nitrogen greater than 28 mg/dL
 - vi. Glucose greater than 252 mg/dL
 - vii. Serum bicarbonate less than 20 mEq/L
 - b. Mortality prediction increases sharply with each additional point, starting at 3% for 0 or 1 point and reaching 90% for 5 or more points. SCORTEN mortality estimates are often used as benchmark rates to assess noncontrolled pharmacotherapy studies.

E. Management and Treatment

- 1. Identification, discontinuation, and avoidance of likely or suspected causes are imperative. Causative agents with a long half-life should be identified and strategies to expedite removal considered.
- 2. Transfer to ICU, preferably at a certified burn center.
- 3. Overt assessment of mucus membranes to prevent extension of injury and related sequelae. This includes the respiratory tract, eyes, and GI tract.
- 4. The cornerstones of management of SJS and TEN are:
 - a. Resuscitation and supportive care
 - i. Goal-directed fluid resuscitation should be initiated immediately to maintain:
 - (a) Mean arterial blood pressure above 65 mm Hg
 - (b) Central venous pressure 8–12 mm Hg
 - (c) Urine output 0.5–1 mL/kg/hour
 - (d) Central venous oxygen saturation above 70%
 - ii. Support respiratory function with respiratory therapy and continual assessment for intubation, as appropriate
 - iii. Avoid using skin to anchor devices and catheters.
 - iv. Physical and occupational therapy when appropriate
 - b. Debridement of necrotic epidermis and coverage of affected areas with artificial or biologic dressing. This may be done serially because progression of affected areas may occur.
 - c. Management of extracutaneous injuries
 - i. Ocular involvement
 - (a) Adequate ocular lubrication
 - (b) Consideration of topical, preservative-free ophthalmic corticosteroid drops
 - (c) Treatment of corneal fluorescein or ulceration
 - ii. Oral involvement
 - (a) Maintain lip barrier integrity (e.g., white paraffin)
 - (b) Consider antiseptic oral rinse (e.g., chlorhexidine)
 - (c) Consider topical corticosteroid rinse (e.g., betamethasone)

- d. Nutrition support (see related chapter)
 - e. Avoidance and treatment of infectious complications
 - i. Implement infection prevention best practices, including minimizing unnecessary devices and procedures related to health care–associated infection.
 - ii. Prophylactic antibiotic therapy is not recommended for SJS and TEN.
 - iii. Empiric antibiotic therapy should be carefully chosen and reserved for suspected infection, as evidenced by signs and symptoms of sepsis or site-specific infection. Continuation of antibiotic therapy should be reserved for confirmed infection, and duration should be limited according to the specific infection.
5. Adjuvant therapies
- a. Plasmapheresis – Support is derived from case series; thought to be generally safe and an effective strategy to remove pathogenic, nondialyzable plasma factors, including some drugs, toxins, metabolites, antibodies, immune complexes, and disease-inducing cytokines
 - b. Immunomodulating therapy
 - i. Corticosteroids – Despite some evidence of benefit, use is controversial and not universally recommended. More recent case reports suggest that high-dose pulse therapy during the first 3 days of presentation decreases disease progression. Associated risks (e.g., infection; hyperglycemia, poor wound healing) may outweigh benefits.
 - ii. Cyclosporine – Information from individual case series suggests benefit at a dose of 3 mg/kg/day. There are no formal recommendations for routine use.
 - iii. Cyclophosphamide – Early case reports suggested benefit, but cyclophosphamide is not recommended.
 - iv. Colony-stimulating factor – May be used in conjunction with cyclosporine in patients with neutropenia and TEN
 - v. IVIG
 - (a) IVIG for SJS and TEN is controversial.
 - (b) In vitro data support that immunoglobulin G (IgG) antibodies against Fas-FasL proteins may decrease keratinocyte apoptosis.
 - (c) Many retrospective single-group and cohort studies suggest benefit (usual dosage 1 g/kg/day for 3 days) over SCORTEN estimated mortality rates and similar control groups, respectively.
 - (d) Given the rare incidence and logistical difficulty of designing a multicenter prospective study, available prospective studies have been small and single center. Results from these studies, however, have shown no benefit to trends of worse outcome.
 - (e) A systematic review and meta-analysis of use in TEN patients found no benefit over standard of care.
 - (f) The decision to administer IVIG remains clinically supported by pathophysiology-pharmacology interactions and observational data. Centers with expertise to care for patients with TEN should assess the utility of IVIG and develop interdisciplinary guidance for local use.
 - vi. Consensus guidelines from the United Kingdom recommend immunomodulating therapies be used under the supervision of skin failure specialists in the context of a clinical study or registry.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

The patient has suspicion for MDR VAP, as evidenced by the presence of clinical signs of infection, the patient's increased sputum production, and the patient's having been in the ICU for 5 days or longer. Empiric antibiotic therapy should be initiated after obtaining a respiratory culture and be based on patient-specific risk factors for MDROs, together with local pathogen prevalence and antibiotic susceptibility, to increase the likelihood of providing timely appropriate antibiotic therapy (Answer A is correct). Gram stain results are often nonsensitive for causative pathogens, and waiting for preliminary or final respiratory culture results, as well as blood or urine cultures, may cause an unacceptable delay in appropriate antibiotic therapy (Answers B–D are incorrect).

2. Answer: B

Although this patient is suspected of having early-onset VAP for the current admission, a history of recent intravenous antibiotic therapy is a risk factor for MDROs. Empiric antibiotic therapy for VAP in patients with MRDO risk factors should include agents active against *P. aeruginosa* and MRSA. Empiric combination therapy against *P. aeruginosa* is recommended to increase the likelihood of appropriate antibiotic therapy (Answer B is correct; Answers A and C are incorrect) with a β -lactam antibiotic as one of the preferred agents (Answer D is incorrect). Atypical bacteria coverage is not necessary because their prevalence is low, although consideration should be given if there is a poor response to initial therapy.

3. Answer: B

Based on the PneumA trial and related meta-analyses, the most recent IDSA VAP guidelines recommend definitive antibiotic therapy duration of 7 full treatment days for all patients. This is further emphasized in this patient, who has VAP caused by *Klebsiella* spp., which are lactose-fermenting gram-negative bacilli, and who received appropriate empiric antibiotic therapy and had an appropriate clinical response during therapy (Answer B is correct; Answers A, C, and D are incorrect).

4. Answer: D

In the absence of other suspected sources (i.e., no change in chest radiograph), CLABSI should be suspected as the cause of new-onset fever and leukocytosis,

given the emergency placement and related duration of the CVC (Answer B is incorrect). Although catheter removal should strongly be considered, cultures should be obtained before catheter removal for documentation if the patient has a bloodstream infection (Answer C is incorrect). Initiation of antibiotic therapy should be considered, if appropriate, but only after cultures of the suspected source are obtained (Answer D is correct; Answer A is incorrect).

5. Answer: D

This patient, who is thought to have a CLABSI, has risk factors for MDROs, given that the patient was hospitalized for 5 or more days. Empiric antibiotic therapy choices should include agents active against MRSE and MRSA as well as *P. aeruginosa* (Answer D is correct; Answer A is incorrect). Linezolid is active against MRSA; however, it should be considered only for definitive therapy because its empiric use in patients with a CLABSI is associated with worse outcomes (Answer C is incorrect). Fluconazole may be considered in addition to antibiotic therapy, but monotherapy is not recommended empirically (Answer B is incorrect).

6. Answer: B

The guideline recommendation for definitive antibiotic therapy duration is 7–14 days from the first negative blood culture in patients with uncomplicated gram-negative CLABSI. Longer durations of therapy should be considered in patients with persistent bacteremia or if the patient has a poor clinical response. (Answer B is correct; Answers A and C are incorrect). Patients with complicated bacteremia (e.g., endocarditis, septic thrombus, chronic intravascular hardware) should receive 4–6 weeks of therapy (Answer D is incorrect).

7. Answer: D

This patient likely has severe influenza amid a local seasonal outbreak. Local infection patterns suggest a prevalence of influenza A and B strains. Empiric influenza-specific therapy against these strains should be initiated in patients with severe influenza before confirmatory test results are known to avoid a delay in appropriate therapy (Answer B is incorrect). Neuraminidase-based therapy is recommended for modern influenza A and B strains (Answer D is correct; Answer C is incorrect). Even if they are outside 48 hours from symptom onset,

patients with severe influenza have benefited from therapy initiated beyond this period (Answer A is incorrect).

8. Answer: D

This patient has complicated intra-abdominal infection from secondary peritonitis caused by colonic perforation. Although it is community acquired, the presence of septic shock suggests severe classification increasing the risk of gram-negative MDROs (Answer C is incorrect). The involvement of the colon also obligates antibiotic therapy active against anaerobes and enterococci (Answer B is incorrect); MRSA is an unlikely pathogen (Answer A is incorrect). According to this, piperacillin/tazobactam is the most appropriate agent listed (Answer D is correct).

9. Answer: D

This patient has acute, severe pancreatitis with CT evidence of pancreatic abscess. Gram stain of fluid obtained from CT-guided drainage suggests the presence of gram-negative bacilli and yeast (Answer A is incorrect). Empiric antimicrobial therapy is indicated for suspected infected pancreatitis. Extended-spectrum carbapenems, which achieve relevant pancreatic fluid concentrations, are effective in the management of infected pancreatitis. Addition of anti-candidal therapy is indicated, given the presence of yeast on the Gram stain (Answer D is correct; Answers B and C are incorrect).

10. Answer: B

This patient is thought to have severe, complicated CDI, given his recent exposure to broad-spectrum antibiotic therapy, signs of infection, CT findings, and the presence of hypotension. Combination therapy with metronidazole and vancomycin is indicated (Answers A and D are incorrect). The presence of ileus requires consideration of intravenous metronidazole and intracolonic vancomycin because of possible impaired delivery to the colon through enteral routes (Answer B is correct; Answer C is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

The patient described has early onset VAP without apparent updated risk factors for MDROs (Answers A, B, and C, are incorrect). Pathogens associated with early onset hospital-acquired pneumonia and VAP are usually community-acquired organisms, including *S. pneumoniae*, MSSA, *H. influenzae*, and enteric gram-negative bacilli (Answer D is correct). Although guideline updates recommend that *P. aeruginosa* coverage be considered as empiric therapy for all patients suspected of VAP, lack of MDRO risk factors decreases the likelihood of MDR strains. Atypical bacteria are rarely associated with early onset VAP. If MDRO risk factors were present, MRSA and *P. aeruginosa* would also be considered.

2. Answer: C

Empiric antibiotic choices for VAP should be based on the likely causative pathogens, the presence of MDRO risk factors, and local antibiotic susceptibility patterns. Ceftriaxone is a reasonable agent for empiric management of early onset VAP with activity against common pathogens (Answer C is correct). Broad-spectrum regimens would provide adequate coverage but would result in an unnecessary breadth of antibiotic exposure (Answer B is incorrect). Empiric monotherapy for gram-positive organisms is insufficient (Answer D is incorrect). Atypical bacteria are rarely associated with early-onset VAP (Answer A is incorrect).

3. Answer: D

Gram-positive organisms are the most common cause of CLABSI, including MRSE and MRSA. Vancomycin is the best option listed for empiric management (Answer D is correct). Although linezolid has a sufficient spectrum of activity against these organisms, it is not recommended for empiric management of CLABSI because of concerns for worse patient outcomes (Answer B is incorrect). The other options are inactive against MRSE and MRSA and could be considered in addition to vancomycin if there were a high suspicion for additional pathogens (Answers A and C are incorrect).

4. Answer: D

Given the high prevalence of the 2009 H1N1 subtype of influenza A, oseltamivir is the empiric drug of choice. In addition, oseltamivir has high-level activity against other

contemporary influenza A and B subtypes (Answer D is correct). Zanamivir also has high-level activity against these strains; however, inhaled therapy through the mechanical ventilator is not indicated because of insufficient systemic delivery, and intravenous zanamivir is available through compassionate use and indicated only if oseltamivir cannot be administered (e.g., patient is unable to receive enteral medications, has poor absorption) (Answers B and C are incorrect). Amantadine has insufficient activity against most contemporary influenza A and B strains (Answer A is incorrect).

5. Answer: B

Although a health care–associated CAUTI is caused by a more diverse spectrum of pathogens, *E. coli* is still the most common pathogen and is responsible for around 30% of cases (Answer B is correct). The other pathogens listed are also possible and should be considered when choosing empiric antibiotic therapy in patients with a suspected CAUTI (Answers A, C, and D are incorrect).

6. Answer: D

This patient has community-acquired complicated intra-abdominal infection involving the middle small intestine. Although enteric gram-negative bacilli (e.g., *E. coli*, *Klebsiella* spp.) are the most common pathogens related to this type of infection, patients with severe disease, as evidenced by concomitant septic shock, are at a higher risk of MDROs, including *P. aeruginosa* and enterococci. Piperacillin/tazobactam has empiric activity against these organisms, whereas the other regimens/agents listed have relevant gaps in the bacterial spectrum relative to these pathogens (Answer D is correct; Answers A–C are incorrect).

7. Answer: A

This patient presents with severe acute pancreatitis with radiographic evidence of pancreatic necrosis. Although the patient presents with SIRS, the absence of significant fluid collection or abscess suggests there is no concomitant infection. As such, there is no indication for empiric antibiotic therapy at this time (Answer A is correct; Answer B is incorrect). Most recent evidence and guideline recommendations do not support prophylactic antibiotic therapy for preventing infection of the necrotic tissue (Answer D is incorrect). The mainstay of therapy

for this patient is volume resuscitation and consideration of surgical debridement of pancreatic necrosis if persistent SIRS is evident (Answer C is incorrect).

8. Answer: B

Metronidazole orally or through a feeding tube is recommended for management of an initial-episode, mild-moderate CDI. The absence of a WBC above 15×10^3 cells/mm³ and no apparent new increase in SCr suggests this is not a severe CDI (Answer B is correct). Intravenous metronidazole and vancomycin are indicated for more severe or recurrent cases of CDI (Answers C and D are incorrect); data for fidaxomicin use in critically ill patients are limited and should only be considered for persistent recurrent CDI (Answer A is incorrect).

9. Answer: A

This patient has a superficial incisional wound infection requiring opening and the local debridement of infected material. Lack of systemic signs of infection and no involvement of the fascia suggest that no antibiotic therapy is necessary at this time (Answer A is correct; Answers B–D are incorrect). If the infection extends to include these features or worsened erythema consistent with cellulitis, empiric antibiotic therapy may be warranted.

10. Answer: B

Similar to severe thermal cutaneous injury, the foundation for managing TEN is volume resuscitation and supportive care as well as removal of all suspected causes (Answer B is correct). The utility of corticosteroids is limited and may be harmful to wound healing (Answer A is incorrect). Addition of unnecessary drugs that could confound response or worsen the injury (e.g., antibiotics) should be avoided (Answers C and D are incorrect).

INFECTIOUS DISEASES II

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Learning Objectives

1. Compose a plan to incorporate quality metrics into pre- and postsurgical care.
2. Identify key members of an antimicrobial stewardship team and common strategies used by the team to optimize antibiotic use.
3. Provide empiric antibiotic therapy recommendations for critically ill patients with community-acquired or health care–associated meningitis.
4. Differentiate different microbiological rapid diagnostic tests and their relative advantages and disadvantages.
5. Devise an antimicrobial management strategy using a procalcitonin-guided strategy.
6. Analyze therapeutic options for the treatment of multidrug-resistant pathogens in the intensive care unit (ICU).
7. Devise an optimal treatment plan for critically ill immunocompromised patients with infectious diseases.
8. Distinguish each of the commonly used antifungal agents and their place in therapy in an ICU setting.

Abbreviations in This Chapter

ACS NSQIP	American College of Surgeons National Surgical Quality Improvement Program
AST	Antimicrobial susceptibility testing
CAUTI	Catheter-associated urinary tract infection
CDC	Centers for Disease Control and Prevention
CLSI	Clinical & Laboratory Standards Institute
CMS	Centers for Medicare & Medicaid Services
CoNS	Coagulase-negative staphylococci
CRE	Carbapenem-resistant Enterobacteriaceae
ESBL	Extended-spectrum β -lactamase
HAART	Highly active antiretroviral therapy
ICU	Intensive care unit
KPC	<i>Klebsiella pneumoniae</i> carbapenemase
LOS	Length of stay
MALDI-TOF	Matrix-assisted laser desorption-ionization/time of flight
MIC	Minimum inhibitory concentration

MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	Methicillin-sensitive <i>Staphylococcus aureus</i>
OI	Opportunistic infection
PCR	Polymerase chain reaction
PCT	Procalcitonin
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PNA FISH	Peptide nucleic acid fluorescent in situ hybridization
SCIP	Surgical Care Improvement Project
SOT	Solid organ transplantation
SSI	Surgical site infection
UTI	Urinary tract infection

Self-Assessment Questions

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

1. A 56-year-old man (weight 140 kg) is scheduled to have elective coronary artery bypass surgery with aortic valve bioprosthetic replacement. The patient has a medical history of diabetes and hypertension. He has no drug allergies and has a calculated creatinine clearance (CrCl) of 90 mL/minute/1.73 m². It is anticipated that the patient will be admitted to the cardiovascular surgery intensive care unit (ICU) after the surgery with two chest tubes placed for drainage. Which is the most appropriate antimicrobial prophylactic regimen for the patient?
 - A. Cefazolin 2 g once within 2 hours before incision and administered every 8 hours until chest tubes are removed
 - B. Vancomycin 2 g once within 2 hours before incision and administered every 12 hours until 48 hours after surgery
 - C. Cefazolin 3 g once within 1 hour before incision, re-dosed if surgery lasts more than 4 hours, and continued for 48 hours after surgery
 - D. Cefazolin 2 g once within 1 hour before surgery, re-dosed if surgery lasts more than 4 hours, and continued for 48 hours after surgery
2. Which statement best describes antimicrobial stewardship in the ICU?

-
- A. Formal antimicrobial stewardship team membership should be reserved for clinical pharmacists with infectious diseases training
- B. The main goal of antimicrobial stewardship efforts is to decrease antimicrobial expenditures
- C. Daily clinical activities of a critical care pharmacist may constitute an antimicrobial stewardship effort
- D. Antimicrobial stewardship should not be instituted in critically ill patients because restriction of antimicrobial choices may worsen outcomes
3. P.G., a 33-year-old woman with a history of hydrocephalus since early childhood requiring placement of an internal cerebrospinal fluid (CSF) shunt, presents with a temperature of 102.8°F (39.3°C), an altered mental status, and a white blood cell count of 19×10^3 cells/mm³. After a computed tomography (CT) scan reveals no cause for concern about brain shift, a lumbar puncture is performed. Initial cell count shows elevated CSF white blood cells with a high proportion of neutrophils and low glucose. Neurosurgery is consulted for a presumed CSF shunt infection. Which empiric system antibiotic regimen is most appropriate?
- A. Ceftriaxone and ampicillin
- B. Ceftriaxone and vancomycin
- C. Piperacillin/tazobactam and tobramycin
- D. Cefepime and vancomycin
4. A 75-year-old man is admitted to the medical ICU from the emergency department with septic shock. He is fluid resuscitated and administered broad-spectrum antibiotics with piperacillin/tazobactam and vancomycin. On day 2 of therapy, the patient remains hemodynamically unstable, requiring norepinephrine. The patient's blood culture is positive, according to the institution's microbiology laboratory, which recently implemented rapid diagnostic tests using nanoparticle microarray technology, and the microarray results show the presence of *Escherichia coli* with the CTX-M resistance gene. Which intervention regarding the patient's antimicrobial therapy is most appropriate?
- A. Change piperacillin/tazobactam to cefepime
- B. Add tobramycin to the current regimen
- C. Add levofloxacin to the current regimen
- D. Change piperacillin/tazobactam to meropenem
5. An 81-year-old man is admitted to the medical ICU with presumed line-associated sepsis. Blood cultures are obtained that grow pan-sensitive *Enterobacter cloacae*. The patient is being treated with intravenous ceftriaxone, and the offending central venous catheter is removed. The patient initially responds, but on day 10 of therapy, he becomes febrile, and blood cultures are re-sent. At that time, the patient was maintained on ceftriaxone because he was hemodynamically stable. Gram stain for the new blood cultures is positive for lactose-positive gram-negative bacilli. Which is the most appropriate action for this patient's antimicrobial management?
- A. Change ceftriaxone to ceftazidime
- B. Change ceftriaxone to piperacillin/tazobactam
- C. Change ceftriaxone to meropenem
- D. Continue ceftriaxone alone
6. An 86-year-old woman with a history of end-stage renal disease is admitted to the hospital with respiratory stress requiring intubation, fluid resuscitation, and hemodynamic monitoring. Bronchoalveolar lavage cultures show methicillin-resistant *Staphylococcus aureus* (MRSA). The patient is being treated with intravenous vancomycin. On day 4 of therapy, the patient develops fever, leukocytosis, and erythema around the insertion site of her tunneled dialysis catheter. Blood cultures are sent, and the dialysis catheter is removed. Gram stain from blood cultures is significant for gram-positive cocci in pairs and chains. The medical team discontinues vancomycin and approaches you to inquire about treatment options for this patient. Which agent is most appropriate for this patient?
- A. Daptomycin
- B. Linezolid
- C. Ceftaroline
- D. Tigecycline
7. A 35-year-old man is admitted to the medical ICU with respiratory distress. He has a 3-week history of cough and pleuritic chest pain that has worsened with time. Chest radiography is performed, which shows bilateral infiltrates with ground-glass opacities. The patient is HIV positive and not currently receiving antiretroviral therapy because of non-adherence. The patient requires intubation and is receiving 40% fraction of inspired oxygen (FiO₂).
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His relevant laboratory values are as follows: SCr 1.0 mg/dL, CD4⁺ count 100/mm³, *lactate dehydrogenase* (LDH) 550 IU/L, partial pressure of arterial oxygen (PaO₂) 80 mm Hg, partial pressure of arterial carbon dioxide (PaCO₂) 40 mm Hg, and white blood cell count (WBC) 4 x 10³ cells/mm³. The patient has a sulfa allergy and a glucose-6-phosphate dehydrogenase deficiency. Which regimen for presumed *Pneumocystis jiroveci* pneumonia (PJP) is most appropriate?

- A. Trimethoprim/sulfamethoxazole 15–20 mg/kg intravenously, divided every 6 hours, plus prednisone 40 mg twice daily
 - B. Pentamidine 4 mg/kg intravenously every 24 hours alone
 - C. Primaquine 30 mg orally once daily plus clindamycin 600 mg intravenously every 8 hours alone, plus prednisone 40 mg twice daily
 - D. Atovaquone 750 mg orally every 12 hours plus prednisone 40 mg twice daily
8. A 50-year-old woman with acute myeloid leukemia is admitted for induction therapy. During the patient's clinical course, she develops respiratory distress, for which she is admitted to the medical ICU. She is found to have neutropenic fever and is empirically treated with meropenem plus gentamicin plus vancomycin. On day 5 of empiric therapy, blood cultures are growing pan-sensitive *E. coli*. The patient's relevant laboratory values and vital signs are as follows: blood pressure 115/70 mm Hg, heart rate 84 beats/minute, temperature 101.2°F (38.4°C), and absolute neutrophil count less than 50 cells/mm³. Which is the most appropriate antimicrobial regimen for the patient?
- A. Continue meropenem, gentamicin, and vancomycin for 14 days
 - B. Discontinue all empiric antimicrobials, and initiate ampicillin intravenously to treat until neutrophils recover
 - C. Discontinue vancomycin, and continue meropenem and gentamicin until neutrophil recovery
 - D. Add voriconazole, and continue all other antimicrobials for 14 days

I. QUALITY IMPROVEMENTS

- A. Sepsis Bundle Project (SEP-1): specifics regarding early broad spectrum antimicrobial administration in the management of severe sepsis and septic shock can be found in the Shock chapter.
 - 1. As of January 1, 2016, all traditional chart abstract Surgical Care Improvement Project (SCIP) measures have been retired. SCIP measures reporting is no longer mandatory.
 - 2. Despite the retirement of SCIP measures, the practices described within the retired SCIP measures still represent best practices and should be continued. The rationale provided by the Joint Commission for the retirement of INF-1 (prophylactic antimicrobial within 1 hour of incision), INF-2 (prophylactic antibiotic selection for survival patients), INF-3 (discontinuation of prophylactic antibiotic within specified time), INF-4 (control of post-cardiac surgery glucose control), and INF-9 (removal of urinary catheter by postoperative day 2) stated that consistently high compliance rates no longer necessitate mandatory reporting.
- B. The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) provides general best-practice guidelines.
 - 1. ACS NSQIP also provides a surgical risk calculator that, depending on the type of surgery and the patient's baseline characteristics, can generate estimated risks of complications, which include pneumonia, cardiac complications, surgical site infections (SSIs), urinary tract infections (UTIs), venous thromboembolism, renal failure, discharge to a rehabilitation facility, and death. (This risk calculator can be accessed at <http://riskcalculator.facs.org/>.)
- C. Prevention of SSIs
 - 1. Epidemiology and clinical significance
 - a. More than 290,000 SSI cases occur each year.
 - b. Mortality rate is 2–12 times higher than in surgical patients without SSIs.
 - c. SSIs account for \$4–\$10 billion in direct costs.
 - 2. Risk factors for SSIs: Advanced age, obesity, hyperglycemia, dyspnea, hypoxia, smoking, alcoholism, recent radiotherapy, preoperative albumin less than 3.5 mg/dL, total bilirubin greater than 1.0 mg/dL, trauma/shock, transfusion, hypothermia, inadequate skin preparation, abdominal surgery, contaminated procedures, cancer, emergency surgery, staphylococcal colonization, and prolonged procedure
 - 3. The Centers for Medicare & Medicaid Services (CMS) no longer provides reimbursement to providers for the treatment of SSIs after cardiac, bariatric, or orthopedic surgical procedures.
 - 4. Prevention strategies: Pharmacy specific
 - a. Preoperative
 - i. Control serum blood glucose in patients with diabetes – ACS NSQIP measure
 - ii. Administer prophylactic antibiotics within 1 hour before surgery (vancomycin and fluoroquinolones should be administered within 2 hours before surgery) – ACS NSQIP
 - iii. Select the appropriate prophylaxis – See Table 1.
 - iv. Adjust dose of antibiotics for obesity – See Table 2 for suggested dosing (ACS NSQIP measure).
 - b. Intraoperative
 - i. Re-dose antibiotics, if necessary – See Table 2 for dosing schedule during surgery (ACS NSQIP measure).
 - ii. In general, antibiotics with short half-lives should be re-dosed at a frequency of 2 times the half-life of the agent.
 - iii. Goal of re-dosing is to maintain bactericidal concentrations throughout the operation. May be prudent to consider re-dosing prophylaxis intraoperatively if large amounts of fluids and/or transfusions are being administered.
 - iv. Maintain normothermia.

- c. Postoperative
- i. Discontinue prophylactic antibiotics within 24 hours after non-cardiac surgery and within 48 hours after cardiac surgery. Drains are not sufficient reason to continue prophylactic antibiotics – ACS NSQIP measure.
5. Management of SSIs: See Infectious Diseases I chapter.

Table 1. Prophylactic Antibiotic Regimens for Surgery

Type of Surgery	Recommended Prophylaxis	Alternative Prophylaxis in Patients with β -Lactam Allergies
Coronary artery bypass grafting Other cardiac surgery Vascular surgery Hip arthroplasty Knee arthroplasty Neurosurgery	Cefazolin Cefuroxime	Vancomycin Clindamycin
Thoracic surgery	Cefazolin Ampicillin/sulbactam	Vancomycin Clindamycin
Gastroduodenal surgery	Cefazolin	• Clindamycin <i>or</i> vancomycin + aminoglycoside <i>or</i> fluoroquinolone <i>or</i> aztreonam
Colorectal surgery	• Cefotetan <i>or</i> cefoxitin <i>or</i> ampicillin/sulbactam <i>or</i> ertapenem • Metronidazole + cefazolin <i>or</i> cefuroxime <i>or</i> ceftriaxone	• Clindamycin + aminoglycoside <i>or</i> fluoroquinolone <i>or</i> aztreonam • Metronidazole + aminoglycoside <i>or</i> fluoroquinolone
Abdominal hysterectomy Vaginal hysterectomy Biliary tract surgery	• Cefotetan <i>or</i> cefoxitin <i>or</i> ampicillin/sulbactam	• Clindamycin <i>or</i> vancomycin + aminoglycoside <i>or</i> fluoroquinolone <i>or</i> aztreonam • Metronidazole + aminoglycoside <i>or</i> fluoroquinolone

Table 2. Recommended Dose and Dosing Interval for Commonly Used Antibiotics for Surgical Prophylaxis

Antimicrobial	Recommended Dose in Adults	Dosing Interval (hr) ^a
Ampicillin/sulbactam	3 g	2
Ampicillin	2 g	2
Aztreonam	2 g	4
Cefazolin	2 g, 3 g for patients weighing ≥ 120 kg	4
Cefuroxime	1.5 g	4
Cefoxitin	2 g	2
Cefotetan	2 g	6
Ceftriaxone	2 g	N/A ^b
Ciprofloxacin	400 mg	N/A ^b
Clindamycin	900 mg	6
Ertapenem	1 g	N/A ^b

Table 2. Recommended Dose and Dosing Interval for Commonly Used Antibiotics for Surgical Prophylaxis (*continued*)

Antimicrobial	Recommended Dose in Adults	Dosing Interval (hr) ^a
Gentamicin	5 mg/kg of actual or adjusted body weight	N/A ^b
Levofloxacin	500 mg	N/A ^b
Metronidazole	500 mg	N/A ^b
Vancomycin	15 mg/kg	N/A ^b

^aWith presumed normal renal function^bOne dose of the antibiotic should suffice for the duration of most surgical procedures.

N/A = not applicable.

D. Prevention of Catheter-Associated Urinary Tract Infections (CAUTIs) – ACS NSQIP Measures

1. Definition – Centers for Disease and Prevention (CDC) – See Figure 1.
2. Epidemiology and clinical significance. UTIs represent 30%–40% of all nosocomial infections. Up to 80% of UTIs are caused by urinary catheterization.
 - a. More than 5% of postoperative patients will experience a UTI.
 - b. CAUTIs account for \$300–\$400 million in additional health care costs.
 - c. CMS no longer provides reimbursement to providers for the treatment of CAUTIs.
3. Risk factors: Increased duration of catheterization, female, diabetes mellitus, bacterial colonization of drainage bag, older age, and azotemia
4. Prevention strategies
 - a. Minimize the use of prolonged urinary catheters. Consider removal of urinary catheters by postoperative day 2.
 - b. Pharmacists may provide reminders as part of a multidisciplinary effort to minimize the placement and duration of urinary catheters.
 - c. Strategies that should NOT be considered:
 - i. Routine use of silver or antibiotic-impregnated catheters. According to the CDC, silver or antibiotic-impregnated catheters can be considered if a comprehensive strategy to reduce CAUTI rates has failed. The ACS NSQIP best-practices guidelines suggest that use of antimicrobial urinary catheters can be considered for high-risk patients, such as those who may require prolonged (greater than 7–10 days) catheterization.
 - ii. Addition of antibiotics to drainage bag
 - iii. Use of systemic antibiotic prophylaxis
 - iv. Routine screening or treatment of asymptomatic bacteriuria
 - v. Bladder irrigation with antibiotics
5. Management of CAUTIs: See Infectious Diseases I chapter.

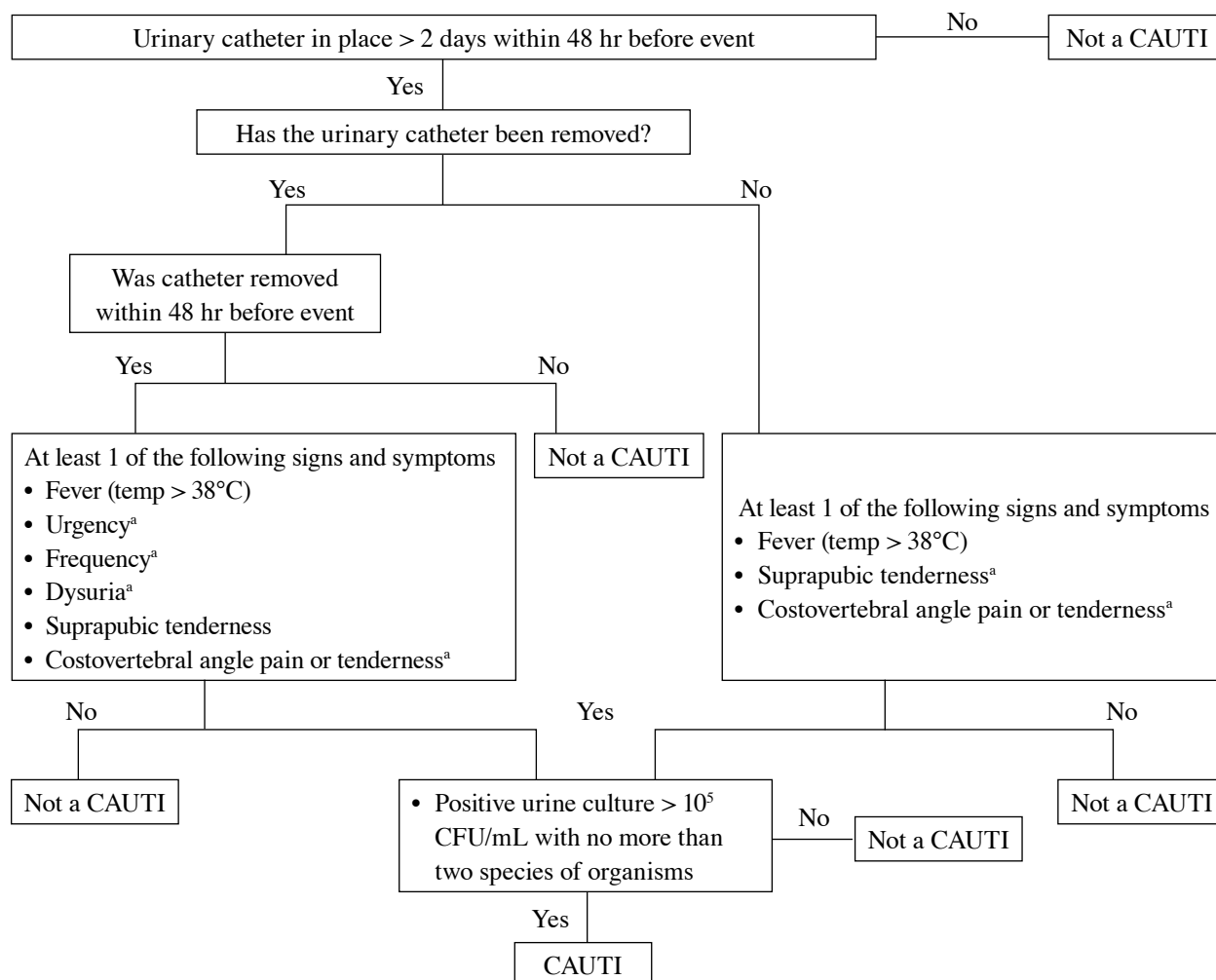


Figure 1. Diagnosis of catheter-associated urinary tract infection according to CDC criteria.

^aWith no other recognized cause

CAUTI = catheter-associated urinary tract infection.

Patient Case

1. C.L is a 55-year-old man admitted to the surgical ICU after exploratory laparotomy for duodenal perforation and peritonitis. The patient was transferred from the operating room to the surgical ICU with a urinary catheter in place. On day 4 of the surgical ICU stay, the patient is extubated, and his urinary catheter is removed. On day 6 of the surgical ICU stay, the patient develops signs and symptoms of UTI with fever, urgency, and frequency. Urinalysis reveals no nitrites or leukocyte esterase. Urine cultures show 100,000 CFU/mL of *E. coli*. You are asked by the quality officer of the surgical ICU to discuss this case and determine whether this patient will qualify for the definition of CAUTI according to CMS criteria. Which statement regarding the diagnosis of CAUTI in this patient is most appropriate?
 - A. Qualifies for definition of CAUTI because the patient is symptomatic and has positive cultures
 - B. Does not qualify for definition of CAUTI because the patient had a negative urinalysis
 - C. Qualifies for definition of CAUTI because the patient is symptomatic and had recent urinary catheter
 - D. Does not qualify for definition of CAUTI because the catheter was removed 2 days before symptoms

E. Prevention of Catheter-Related Bloodstream Infections – ACS NSQIP

1. Definition (CDC): Must satisfy both criteria
 - a. Laboratory-confirmed bloodstream infection
 - i. Definition 1: A recognized pathogen (not a common skin contaminant) found in one or more blood cultures AND the organism is not related to an infection at a separate site
 - ii. Definition 2: At least one sign or symptom of infection (temperature greater than 100.4°F [38°C], chills, hypotension) AND a common skin flora is cultured from two or more blood samples AND organism is not related to an infection at a separate site
 - b. Central line placed for more than 2 days on the date of event and central line must be present or removed within 24 hours of blood cultures being obtained.
2. Epidemiology and clinical significance
 - a. Incidence of catheter-related bloodstream infections: 2.7–7.4 infections per 1000 catheter-days
 - b. Accounts for 14,000–28,000 deaths per year
 - c. Increases mean length of stay (LOS) by 7 days
 - d. CMS no longer provides reimbursement to providers for the treatment of catheter-related bloodstream infections.
3. Risk factors
 - a. Patient factors: Male, diabetes, hypotension, neutropenia, parenteral nutrition, prolonged hospitalization before catheter placement
 - b. Catheter-related factors: Internal jugular or femoral vein placement site (compared with subclavian vein), heavy microbial colonization at insertion site, use of non-tunneled catheters, inadequate catheter care, prolonged duration of venous catheterization
4. Prevention strategies
 - a. Use appropriate techniques for catheter insertion (e.g., skin preparation and maximal sterile barrier precautions) and management (e.g., daily site care, routine site evaluation for local erythema). Minimize the use of central venous catheters. Pharmacists may provide reminders as part of a multidisciplinary effort to minimize the placement and duration of venous catheters.
 - b. Consider antibiotic lock therapy in patients with limited venous access or a history of catheter-related bloodstream infections.
 - c. Do not routinely use systemic antibiotic prophylaxis.
 - d. Antimicrobial/silver-impregnated catheter should be considered in patients with an anticipated catheter duration greater than 5 days if rates of catheter-related bloodstream infections have not decreased despite the implementation of a comprehensive prevention strategy.
5. Management: See Infectious Diseases I chapter.

II. BACTERIAL MENINGITIS**A. Epidemiology**

1. Bacterial meningitis is a neurologic emergency involving mild to severe inflammation of the meningeal layers encasing the central nervous system (CNS). The CSF is intimate to the meninges, serving as pathogen media and diagnostic fluid.
2. Bacterial meningitis is community acquired or health care associated, the latter of which is usually associated with neurotrauma or neurosurgical procedures.

3. Community-acquired bacterial meningitis has an annual incidence in adults of about two cases per 100,000 people. The incidence has been decreasing in recent years (two cases per 100,000 in 1998 to 1.38 cases per 100,000 in 2006; 31% decrease), likely because of increased vaccination. The incidence of nosocomial bacterial meningitis varies depending on the mechanism of neuro-anatomic disruption and ranges from 1.5% of patients undergoing craniotomy to 25% of post-trauma patients with basilar skull fracture.
4. Delayed CSF sterilization beyond 24 hours is a risk factor for subsequent neurologic sequelae, including intracranial hypertension, seizures, and permanent neurologic deficit. Clinical presentations of septic shock, altered mental status, and seizures are associated with worse outcomes. Additional complications include respiratory failure and hyponatremia.
5. Crude mortality for community-acquired meningitis is 19%–37%, whereas mortality for health care–associated meningitis is generally lower, particularly if associated with a reversible procedure or removable device.

B. Definitions

1. Community-acquired meningitis is an infection unrelated to a neurosurgical procedure, neurotrauma, or hospitalization.
2. Health care–associated or nosocomial meningitis is an infection related to invasive procedures, including craniotomy, internal or external ventricular catheters, lumbar puncture, intrathecal medication administration, and spinal anesthesia. Additional causes include complicated closed or open cranial trauma, traumatic brain injury, and hematogenous spread in patients with hospital-acquired bacteremia.

C. Diagnosis

1. The clinical diagnosis of meningitis is nonspecific and difficult to distinguish from that of other infections. Although headache, fever, neck stiffness, and altered mental status are present in almost 95% of patients with community-acquired meningitis, fever and a decreased level of consciousness are the most consistent clinical features in patients with health care–associated meningitis.
2. Lumbar puncture or other method (e.g., from existing drain or shunt) to sample CSF for cell count and analysis, as well as Gram stain and culture, is necessary for definitive diagnosis. Neuroimaging with head CT to detect prelumbar brain shift and risk of brain herniation should be done before lumbar puncture in patients with suspected cranial mass (e.g., immunosuppressed, papilledema, history of CNS disease, new-onset seizure, and focal neurologic deficit).
 - a. Opening pressure during lumbar puncture is usually increased in bacterial meningitis.
 - b. Cell count and fluid analysis
 - i. Community-acquired bacterial meningitis can be differentiated from other causes of meningitis (e.g., viral, aseptic). In general, bacterial meningitis is associated with CSF that is predominantly neutrophilic and has lower glucose concentration. Individual strong predictors of bacterial meningitis include:
 - (a) CSF glucose less than 34 mg/dL
 - (b) Ratio of CSF to blood glucose less than 0.23
 - (c) CSF protein greater than 220 mg/dL
 - (d) CSF leukocyte count greater than 2000 cells/mm³
 - (e) CSF neutrophil count greater than 1180 cells/mm³
 - ii. The diagnostic utility of CSF cell count and fluid analysis in health care–associated meningitis is unknown but is likely limited because of concomitant reasons for local inflammation related to devices or recent procedures. Elevated CSF lactate concentration may be useful to distinguish meningitis from other infectious sources.

- c. Gram stain and culture: Bacteriologic examination of CSF can provide rapid and reliable identification of the causative pathogen(s). Although CSF cell count and analysis is the diagnostic foundation for community-acquired meningitis, CSF culture is the most specific test for health care–associated meningitis.

D. Management and Treatment

1. Appropriate empiric antibiotic therapy administered intravenously, targeted against likely pathogens, and guided by local antibiotic susceptibility patterns should be initiated as soon as possible after bacterial meningitis is suspected. See Table 3 for common pathogens and recommended empiric therapy.
2. Antibiotic dosing and administration strategies should be chosen to optimize CSF concentrations relative to bacterial minimum inhibitory concentration (MIC) and antibiotic pharmacodynamic (PD) properties. Although meningeal inflammation may promote CSF penetration, data are inconsistent.
3. Gram stain can be used to broaden bacterial coverage, but final culture should be reserved for antibiotic de-escalation and definitive antibiotic regimen.
4. Role of corticosteroids
 - a. Adjunctive corticosteroids may improve outcomes by reducing reactive meningeal inflammation and neurologic sequelae related to antibiotic-induced bacterial lysis.
 - b. Conflicting results are published regarding the effects of systemic corticosteroids on neurologic sequelae and mortality among patients with bacterial meningitis.
 - c. Studies from high-income countries tend to suggest that systemic corticosteroids decrease or trend toward a decrease in mortality and neurologic sequelae.
 - d. The outcome benefit associated with systemic corticosteroids seems most pronounced with patients with *Streptococcus pneumoniae* meningitis. However, because corticosteroids must be administered before the receipt of antimicrobials, it is unlikely that clinicians will know the etiology of the disease when making the decision for steroids.
 - e. The Infectious Diseases Society of America (IDSA) guidelines recommend administering dexamethasone 0.15 mg/kg every 6 hours for up to 96 hours, with the first dose administered 10–20 minutes before, or at least concomitant with, the first dose of antimicrobial therapy. The IDSA guidelines also recommend for continuation of dexamethasone only if cultures show the presence of *S. pneumoniae*, although this recommendation is not supported by strong clinical evidence.
5. Health care–associated meningitis
 - a. See Table 3 for empiric treatment of health care–associated meningitis.
 - b. In patients with CSF shunts, removal or replacement of drains or catheters should be considered. CSF shunt replacement should not be done until after at least 7 days of appropriate antibiotic therapy.
 - c. In selected patients with bacterial meningitis after placing a CSF shunt, the IDSA recommends direct instillation of antimicrobial agents intraventricularly through either an external ventriculostomy or shunt reservoir. This practice should only be considered in patients with pathogens that are difficult to eradicate or for those who cannot undergo the surgical component of therapy. See Table 4 for selected antimicrobial intraventricular dosing.
6. Definitive antibiotic therapy can be determined according to finalized cultures and susceptibility results. In general, definitive therapy should entail choosing the therapy with the most appropriate spectrum of activity and an adequate penetration into the CSF. Therapy should be continued for at least 7 days in all patients with meningitis. *S. pneumoniae* should be treated for 10–14 days and gram-negative bacilli, *Listeria monocytogenes*, and *S. aureus* for at least 21 days. CSF should be negative for *S. aureus* for at least 10 days before shunt replacement.

Table 3. Common Pathogens Seen in Different Bacterial Meningitis Populations and the Corresponding Recommended Empiric Therapy

Patient Group	Common Pathogens	Recommended Empiric Therapy
Community Acquired		
18–50 yr	<i>N. meningitidis</i> , <i>S. pneumoniae</i>	Vancomycin + third-generation cephalosporin (e.g., ceftriaxone)
> 50 yr or any age with predisposing condition ^a	<i>N. meningitidis</i> , <i>S. pneumoniae</i> , <i>L. monocytogenes</i> , <i>H. influenzae</i> , aerobic GNB (e.g., <i>E. coli</i>)	Vancomycin + third-generation cephalosporin (e.g., ceftriaxone) + ampicillin
Health care–associated or nosocomial		
Basilar skull fracture (communication with sinuses or oropharynx)	<i>S. pneumoniae</i> ; <i>H. influenzae</i> ; group A β -hemolytic streptococci	Vancomycin + third-generation cephalosporin (e.g., ceftriaxone)
Penetrating trauma	<i>S. aureus</i> , CoNS, aerobic enteric (e.g., <i>E. coli</i>) and non-lactose-fermenting (e.g., <i>P. aeruginosa</i>) gram-negative bacilli	Vancomycin + cefepime <i>or</i> ceftazidime <i>or</i> meropenem
Post-neurosurgery	Aerobic enteric (e.g., <i>E. coli</i>) and non-lactose-fermenting (e.g., <i>P. aeruginosa</i>) gram-negative bacilli, <i>S. aureus</i> , CoNS	Vancomycin + cefepime <i>or</i> ceftazidime <i>or</i> meropenem
CSF shunt	Aerobic enteric (e.g., <i>E. coli</i>) and non-lactose-fermenting (e.g., <i>P. aeruginosa</i>) gram-negative bacilli, <i>S. aureus</i> , <i>Propionibacterium acnes</i>	Vancomycin + cefepime <i>or</i> ceftazidime <i>or</i> meropenem

^aAltered immune status, alcoholism

CoNS = coagulase-negative staphylococci; GNB = gram-negative bacteria.

Table 4. Selected Antibiotic CSF Penetration and Dosages for Meningitis

Agent	CSF Penetration, % of Serum Concentration	Dosage for Meningitis
Amikacin	Low	Conventional: 10–15 mg/kg IV q8–12hr Extended interval: 20–25 mg/kg IV once daily Intraventricular: 30 mg QD
Ampicillin	13–14	2 g IV q4hr
Cefazolin	8–15	2 g IV q8hr
Cefepime	10–20	2 g IV q8hr
Cefotaxime	10–12	2 g IV q4hr
Ceftazidime	30–40	2 g IV q8hr
Ceftriaxone	8–12	2 g IV q12hr
Ciprofloxacin	20–25	400 mg IV q8hr
Colistin	Low	Intraventricular: 10 mg QD
Meropenem	6–21	2 g IV q8hr
Nafcillin	1–2.5	2 g IV q4hr
Piperacillin/tazobactam	20–30	Not recommended because of low penetration of tazobactam

Table 4. Selected Antibiotic CSF Penetration and Dosages for Meningitis (*continued*)

Agent	CSF Penetration, % of Serum Concentration	Dosage for Meningitis
Tobramycin	10–20	Conventional 2–3 mg/kg IV q8–12hr Extended interval: 5–7 mg/kg IV QD Intraventricular 10–20 mg QD
Vancomycin	30	15–20 mg/kg IV q8–12hr Intraventricular 10–20 mg QD

IV = intravenous(ly); q = every; QD = once daily.

Patient Case

2. H.K. is a 42-year-old woman who presents with her husband to the emergency department from home with mental status changes, lethargy, and a temperature of 102.9°F (39.4°C). Her husband reports that she had a severe headache 24 hours earlier. She has no significant medical history. Diagnostic workup results are highly suggestive of meningitis. A lumbar puncture is performed, during which a high initial pressure is noted. Which intervention would be best initially for H.K.?
- Administer dexamethasone 0.15 mg/kg intravenously.
 - Await laboratory and microbiologic analysis.
 - Initiate empiric ceftriaxone and vancomycin.
 - Initiate empiric ampicillin, cefepime, and vancomycin.

III. ANTIMICROBIAL STEWARDSHIP

- Goals: To optimize clinical outcome while minimizing unintended consequences of antimicrobial use, which include the emergence of antimicrobial resistance and adverse drug reactions. In addition, a responsible approach to the use of antimicrobial agents should reduce the overall costs associated with treatment.
 - Antibiotics are the second most common class of drugs that cause adverse effects.
 - Antibiotics are the most common class of medication to be associated with prescribing errors.
 - Minimizing antimicrobial resistance by optimizing therapy should lead to measurable benefits on the patient level because studies have shown the negative effect of antimicrobial resistance on several clinical outcomes.
- Definition: Multidisciplinary coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents to promote the selection of optimal antimicrobial drug regimen, including dosing, duration, and route of administration.
 - Core members of a multidisciplinary antimicrobial stewardship team should include an infectious diseases physician, a clinical pharmacist, a clinical microbiologist, an information systems specialist, an infection control professional, and a hospital epidemiologist.
 - Broad-spectrum antimicrobials are often necessary in the ICU to provide early effective therapy. However, continued use of broad-spectrum antimicrobials may lead to the selection of pathogenic organisms (i.e., *Clostridium difficile*, *Candida* spp.), nephrotoxicity, and the emergence of resistance.

- C. Critical Care Pharmacists – Well positioned to provide guidance on antimicrobial therapy, including expedited selection of appropriate initial agents, aggressive dosing to optimize PD, interpretation of microbiological evidence, appropriate de-escalation of antimicrobials, monitoring of response and potential adverse effects, and determination of the appropriate treatment duration
1. Critical care pharmacists could either have an active role as a member of a multidisciplinary antibiotic stewardship team or serve in many of the different roles and activities of antibiotic stewardship.
 2. Core activities that can be pursued through formal pathways or everyday clinical interventions
 - a. Education with active intervention – Interpretation of rapid identification tests and susceptibility testing
 - b. Guidelines and clinical pathway development. Recent IDSA guidelines recommend facility-specific clinical practice guidelines or algorithms as an effective way of standardizing prescribing practices.
 - c. Streamlining or de-escalation of therapy
 - i. Shortening therapy duration
 - ii. Discontinuing unnecessary antimicrobials
 - d. Dose optimization
 - i. Application of pharmacokinetic (PK)/PD principles. Per IDSA recommendations, PK and dose-monitoring programs specifically recommended for vancomycin and aminoglycosides.
 - ii. Dose adjustments based on organ function
 - iii. Allergy detection and assessment, in particular promotion of β -lactam skin testing when appropriate
 - e. Parenteral to oral conversion
 - f. Recent IDSA guidelines recommend against the use of didactic education alone for stewardship.
 3. Support from microbiology laboratory and electronic medical record system surveillance and decision support may further enhance stewardship efforts.
- D. Two Strategies, Which Could Be Used Synergistically Together
1. Prospective audit with intervention and feedback (“back-end” strategy)
 - a. Allows flexibility and minimizes delay in administering therapy
 - b. The most successful strategy involves direct communication with treating physicians and required documentation for acceptance of recommendation or rationale for denial.
 2. Formulary restriction and preauthorization (“front-end” strategy).
 - a. May be resourceintensive, and prescribers may feel a loss of autonomy
 - b. Initial choices of antimicrobials may be optimized through consultation with infectious disease experts.
 - c. Antimicrobial cycling: An example of formulary restriction in which there is a scheduled removal and substitution of a specific antimicrobial or an antimicrobial class. It is an effort to minimize antimicrobial selection pressures. Evidence is insufficient to suggest that antimicrobial cycling strategies are effective. IDSA stewardship guidelines recommend against the use of antimicrobial cycling as a stewardship strategy.
 3. Regardless of the strategies used or the quality of clinical pathways, programmatic antibiotic stewardship is not a substitute for clinical judgment.
 4. Process measures and outcome measures should be used.
 5. Both strategies should be supported by health care information technology and the electronic medical record system. Clinicians should consult with information technology experts to optimize the use of technology for screening and monitoring antibiotic stewardship activity to maximize scope while minimizing manpower.

E. Effective Antimicrobial Stewardship Programs Can Be Financially Self-Supporting

1. Antimicrobials can account for up to 30% of hospital pharmacy budgets, with up to 50% of antimicrobial use being inappropriate, leading to increased cost, increased selection of resistant pathogens, and increased selection of opportunistic infections (OIs).
2. Several studies have shown the cost savings associated with an antimicrobial stewardship program. However, most of these studies focused on antimicrobial costs, with little focus devoted to indirect costs and implementation costs.
3. There is currently a proposed CMS rule for incorporating antibiotic prescribing patterns as one of the quality-reporting metrics. Many CMS quality metrics are tied to reimbursement. If this metric becomes tied to reimbursement, there will be further incentives to implement antimicrobial stewardship programs.

F. Evidence Supporting Antimicrobial Stewardship Efforts in Critically Ill Patients

1. Studies in this area have been limited by poor study design. However, most studies have reported a decreased use in either antibiotics overall or a targeted class of antibiotics. Some studies have also reported a decrease in key resistance rates.
2. Antimicrobial stewardship strategies used in the studies have varied widely, including restriction, formal infectious disease physician consultation, protocols for de-escalation, implementation of computer-assisted decision support, and formal reassessments of the empiric antibiotics by a stewardship team. The compensatory overuse of another class of antibiotics has been reported when attempts to restrict a different class of antibiotics were implemented.

IV. RAPID DIAGNOSTIC TESTS

A. Rationale

1. There is an association between delay in administration of appropriate antimicrobials and decreased survival.
2. Broad-spectrum antimicrobials are usually used in severe infections to ensure that all potential pathogens are covered.
3. Rapid diagnostic tests may assist in de-escalation efforts in an attempt to practice antimicrobial stewardship. Critical care pharmacists are appropriate advocates for the appropriate use of antimicrobials according to the results of rapid diagnostic tests.
4. In many cases, the implementation of rapid diagnostic tests may be costneutral, or even constitute a cost savings, when antimicrobial stewardship efforts leading to decreased consumption of antibiotics occur.
5. Recommended by IDSA antimicrobial stewardship guidelines in combination with stewardship team to optimize antibiotic therapy and improve clinical outcomes

B. Early Pathogen Identification from Positive Bloodstream Cultures

1. All discussed methods try to shorten the time from blood culture positivity to species identification or susceptibility testing. Traditional pathogen identification and susceptibility testing can take 72–96 hours. Early pathogen identification techniques seek to provide clinically actionable information within the first 24 hours from the time of culture positivity. See Table 5 for examples of rapid diagnostic tests, corresponding targets, and respective turnaround times.

2. Most of these techniques, when combined with antibiotic stewardship efforts, lead to significant reductions in health care costs and improvements in clinical outcomes. Many of these were single-center studies, which makes clinical applicability questionable. The overall impact of the implementation of rapid diagnostic tests in a single institution is determined by several factors.
 - a. Epidemiology of targeted organisms
 - b. Presence and actions of existing antimicrobial stewardship teams
 - c. Current clinician prescribing patterns
 - d. Patient population
3. The inability to detect polymicrobial infections is a common limitation to most of the techniques described.
4. Newer methods using whole blood (vs. blood culture medium or agar plates) are being developed, but most are not currently U.S. Food and Drug Administration (FDA) approved (LightCycler SeptiFast, SepsiTTest).
5. Some of the technology discussed has been developed for respiratory cultures, but the clinical adaptation in that arena is considerably less than that for blood cultures.
6. Application of rapid diagnostic tests that detect genetic encoding of resistance mechanisms requires further education and guidelines to assist clinicians in choosing the proper therapy because traditional susceptibility results are not available. See Table 6 for a reasonable approach based on the detection of resistance genes and species.
7. Peptide nucleic acid (PNA) fluorescent in situ hybridization (FISH)
 - a. Mechanism: Targets species-specific ribosomal RNA from positive blood cultures
 - b. Sensitivity and specificity: 96%–100%
 - c. Limitations: Does not provide antimicrobial sensitivity data. Currently available FISH products are only used for species identification; however, recently, the FDA approved a new product that could detect the *mecA* gene for detecting the presence of methicillin resistance. This product is not currently commercially available.
 - d. Application
 - i. Separates *S. aureus* from possible skin flora contamination of coagulase-negative staphylococci (CoNS).
 - ii. Differentiates *Enterococcus faecium* (which is often resistant to ampicillin and vancomycin) from *Enterococcus faecalis*.
 - iii. Identifies fluconazole-sensitive *Candida* spp. for patients empirically treated with echinocandins.
 - iv. Detects *Pseudomonas* versus non-*Pseudomonas* gram-negative spp. in patients treated with combination gram-negative therapy.
 - e. Studies
 - i. A retrospective study evaluating the outcome and economic benefit of PNA FISH methods for the early differentiation of CoNS and *S. aureus* bacteremia in clinical practice showed a significant cost savings and a decrease in median LOS. Of note, the PNA FISH results were combined with the efforts of an antimicrobial therapy team. Similar results have been shown with PNA FISH implementations for other pathogens, including *Enterococcus* spp. and *Candida* spp. These results are in contrast to those of another study that evaluated the pre- and post-staphylococci PNA FISH implementation results without the use of an antimicrobial stewardship team. This study found no significant effects on patient LOS or vancomycin use. This shows that rapid identification tests are probably beneficial only when combined with educational efforts and prospective alerts to notify clinicians of the clinical applicability of the test results.
 - ii. In a prospective randomized controlled study in which patients were randomized to early notification of PNA FISH results for CoNS or *S. aureus* within 3 hours or usual care, intervention was associated with decreased mortality, decreased antibiotic use, and decreased LOS. The most pronounced benefits occurred in critically ill patients.

8. Mass spectroscopy: Matrix-assisted laser desorption-ionization/time of flight (MALDI-TOF)
 - a. Mechanism: Mass spectroscopy is compared with library standards for identifying pathogen species and/or resistance mechanisms.
 - b. Sensitivity and specificity: 98%–100%
 - c. Limitations
 - i. Similar to PNA FISH, no antimicrobial susceptibility is reported; however, the technology could detect genes encoding resistance. MALDI-TOF for resistance genes is currently not commercially available.
 - ii. Cannot be used for polymicrobial cultures
 - iii. No library is available for unusual organisms, though pathogen libraries are consistently being updated.
 - d. Application: Potentially wider clinical applicability than PNA FISH (which is limited by the availability of specific tests for certain pathogens) with early identification of many more pathogens. Additional library standards for different pathogens are continually being added.
 - e. Studies: This strategy has been evaluated in several studies. In a before-and-after study of MALDI-TOF implementation, a shortened time to pathogen identification and a decrease in LOS, recurrent infections, and mortality were seen. Of note, the implementation of MALDI-TOF included communicating the results to the treatment clinicians by an antimicrobial stewardship team with evidence-based antibiotic recommendations.
9. Polymerase chain reaction (PCR)-based detection systems
 - a. MRSA PCR test
 - i. Mechanism: Novel multiplex real-time assay for *mecA* gene
 - ii. Sensitivity and specificity: 98%–100% for MRSA and methicillin-sensitive *S. aureus* (MSSA) identification
 - iii. Application: Earlier de-escalation of anti-MRSA antimicrobials and earlier appropriate treatment with antistaphylococcal penicillin (oxacillin, nafcillin) for MSSA
 - iv. Studies: In a before-and-after study, implementation of the MRSA PCR test resulted in reduced time to appropriate therapy and duration of unnecessary MRSA coverage. In addition, the mean hospital costs were decreased, and there was a trend toward decreased LOS. In a very similar study, the combination of the MRSA PCR test with antimicrobial stewardship efforts resulted in significant decreases in LOS and cost and a trend toward decreased mortality (18% vs. 26%).
 - b. FilmArray System
 - i. Mechanism: Uses multiplex PCR technology
 - ii. Sensitivity and specificity
 - (a) For species identification: Greater than 90%
 - (b) For resistance genes: 100% (currently only available for *mecA* - methicillin resistance; van A/B - vancomycin resistance; *Klebsiella pneumoniae* carbapenemase [KPC] - carbapenem resistance)
 - iii. Application: Earlier escalation or de-escalation of antimicrobial agents
 - iv. Studies: No studies regarding the clinical effects of FilmArray implementation are available. However, studies have shown an earlier time to pathogen identification.
10. Nanoparticles: Verigene blood culture test
 - a. Mechanism
 - i. Direct detection from positive blood culture medium using nanoparticle technology
 - ii. Nucleic acid extraction and array hybridization
 - b. Most-developed commercially available product with resistance gene detection
 - c. Sensitivity and specificity: 93%–100%

- d. Studies: Currently, most studies are limited to in vitro evaluations, which showed high levels of accuracy and decreased time to pathogen and resistance mechanism identification. Limited clinical evidence; however, two small single-center studies have evaluated the use of Nanosphere technology to augment clinical decisions. These studies showed a decrease in time to appropriate antimicrobials, in addition to decreased LOS and overall cost.
11. Chromogenic media
 - a. Mechanism
 - i. Microbiological media used to identify different microorganisms by color production
 - ii. Growth media use enzyme substrates that release colored dyes on hydrolysis, with a wide range of enzymes that can be targeted
 - iii. Potential advantage of being able to detect polymicrobial growth
 - b. Sensitivity and specificity: 95%–100%
 - c. Limitations
 - i. Many different companies make different chromogenic agar media (Brilliance, chromID, CHROMagar). Slight differences in sensitivity and specificity were seen in studies; however, all were within acceptable ranges.
 - ii. Time to identification is longer than with other rapid diagnostic tests.
 - iii. Different manufacturers' chromogenic agar produces different colors for positive identification. Readers of chromogenic agar should be sufficiently trained and familiar with the product used by the local institution.
 - d. Application
 - i. Isolation of *S. aureus* from other *Staphylococcus* spp.
 - ii. Detection of methicillin resistance among *S. aureus*
 - iii. Detection of vancomycin resistance
 - iv. Detection of specific Enterobacteriaceae: *Salmonella*, *E. coli* O157, extended-spectrum β -lactamase (ESBL) production
 - v. Differentiation of different *Candida* spp.
 - vi. Detection of KPC
 - e. Studies: Many clinical studies have shown significant advantages over conventional culture media. With the advent of newer technology and shorter detection times, the clinical applicability of chromogenic media may be limited. However, few microbiology laboratories have implemented rapid diagnostic methods because of the considerable upfront costs. Centers where chromogenic media are being used may continue to rely on this technology.

Table 5. Examples of Rapid Diagnostic Tests of Positive Blood Cultures and Their Characteristics

Assay Technology	Manufacturer/Trade Name	Organisms/Antimicrobial Resistance Targets	Detection Time After Positive Growth on Blood Culture
PNA FISH	- AdvanDx/PNA FISH, Traffic Light - AdvanDx/QuickFISH	<i>S. aureus</i> , CoNS, <i>E. faecalis</i> , <i>E. faecium</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , <i>C. albicans</i> , <i>C. glabrata</i> , <i>C. parapsilosis</i> , <i>C. tropicalis</i> , <i>C. krusei</i>	1.5 hr – PNA FISH 20 min – QuickFISH – Not currently FDA approved for <i>Candida</i> spp.
PCR	- BD GeneOhm/Staph SR - Cepheid/Xpert MRSA	<i>S. aureus</i> , CoNS/ <i>mecA</i> (methicillin)	1–2 hr

Table 5. Examples of Rapid Diagnostic Tests of Positive Blood Cultures and Their Characteristics (*continued*)

Assay Technology	Manufacturer/Trade Name	Organisms/Antimicrobial Resistance Targets	Detection Time After Positive Growth on Blood Culture
PCR	• BioFire/ FilmArray	<i>Enterococcus</i> spp., <i>L. monocytogenes</i> <i>S. aureus</i> , <i>S. agalactiae</i> , <i>S. pneumoniae</i> , <i>S. pyogenes/mecA</i> (methicillin), vanA/B (vancomycin) <i>A. baumannii</i> , <i>H. influenzae</i> , <i>N. meningitidis</i> , <i>P. aeruginosa</i> , <i>E. cloacae</i> , <i>E. coli</i> , <i>K. oxytoca</i> , <i>K. pneumoniae</i> , <i>Proteus</i> spp., <i>S. marcescens/KPC</i> (carbapenem) <i>C. albicans</i> , <i>C. glabrata</i> , <i>C. krusei</i> , <i>C. parapsilosis</i> , <i>C. tropicalis</i>	1 hr – Direct from blood culture media
MALDI-TOF	• BioMérieux/ Vitek MS • Bruker/ Microflex	Several pathogens, including bacteria, yeast, mold, mycobacteria/resistance mechanisms are in development ^a	10–30 min
Nanoparticles	• Nanosphere/ Verigene	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>S. lugdunensis</i> , <i>S. anginosus</i> , <i>S. agalactiae</i> , <i>S. pneumoniae</i> , <i>S. pyogenes</i> , <i>E. faecalis</i> , <i>E. faecium</i> , <i>Staphylococcus</i> spp., <i>Streptococcus</i> spp., <i>Micrococcus</i> spp., <i>Listeria</i> spp./ <i>mecA</i> (methicillin), vanA (vancomycin), vanB (vancomycin) <i>E. coli</i> , <i>K. pneumoniae</i> , <i>K. oxytoca</i> , <i>P. aeruginosa</i> , <i>S. marcescens</i> , <i>Acinetobacter</i> spp., <i>Citrobacter</i> spp., <i>Enterobacter</i> spp., <i>Proteus</i> spp./ CTX-M (ESBL), IMP (carbapenemase), KPC (carbapenemase), NDM (carbapenemase), OXA (carbapenemase), VIM (carbapenemase) <i>Candida</i> spp. in development	2 hr – Direct from blood culture media
Chromogenic media	• CHROMagar	<i>S. aureus</i> , MRSA, <i>Enterococcus</i> spp., VRE, <i>S. agalactiae</i> , <i>E. coli</i> (Shiga toxin, EC-O157), <i>Klebsiella</i> spp., <i>Proteus</i> spp., <i>Pseudomonas</i> spp., <i>Acinetobacter</i> spp., <i>Yersinia</i> spp.; KPC (carbapenem), CTX-M (ESBL) <i>C. albicans</i> , <i>C. tropicalis</i> , <i>C. krusei</i>	24–48 hr

^aThe mass spectrometry database of organisms is constantly changing and growing.

ESBL = extended-spectrum β -lactamase; KPC = *Klebsiella pneumoniae* carbapenemase; MALDI-TOF = matrix-assisted laser desorption-ionization/time of flight; MRSA = methicillin-resistant *S. aureus*; NDM = New Delhi metallo- β -lactamase; PCR = polymerase chain reaction; PNA FISH = peptide nucleic acid fluorescent in situ hybridization; VRE = vancomycin-resistant enterococci.

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Table 6. Reasonable Empiric Treatment Approach Associated with Detection of Antimicrobial Resistance Encoding Genes from Rapid Diagnostic Tests for Positive Blood Cultures^a

Resistance Genes	Species	Recommended Therapy	Alternative Therapy
<i>mecA</i> -negative	<i>S. aureus</i>	Oxacillin Nafcillin	Cefazolin Vancomycin (if allergic to β -lactams)
<i>mecA</i> -positive	<i>S. aureus</i>	Vancomycin	Daptomycin Linezolid Ceftaroline
<i>vanA/B</i> -negative	<i>E. faecalis</i>	Ampicillin	Vancomycin (if allergic to β -lactams)
<i>vanA/B</i> -positive	<i>E. faecalis</i>	Daptomycin	Linezolid Ceftaroline
<i>vanA/B</i> -negative	<i>E. faecium</i>	Vancomycin	Daptomycin (if allergic to vancomycin)
<i>vanA/B</i> -positive	<i>E. faecium</i>	Daptomycin	• Linezolid
CTX-M (ESBL) ^a	Enteric gram-negative pathogens	Carbapenems (ertapenem, imipenem, meropenem, ertapenem)	Ceftazidime/avibactam
KPC ^a	<i>K. pneumoniae</i> and other enteric gram-negative pathogens	Colistin Tigecycline Ceftazidime/avibactam	
NDM carbapenemase ^a	<i>K. pneumoniae</i> and other enteric gram-negative pathogens	Colistin Tigecycline	
VIM or IMP carbapenemase ^a	<i>P. aeruginosa</i>	Colistin Aztreonam	
OXA β -lactamase ^a	<i>P. aeruginosa</i>	Colistin Carbapenem ^b	
OXA β -lactamase ^a	<i>A. baumannii</i>	Colistin Tigecycline Carbapenem ^b	

^aResistance mechanisms associated with gram-negative pathogens are more complicated. Often, there is more than one resistance mechanism. Hence, the recommended therapies represent reasonable empiric approaches before full antimicrobial susceptibility reports. However, therapy may be tailored to either a broader or a narrower spectrum.

^bCarbapenem may have a higher MIC in the presence of OXA β -lactamase. If using carbapenem, may consider using maximal doses.

Patient Case

3. A 54-year-old man is admitted to the medical ICU with acute necrotizing pancreatitis. He is found to have an infected pancreatic abscess, which is being treated with meropenem and vancomycin. Two weeks into the course, the patient develops a fever and leukocytosis. He also becomes hemodynamically unstable and oliguric. He is initiated on caspofungin empirically to cover for possible invasive candidiasis. Blood cultures are obtained, which become positive with a preliminary result of yeast. This institution is equipped with PNA FISH technology, which identifies the yeast as *Candida parapsilosis* on day 2 of therapy. The patient remains hemodynamically unstable. Which is the most appropriate choice for this patient's antifungal therapy?
- A. Continue caspofungin while fungal susceptibilities are finalized.
 - B. Change to voriconazole 6 mg/kg every 12 hours.
 - C. Change to liposomal amphotericin 5 mg/kg/day.
 - D. Change to fluconazole 400 mg intravenously daily.

C. Early *C. difficile* Identification

1. Traditional methods for identifying *C. difficile* toxins (cytotoxin neutralization assay and rapid enzyme immunoassays) attain a sensitivity of 60%–70%.
 - a. Usually targeting toxin A, toxin B, or both
 - b. Recommend up to three serial tests to improve sensitivity
2. Nucleic acid amplification methods (PCR and loop-mediated isothermal amplification)
 - a. Assays are targeting DNA sequence for the toxin A or toxin B gene.
 - b. Turnaround time: 1–3 hours
 - c. Sensitivity and specificity: 90%–96%
 - i. Because of increased sensitivity, the false-positive rates may be increased.
 - ii. As the prevalence of *C. difficile* decreases, the positive predictive value decreases, which may lead to unnecessary overtreatment.
 - iii. Educational efforts should be made to discourage the practice of over-ordering *C. difficile* rapid nucleic acid amplification tests. In addition, clinicians should be discouraged from ordering serial tests, which was a common practice when enzyme immunoassays were used. Because the sensitivity is sufficiently high, serial ordering only furthers the chance of false positivity.

D. Early Identification of Fungal Organisms

1. Up to 50% of patients with histopathologically proven invasive candidiasis have negative blood cultures.
2. Cultures for *Aspergillus* lack sensitivity and may require significant growth time.
3. Biopsies are often not feasible in critically ill patients.
4. Surrogate markers of fungal infections are needed for early diagnosis and to avoid delays in treatment, which have been associated with worsened outcomes.
5. β -d-Glucan
 - a. Found in the cell membrane of most fungal pathogens (except for *Mucor* and *Cryptococcus*). Potentially a screening tool for *Candida*, *Aspergillus*, and *Pneumocystis*.
 - b. Fungitell assay can detect β -d-glucan in serum and provide results within 2 hours.
 - c. Variable cutoffs are described in the literature for a positive result. A suggested cutoff for positive results, as used in a recent study evaluating prophylactic and preemptive antifungal therapy in critically ill patients, is greater than 80 pg/mL.
 - d. Considerable differences in sensitivity and specificity values have been seen in different populations.

- e. Consistently high negative predictive values and low positive predictive values have been seen for the diagnosis of invasive fungal infections, which suggests that it is best used as a screening-out tool when the values are low. Low positive predictive value may occur because many clinical scenarios could lead to false-positive results.
 - i. Exposure to β -d-glucan-containing surgical supplies and topical products
 - ii. Colonization with *Candida*
 - iii. Thrush and mucositis
 - iv. Cellulose membranes from dialysis filters
 - v. Bacterial infections
 - vi. Receipt of β -lactam antibiotics
 - f. When used as a tool to potentially initiate treatment, optimal results occur when two consecutive tests are positive.
 - g. Nonspecific fungal element makes interpretation difficult. May detect elements from *Aspergillus*, *Candida*, and *Pneumocystis*. Does not detect different species.
 - h. Has been evaluated in combination with clinical prediction scores for invasive candidiasis in critically ill patients for initiating empiric antifungal therapy. When using β -d-glucan as a screening tool, empiric echinocandin therapy does not result in any significant differences in clinical outcomes compared with placebo.
- 6. T2 Magnetic Resonance
 - 7. Nanodiagnostic approach, which detects amplified *Candida* DNA. Similar to traditional MRI techniques, but done on a micro scale.
 - 8. Performed on whole blood, where magnetic particles that are coated with agents specific for binding to *Candida* DNA.
 - 9. When *Candida* is present in whole blood, it will bind to the particles and cluster, causing microscopic disruptions in the magnetic fields.
 - 10. Currently, FDA approved for 5 pathogenic *Candida* species
 - 11. High sensitivity (91%) and specificity (98%) but lacks clinical study application
 - 12. Galactomannan
 - a. Cell wall component of *Aspergillus* spp.
 - b. Platelia enzyme immunoassay can detect galactomannan in serum or other sterile fluids (bronchoalveolar lavage) within 4 hours.
 - c. Variable sensitivity and specificity, with generally better positive and negative predictive values for the detection of *Aspergillus* in the patient population with hematologic malignancies than in the solid organ transplant (SOT) population
 - d. False positives can occur with the simultaneous administration of certain β -lactam antibiotics (piperacillin/tazobactam, amoxicillin/clavulanic acid) or the presence of other invasive mycoses (*Penicillium*, histoplasmosis, blastomycosis).
 - 13. Other *Candida* early diagnostic tools such as PCR, mannan, and d-arabitol require additional investigation before wide clinical adaptation.
- E. Procalcitonin (PCT)
- 1. An inflammatory biomarker that reflects host response to bacterial infections
 - 2. PCT synthesis is up-regulated by bacterial toxins and certain bacterial proinflammatory mediators such as interleukin (IL)-1b, IL-6, and tumor necrosis factor alpha (TNF α), but it is neutral to cytokines that are normally released for viral infections such as interferon- γ . Usual concentrations of PCT are undetectable (less than 0.05 ng/mL). However, on exposure to bacterial toxins, PCT is rapidly released within 2–4 hours. The plasma half-life of PCT is 24 hours. Concentrations seen in the literature for infected patients vary greatly; however, it appears that higher max concentration of PCT during infection correlates with a higher incidence of mortality.

3. PCT is used in many roles, including the diagnosis and prognostication for sepsis and severe sepsis. IDSA stewardship guidelines recommend serial measurements be used in conjunction with other stewardship interventions to decrease antibiotics use. Surviving sepsis campaign provides a weak recommendation (Grade 2C) for the use of low PCT to assist clinicians in the discontinuation of empiric antibiotics when no evidence of infection is found.
4. For clinical decisions regarding antibiotic use and duration, PCT has been evaluated for antibiotic initiation, antibiotic cessation, and the combination of both strategies. These strategies assume PCT availability from an institutional laboratory. If the PCT turnaround time is more than 24 hours, the effects of minimizing antimicrobial treatment days may be limited.
5. According to current evidence, PCT should not routinely be measured in patients without signs and symptoms of infection. The decision to initiate patients on antibiotics without signs and symptoms of infection using PCT alone would probably lead to antimicrobial overuse and possible adverse effects associated with antimicrobial therapy. In the largest PCT study of critically ill patients to date, 1200 patients were randomized to either a PCT alert strategy or a standard of care. For those randomized to intervention, a PCT concentration greater than 1.0 mcg/L generated an alert that mandated clinical intervention, which included microbiological cultures, additional radiologic assessment, and/or initiation or expansion of antimicrobial coverage. Overall, this strategy did not lead to an improvement in mortality or time to appropriate antibiotics. In contrast, patients experienced a greater need for mechanical ventilation, prolonged ICU LOS, and prolonged antibiotic use.
6. In critically ill patients with signs and symptoms of infection, a baseline PCT (at the time of the symptoms) should not be used to determine whether antibiotics should be initiated. The compliance rate for withholding antibiotics for a low PCT in this scenario has consistently been low. The compliance rate in clinical practice is likely even lower than that in clinical studies; however, this has not been evaluated. If a baseline PCT is obtained, it should be used to trend the PCT for the possible early discontinuation of antibiotics. In a study of patients with signs and symptoms of infections to determine whether a PCT-guided strategy would limit the initiation of antibiotics, no difference in antibiotic use was seen. However, this was probably because only 36% of clinicians were compliant with the recommendation to withhold antimicrobials when the PCT was low. This is in stark contrast with the 86% compliance rate with the recommendation to initiate antibiotics when the PCT was high.
7. Critically ill patients with signs and symptoms of infection should have a baseline PCT obtained for trending purposes. A low PCT (or substantial decrease from baseline) during antibiotic treatment should be used to shorten the duration of antimicrobial therapy. This could be accomplished through either eliminating unnecessary antibiotics in patients who are not infectious or shortening the course of therapy for patients who are infectious. This strategy has been proved safe and effective in a wide spectrum of critically ill patients. Several studies have evaluated the utility of a PCT-guided strategy for determining the appropriate time to discontinue and/or de-escalate antibiotics. These studies consistently show that PCT guidance for discontinuing antimicrobial therapy led to decreases in antibiotic use without an untoward outcome effect. This has been shown in various ICU populations, in patients with differing severity of illness, and in those with proven infections. The largest PCT study in critically ill patients was recently published. It demonstrated a significant decrease in the use of antimicrobials (median 5 days vs. 7 days) and 28-day mortality (20% vs. 25%).
8. Many different PCT guidance algorithms exist; Figure 2 represents a reasonable approach to using PCT for antibiotic cessation.

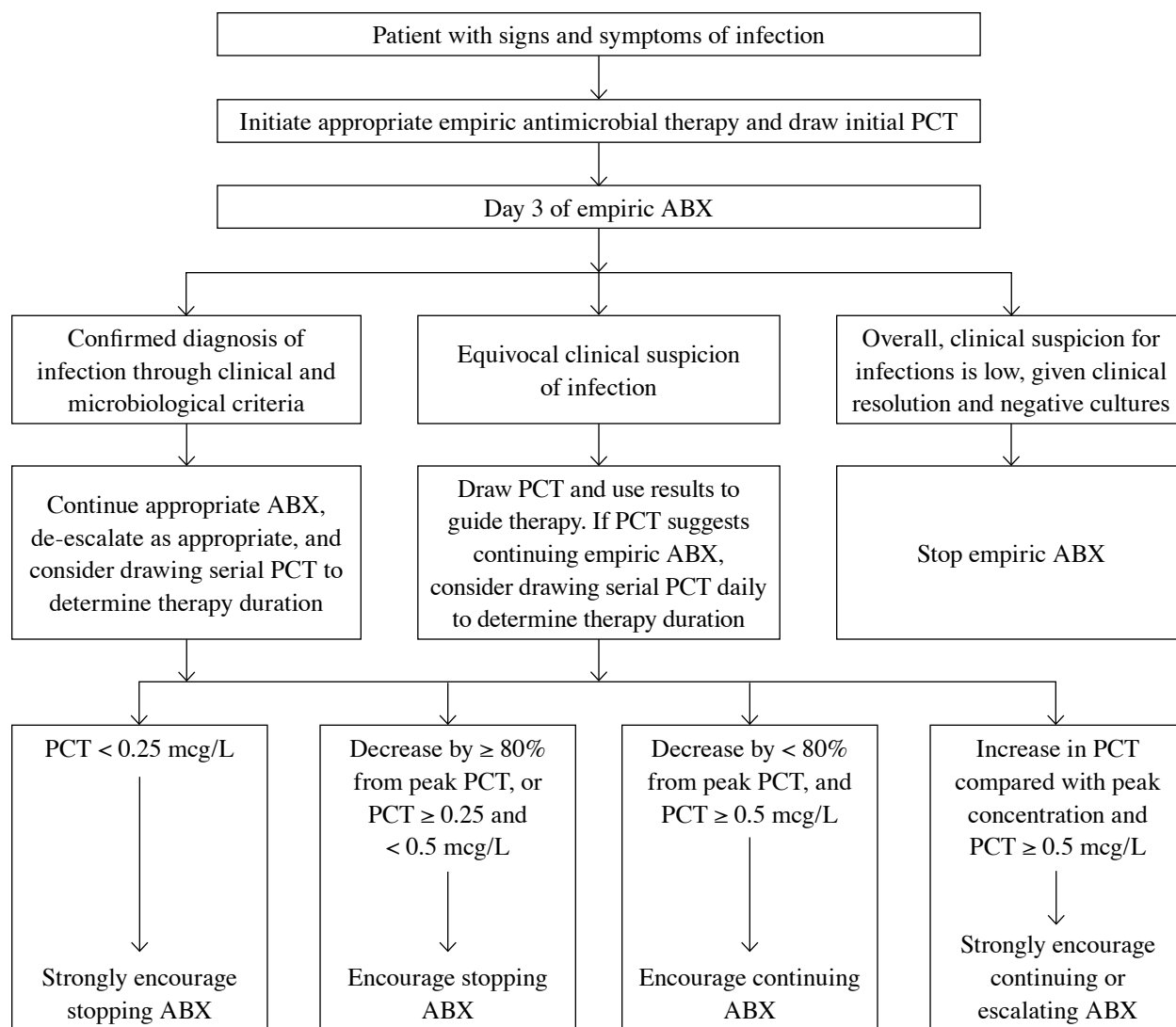


Figure 2. Sample procalcitonin-guided antimicrobial management algorithm.

ABX = antibiotics; PCT = procalcitonin.

Patient Case

4. A 64-year-old woman is admitted to the medical ICU with possible community-acquired pneumonia. The patient is initiated on ceftriaxone and azithromycin. Chest radiography reveals focal infiltrate. On admission, she is dyspneic with a respiratory rate of 33 breaths/minute. Her vital signs and laboratory values are as follows: blood pressure 90/50 mm Hg, heart rate 101 beats/minute, WBC 18×10^3 cells/mm³, and lactate 4.2 mmol/L. A PCT is obtained on admission. The results are available 12 hours after antibiotics are initiated. The PCT result is 0.1 mcg/L. Which is the most appropriate option, given the PCT result?
 - A. Continue all current antibiotics.
 - B. Discontinue all antibiotics.
 - C. Escalate antibiotics to piperacillin/tazobactam.
 - D. Discontinue ceftriaxone only.

V. INTERPRETING SUSCEPTIBILITY REPORTS

- A. Rationale: Identifying microorganisms and antibiotic susceptibilities is integral to the care of critically ill patients with infections. An understanding of the microbiology laboratory methods for pathogen identification and susceptibility testing will further equip critical care pharmacists with the ability to use the most appropriate antimicrobial regimens for the treatment of critical care–associated infections. Standards for antimicrobial identification, sensitivity testing, and determination of MIC breakpoints are determined by the Clinical & Laboratory Standards Institute (CLSI). CLSI is a volunteer-driven standards development organization that promotes the development and use of laboratory consensus standards and guidelines within the health care community.
- B. Methods for Antimicrobial Susceptibility Testing (AST)
1. Disk diffusion (Kirby-Bauer)
 - a. Test agar plates are swabbed with a standardized concentration of the test organisms; paper disks containing a defined antibiotic concentration are then placed on the plates. The diameter of the zone of inhibited growth is inversely proportional to the MIC value.
 - b. Usually reported qualitatively as sensitive, intermediate, or resistant
 2. Dilution methods (i.e., broth dilution, agar dilution)
 - a. Two-fold serial dilutions of antibiotics are prepared (in either broth or agar), which are then inoculated with a standardized concentration of test organisms.
 - b. The MIC is determined.
 - c. Precision of this method is within one 2-fold concentration in either direction.
 - d. Many prefabricated broth microdilution plates are commercially available.
 3. E-test
 - a. A calibrated plastic strip with a range of continuous MIC values (with 15 2-fold dilutions) is placed on an inoculated agar plate. The MIC can be determined by the intersection between the zone of inhibition and the edge of the calibrated strip.
 - b. Complement other systems to determine the MIC for specific antibiotics and test for resistance and for confirmatory testing
 - c. Studies have shown that the reading of the exact MIC on an E-test strip is subject to the user's interpretation and could lead to a one- or two-dilution error in either direction compared with standardized methods.
 4. Automated systems (e.g., Vitek, Microscan, Sensititre, Phoenix)
 - a. Uses computerized algorithms for interpreting MIC values
 - b. Can usually perform AST more quickly than traditional methods
 - c. More than 80% of all clinical microbiology laboratories report using an automated system as their primary method of susceptibility testing.
 - d. May be unable to detect certain resistance mechanisms (i.e., inducible enzymes)
 - e. Standard inoculums of pathogens are used. For infections in which the in vivo inoculum may be higher, certain antimicrobials may have higher MIC values.
 5. Specific confirmatory tests for antimicrobial resistance
 - a. Macrolide-lincosamide-streptogramin resistance
 - i. Strains of *Staphylococcus* spp. can have a transferable resistance mechanism called macrolide-lincosamide-streptogramin, which is inducible by clindamycin and can lead to treatment failure.
 - ii. Inducible resistance is not detected by routine AST.
 - iii. Detected using double-disk diffusion. See Figure 3 for an example of the double-disk diffusion results.
 - b. ESBL

- i. CLSI procedures exist for *K. pneumoniae*, *Klebsiella oxytoca*, *E. coli*, and *Proteus mirabilis*.
- ii. Initial screening with susceptibility testing for ceftazidime, aztreonam, cefotaxime, or ceftriaxone
- iii. Confirmatory testing with broth microdilution, disk diffusion, or E-test strips. See Figure 3 for an example of the ESBL E-test confirmatory results. Presence of ESBL is confirmed if adding clavulanic acid results in three 2-fold dilution decreases in the paired-cephalosporin MIC.
- iv. Beginning in 2010, CLSI adopted lower MIC breakpoints for many cephalosporins for Enterobacteriaceae (see Table 7). The rationale for this change is that the lower MIC may more readily detect the presence of ESBL, hence eliminating the need for the labor-intensive confirmatory tests. Compliance with this new practice is variable among clinical microbiology laboratories. Clinicians should inquire within their local clinical microbiology laboratory regarding whether the new standards have been adopted. If a microbiology laboratory has adopted the new CLSI recommendations for ESBL detection, confirmatory tests are unnecessary.

Table 7. Changes to CLSI Enterobacteriaceae Breakpoints with 2010 Updates

Agent	Pre-2010 CLSI Breakpoints			2010 CLSI Breakpoints		
	S	I	R	S	I	R
Cefazolin	≤ 8	16	≥ 32	≤ 1	2	≥ 4
Cefotaxime	≤ 8	16–32	≥ 64	≤ 1	2	≥ 4
Ceftriaxone	≤ 8	16–32	≥ 64	≤ 1	2	≥ 4
Ceftazidime	≤ 8	16	≥ 32	≤ 4	8	≥ 16
Aztreonam	≤ 8	16	≥ 32	≤ 4	8	≥ 16

- c. AmpC β -Lactamase
 - i. Inhibitor-resistant β -lactamase (e.g., clavulanic acid, tazobactam)
 - ii. Maintains sensitivity with cephamycins (e.g., cefotetan, cefoxitin) and cloxacillin
 - iii. Confirmatory test with E-test containing cephamycin alone or a combination of cephamycin and cloxacillin. If the MIC is decreased by more than three 2-fold dilutions, the presence of AmpC β -lactamase is confirmed.
- d. Carbapenemase
 - i. Metallo- β -lactamase (e.g., New Delhi metallo- β -lactamase [NDM]; Verona integrin-encoded metallo- β -lactamase [VIM]); IMP-type carbapenemase)
 - (a) Hydrolyzes both β -lactam and carbapenem antibiotics, but aztreonam maintains susceptibility. Clinically, about 80% of metallo- β -lactamase-containing pathogens are resistant to aztreonam because of other resistance mechanisms.
 - (b) Zinc-mediated metallo- β -lactamase can be repressed by ethylene-diamine tetraacetic acid (EDTA). Reduction in imipenem MIC by more than three 2-fold dilutions in the presence of EDTA confirms presence of zinc-mediated metallo- β -lactamase.
 - ii. KPC
 - (a) KPC enzyme can produce a slightly higher MIC that may still be in the range considered sensitive. This is in contrast to other carbapenem-resistant mechanisms in *Pseudomonas* and *Acinetobacter*, which generally produce a fully resistant MIC. Hence, a carbapenem MIC of 1 mcg/mL or greater in an Enterobacteriaceae should be evaluated through further confirmatory testing.

- (b) Modified Hodge test should be performed for pathogens with an elevated carbapenem MIC. See Figure 3 for an example of the modified Hodge test result.
 - (1) Plate standard sensitive *E. coli* strain on entire plate.
 - (2) Place meropenem or carbapenem disk in center of test area.
 - (3) Streak test organism in a straight line from edge of carbapenem disk to edge of plate (up to four different organisms can be tested).
 - (4) Positive carbapenemase results from modified Hodge test have a clover leaf-like indentation of the *E. coli* growing along the test organism's streak.
- (c) Starting in 2010, CLSI lowered the susceptibility breakpoints for carbapenem (0.5 mcg/mL and 1.0 mcg/mL or less for ertapenem and other carbapenems, respectively), with the intent of eliminating the need for confirmatory tests.
 - (1) Clinicians should inquire about the practices of their local microbiology laboratory regarding carbapenem susceptibility.
 - (2) Particularly when confirmatory tests are not being performed, and a laboratory continues to use the older MIC breakpoints, a higher clinical suspicion for carbapenemase is warranted.
 - (3) Ertapenem resistance seen on AST is a sensitive marker for the presence of carbapenemase. Before the 2010 reclassification of carbapenem susceptibility breakpoints, there were reports of up to 46% of clinical isolates with genotypic evidence of KPC-producing enzymes being inadvertently labeled as imipenem sensitive.
 - (4) Deleterious outcomes associated with the use of carbapenems in carbapenemase-producing organisms have been reported.

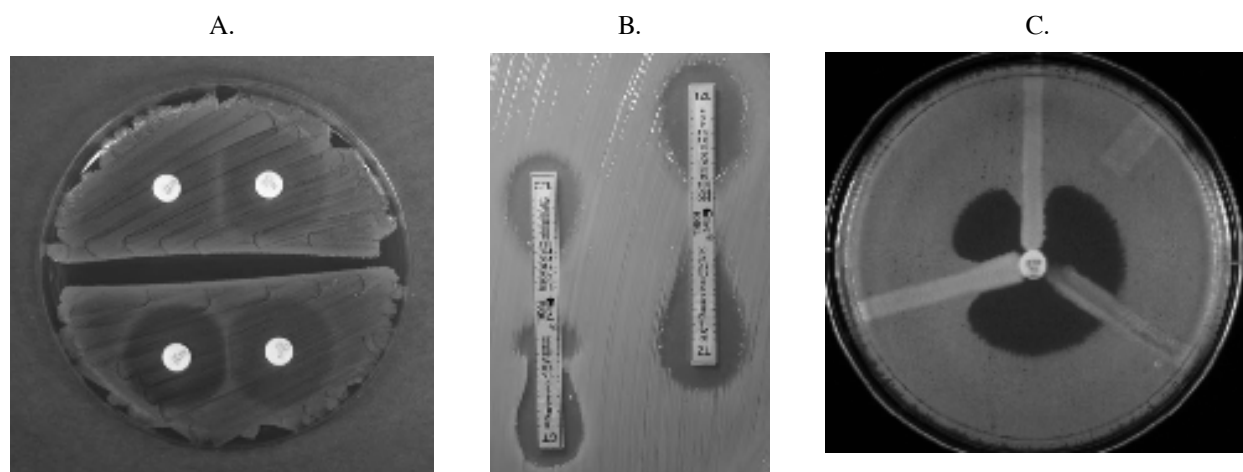


Figure 3. Sample microbiology confirmatory tests for specific resistance mechanisms.

(A) Positive double-disk diffusion test (D-test) shows the induction of clindamycin resistance by erythromycin. This is indicated by a flattening of the zone in the area between the disks where both drugs have diffused.

(B) Confirmatory tests for ESBL with the use of an E-test. The strip on the left contains cefotaxime plus clavulanic acid (CTL) and cefotaxime alone (CT). The strip on the right contains ceftazidime plus clavulanic acid (TZL) and ceftazidime alone (TZ). ESBL confirmation can be determined by the distortion of the cefotaxime eclipse. It could also be confirmed by three or more 2-fold dilution decreases in MIC with the addition of clavulanic acid.

(C) Streaks 1 and 3 represent positive modified Hodge test results, and streak 2 represents a negative result.

Reproduced with permission from: Kuper KM, Boles DM, Mohr JF, et al. Antimicrobial susceptibility testing: a primer for clinicians. *Pharmacotherapy* 2009;29:1326-43.

- C. MIC Breakpoints: Determining the correct MIC breakpoint by the governing standards is a complicated process. CLSI promotes the development of voluntary consensus standards within the medical community. Determining CLSI breakpoints could be based on several conflicting interests, which may include some of the following:
1. Microbiological: MIC that distinguishes wild-type bacteria from those that have acquired additional resistance mechanisms
 2. PK/PD: Derived from human or animal data and modeled to determine the likelihood that standard prescribed doses will meet specified PD criteria for suppressing bacterial growth
 3. Breakpoints that may decrease the need for confirmatory tests, hence decreasing the microbiology laboratory workload. Such an approach, although possibly sensitive for determining the presence of resistance mechanisms, may potentially lead to the compensatory use of broader antimicrobials.
 4. The CLSI breakpoints may be inconsistent with the breakpoints established by the FDA. Automated systems report MIC breakpoints according to FDA approvals. Changes to reporting and labeling require additional clearance from the FDA. Unfortunately, the FDA labeling may not be up to date with the current CLSI recommendations. Hence, despite newer CLSI recommendations, many institutions may still be reporting susceptibility results that are based on their respective FDA labeling breakpoints. These breakpoints may result in pathogens being labeled as sensitive, even though, according to the current CLSI standards, they would be considered resistant.
 5. The exact MIC breakpoints that are used by a local microbiology laboratory can be variable, depending on the laboratory's adaptation of new standards. In addition, there are significant variations in the FDA-approved breakpoints used by automated AST methods and updated CLSI guidelines. Once again, this highlights the importance of a clinician's understanding of the exact methods and breakpoints that are used in his or her institution.
- D. Minimum Information That Critical Care Pharmacists Should Recognize About Their Local Microbiology Laboratory Practices
1. Routine methods for AST
 2. Availability of rapid diagnostic tests for speciation or resistance gene identification
 3. If additional tests are available (E-test, genotyping, etc.) and how to go about requesting additional information
 4. Are confirmatory tests for resistance mechanisms routinely done (e.g., double-disk diffusion for macrolide-lincosamide-streptogramin-inducible resistance, ESBL and KPC confirmatory tests)?
 5. What is the usual procedure for censoring the AST results?
 - a. Does the AST result try to guide clinical decision (i.e., if pathogen were sensitive to oxacillin, would vancomycin results be censored)?
 - b. If certain resistance mechanisms are detected, would the laboratory automatically update susceptibility results (i.e., if ESBL were detected, would β -lactam/ β -lactamase combination antibiotics automatically be changed to resistant)?
 - c. Are any antibiotics part of the standard panel but routinely hidden from clinical reports?
 - d. Most microbiology laboratories would retain all the information, even if parts of the results had been censored. Critical care pharmacists should consider contacting the microbiology laboratories to see whether additional information regarding the pathogen is available.
 6. When an MIC is reported, is only the MIC breakpoint reported (i.e., MIC 2 mcg/mL or less), or is the actual MIC reported (i.e., 0.25 mcg/mL)?
 7. Are the breakpoints reported consistent with the updated CLSI recommendations?

E. Clinical Application of Interpreting AST

1. The ideal application of AST interpretation and clinical therapeutics may include the following:
 - a. Knowledge of the individual pathogen and the corresponding MIC breakpoints for each of the tested antibiotics
 - b. Potential reasoning behind each of the clinical breakpoint designations (i.e., wild-type selection, PK/PD breakpoints assessment, screening for resistance)
 - c. Accurate comprehension of the local AST methods used and potential limitations of the MIC reported
 - d. Understanding of the tested antimicrobial's PD parameters, which conveys the highest likelihood for eradication of the microorganism
 - e. Selecting the most appropriate antibiotic according to an assessment of the following:
 - i. What genotypic resistance mechanisms may be suggested by the phenotypic representation of the AST?
 - ii. How may the underlying resistance mechanisms affect the choice of antimicrobial therapy?
 - iii. The PK characteristics of the medication and patient characteristics that may affect the antimicrobial's PK
 - iv. The likelihood that the considered antimicrobial agent will reach its PD targets for optimal therapy at the local site of infection
 - v. Selecting the antimicrobial according to a balance of antimicrobial stewardship principles, adverse effects profile, allergies, and cost
2. AST interpretation and selection of the optimal antibiotic is a small part of determining a patient's clinical course. Studies have mainly shown that the therapeutic outcome in infections when treated with antibiotics deemed susceptible by AST is around 90%, whereas the response to antibiotics deemed resistant is about 60%. This could partly explain why many clinical studies evaluating the optimization of PK/PD parameters have equivocal findings. However, although clinical studies have conflicting results regarding the utility of AST interpretation and optimization of PK/PD, the biologic plausibility of this approach will probably allow the best opportunity of recovery for each patient.
3. When an antimicrobial must be chosen despite its having a higher-than-ideal MIC, the penetration into the site of infection is questionable, or the correlation of PK and PD target attainment is not available, additional interventions may be required. Optimization of therapy should be tried through one or more of the following: using a higher dose, using administration strategies that may optimize PK/PD (i.e., extended- or continuous-infusion β -lactams), or combination therapy.

VI. MECHANISMS OF ANTIBACTERIAL RESISTANCE AND TREATMENT OF MULTIDRUG-RESISTANT PATHOGENS

- A. Epidemiology and Clinical Significance: The World Health Organization has identified antimicrobial resistance as one of the three greatest threats to human health.
 1. The National Healthcare Safety Network for the CDC reports recent resistance rates among commonly encountered pathogens. More than 2000 U.S. hospitals participate in this national surveillance program, with more than 80,000 pathogens reported and about 70% of the reporting from critical care sites. See Table 8 for selected resistance rates in different hospital-acquired infections.
 2. Resistance rates continue to be high, with trends toward an increase in certain pathogens compared with the reports from previous years.

3. Resistant pathogens consistently correlate with worse clinical outcomes, which may partly be explained by the higher likelihood of empiric treatment with a resistant antibiotic.
4. The antibiotic pipeline has slowed down considerably, with consistent decreases in FDA approvals of antimicrobial agents during the past 3 decades. The combination of prevailing resistance, including the emergence of pan-resistant pathogens, with the lack of new antimicrobial agents presents a potential global health problem.
5. An understanding of resistance mechanisms would assist the ICU clinician in effectively treating current resistant pathogens while incorporating antimicrobial stewardship principles to prevent further resistance. See Table 9 for common mechanisms of resistance.

Table 8. Recent Resistance Rates in Hospital-Acquired Infection (2009–2010)

Pathogen (total n)	CLABSI % Resistance	CAUTI % Resistance	VAP % Resistance	SSI % Resistance
Gram-negative Bacteria				
<i>E. coli</i> (9351)				
Third-generation cephalosporins	19.0	12.3	16.3	10.9
Carbapenem	1.9	2.3	3.5	2.0
Fluoroquinolone	41.8	31.2	35.2	25.3
Multidrug resistant ^a	3.7	2.0	3.3	1.6
<i>K. pneumoniae/oxytoca</i> (6470)				
Third-generation cephalosporins	28.8	26.9	23.8	13.2
Carbapenem	12.8	12.5	13.4	7.9
Multidrug resistant ^a	16.8	16.1	13.4	6.8
<i>P. aeruginosa</i> (6111)				
Aminoglycosides	10.0	10.9	11.3	6.0
Ceftazidime or cefepime	26.1	25.2	28.4	10.2
Fluoroquinolones	30.5	33.5	32.7	16.9
Carbapenem	26.1	21.3	30.2	11.0
Piperacillin/tazobactam	17.4	16.6	19.7	6.8
Multidrug resistant ^a	15.4	14.0	17.7	53.3
<i>Enterobacter</i> spp.(3821)				
Third-generation cephalosporins	37.4	38.5	30.1	27.7
Carbapenem	4.0	4.6	3.6	2.4
Multidrug resistant ^a	3.7	4.8	1.4	1.7
<i>A. baumannii</i> (1490)				
Carbapenem	62.6	74.2	61.2	37.3
Multidrug resistant	67.6	77.6	63.4	43.9

Table 8. Recent Resistance Rates in Hospital-Acquired Infection (2009–2010) (*continued*)

Pathogen (total n)	CLABSI % Resistance	CAUTI % Resistance	VAP % Resistance	SSI % Resistance
Gram-positive Bacteria				
<i>S. aureus</i> (12,635) Oxacillin	54.6	58.7	48.4	43.7
<i>E. faecalis</i> (5484) Vancomycin	82.6	82.5	82.6	62.3
<i>E. faecium</i> (3314) Vancomycin	9.5	8.4	9.8	6.2

**Multidrug resistant* is defined as being either intermediate or resistant to at least one drug in three of the following five classes: third- and fourth-generation cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, and piperacillin and/or piperacillin/tazobactam.

CAUTI = catheter-associated urinary tract infection; CLABSI = central line-associated bloodstream infection; SSI = surgical site infection; VAP = ventilator-associated pneumonia.

Table 9. Common Resistance Mechanisms

Antibacterial Agent	Mechanism of Resistance
β -Lactams	β -Lactamases (AmpC, ESBL, KPC) Reduced permeability Altered penicillin binding proteins Increased efflux
Fluoroquinolones	Altered DNA gyrase and topoisomerase Increased efflux Decreased protein targets
Macrolides	Increased efflux Methylating enzymes
Aminoglycosides	Aminoglycoside-modifying enzymes Increased efflux Modification of target proteins
Glycopeptides	Altered target Decreased permeability
Tetracyclines	Increased efflux Protection of target proteins
Trimethoprim	Increased efflux Altered dehydrocholate reductase
Rifamycin	Altered RNA polymerase

- B. Mechanisms of Resistance (bacteria often possess several mechanisms)
1. Decreased permeability (i.e., porin loss, thickened cell wall)
 2. Increased efflux (i.e., macrolide efflux pump)
 3. Target modification (i.e., alteration in penicillin-binding proteins)
 4. Hydrolysis (i.e., β -lactamases, aminoglycoside-modifying enzymes)

C. Factors Associated with Resistance Acquisition

1. Crowding of patients with high levels of disease acuity and/or antimicrobial use
2. Prolonged hospital LOS
3. Colonization pressure: Proportions of people colonized with resistant bacteria. Combated by strict compliance with infection control procedures to prevent colonization, adequate nurse staffing ratios, and hand hygiene.
4. Use of invasive devices (endotracheal tubes, intravascular catheters, and urinary catheters)
5. Previous use of antibiotics

D. Clinical Approach to Common Pathogen Resistance Seen in Critically Ill Patients**1. ESBL**

- a. Confers resistance to third-generation cephalosporins and aztreonam
- b. Found primarily in *E. coli* and *K. pneumoniae* spp. but can also be seen in other Enterobacteriaceae
- c. Carbapenems should be considered the drug of choice in severe infections.
- d. Non- β -lactams could be used if they showed sensitivity on AST; however, because ESBLs are usually plasmid mediated, there are often other acquired resistance mechanisms. The rates of cross-resistance to other classes of antibiotics are 55%–100%.
- e. β -lactam/ β -lactamase inhibitors and cefepime often have in vitro activity, though clinical failures have been reported.
 - i. Several early reports showed that carbapenems, compared with non-carbapenems, result in improvements in clinical and microbiological outcomes. These studies were usually observational and contained relatively few patients. This led to several expert recommendations to use carbapenems exclusively for the treatment of ESBL infections. Furthermore, although never endorsed by CLSI, many microbiology laboratories decided to censor all β -lactam/ β -lactamase inhibitor AST results to show resistance if ESBL were detected. Hence, controlled studies of β -lactam/ β -lactamase inhibitors or cefepime versus carbapenem were never performed.
 - ii. A recent study performed a post hoc analysis of six prospective cohort studies and compared the use of β -lactam/ β -lactamase inhibitors with carbapenems for the empiric and definitive treatment of ESBL-producing *E. coli* bacteremia. Neither univariate nor multivariate analysis showed that β -lactam/ β -lactamase inhibitor use was associated with worsening mortality or hospital LOS. Two important caveats came from this study. Of note, the sickest patients in this study were treated with carbapenems. In addition, in most patients, either the urinary or the biliary tract was the source of the bacteremia. Finally, the study routinely used the maximum dose of piperacillin/tazobactam (4.5 g every 6 hours). Taken together, this would suggest that using high-dose β -lactam/ β -lactamase inhibitors to treat ESBL should be reserved for relatively stable patients, with a source of infection with relatively low inoculums.
 - iii. A subsequent study showed that the piperacillin/tazobactam MIC was significantly correlated with outcomes in patients with ESBL bacteremia. All patients with a urinary source of bacteremia survived regardless of the piperacillin/tazobactam MIC as long as it was within the sensitive breakpoint. However, in non-urinary tract sources of bacteremia, an MIC greater than 2 mcg/mL was associated with worse outcomes.
 - iv. Data are conflicting regarding the use of cefepime for treating ESBL infections. Some studies show worse outcomes, whereas others show no difference compared with carbapenems. This may partly be explained by the cefepime MIC distribution. Traditionally (before 2014), the sensitive breakpoint for cefepime for Enterobacteriaceae was 8 mcg/mL or less. However, in 2014, CLSI recommended decreasing the sensitive cefepime MIC breakpoint to 2 mcg/mL, in addition to a new category for sensitive-dose dependent, where maximal doses of cefepime are recommended for MICs of 4 and 8 mcg/mL. Hence, for many years, cefepime may have been used in ESBL infections when the MIC was 4–8 mcg/mL, but doses were not optimized.

- v. Of interest, a recent investigation correlated ceftazidime MIC to ESBL Enterobacteriaceae with mortality, where a ceftazidime MIC of 1 mcg/mL or less was associated with significantly lower mortality compared with other MIC values. Together, given the conflicting clinical results, it is difficult to endorse the use of ceftazidime for the treatment of ESBL infections. However, in a stable patient with an ESBL infection having a ceftazidime MIC of 1 mcg/mL or less, ceftazidime may be considered for consolidative therapy to minimize carbapenem use.
2. AmpC β -lactamases
- a. Confer resistance to penicillins and narrow-spectrum cephalosporins
 - b. β -Lactamase inhibitor resistant; hence, tazobactam and clavulanic acid would not provide additional coverage
 - c. Innate low-level production in many gram-negative bacteria (i.e., *Enterobacter*, *Citrobacter*, *Serratia*, *Morganella*, *Providencia*, and *Pseudomonas*). This low-level production leads to resistance against penicillin, ampicillin, and first-generation cephalosporins.
 - d. Genetic mutation leading to sustained high-level production is possible (derepressed mutants).
 - i. Theoretically, treatment with third-generation cephalosporins or broad-spectrum cephalosporins for non-derepressed mutants may select species with the mutation. The actual incidence of breakthrough infections is unknown with derepressed mutants when bacteria with innate AmpC β -lactamase production are treated with third-generation cephalosporins or extended-spectrum penicillins. However, it is believed to be low.
 - ii. Several epidemiologic studies have linked the use of third-generation cephalosporins with the increase in pathogenic species of AmpC hyperproducing Enterobacteriaceae.
 - iii. Derepression confers resistance to third-generation cephalosporins and broad-spectrum penicillins (piperacillin, ticarcillin).
 - iv. Commonly occurs in *E. cloacae* and *Citrobacter freundii*
 - v. Cefepime generally retains activity against derepressed mutants.
 - vi. Carbapenem and cefepime should be considered the drugs of choice in severe infections.
 - vii. Because derepression results from the mutation of a chromosomal-mediated β -lactamase, not from plasmids, many hyperproducers of AmpC retain activity against other non β -lactam antimicrobials (e.g., fluoroquinolones, aminoglycosides).

Patient Case

5. A 74-year-old man is admitted to the surgical ICU after elective hip replacement surgery. The patient, who has a history of chronic pulmonary obstructive disease, cannot be weaned off the ventilator after surgery. During the patient's course, he develops signs and symptoms of infection. His vital signs and laboratory values are as follows: blood pressure 94/55 mm Hg, heart rate 114 beats/minute, temperature 101.9°F (38.8°C), WBC 18×10^3 cells/mm³, and lactate 3.2 mmol/L. The patient is empirically initiated on piperacillin/tazobactam and vancomycin and given 2 L of crystalloid fluids; pan cultures are sent. Urinalysis reveals pyuria, positive leukocyte esterases, and nitrites. Blood and sputum cultures are negative, but urine culture shows *E. coli*. The patient's urinary catheter is removed, and vancomycin is discontinued. On day 3 of therapy, antibiotic susceptibility results are available. The patient's *E. coli* is resistant to third-generation cephalosporins with laboratory confirmation of the presence of ESBL. The laboratory reports the following antimicrobials and corresponding MIC values: piperacillin/tazobactam less than 2 mcg/mL – S; cefepime 4 mcg/mL – S; imipenem 0.5 mcg/mL – S; and ciprofloxacin 1 mcg/mL – S. The patient's vital signs and laboratory values are as follows: blood pressure 110/70 mm Hg, heart rate 98 beats/minute, respiratory rate 30 breaths/minute, temperature 98.7°F (37.1°C), and WBC 9×10^3 cells/mm³. Which is the most appropriate antibiotic option?
- Change piperacillin/tazobactam to imipenem.
 - Continue piperacillin/tazobactam alone.
 - Change piperacillin/tazobactam to cefepime.
 - Add ciprofloxacin to piperacillin/tazobactam.

3. Carbapenemase

- Seen in *Acinetobacter*, *Pseudomonas*, and Enterobacteriaceae
- The global spread of carbapenem resistance has become an epidemic.
- The CDC recently reported that carbapenem-resistant Enterobacteriaceae (CRE) is at an urgent hazard level, where high consequence and probability for widespread public health concerns exist.
- Confers resistance to most β -lactams, including carbapenems, cephalosporins, monobactam, and broad-spectrum penicillins
- Treatment options
 - Tigecycline:
 - Glycylcycline antibiotic, which is structurally similar to tetracyclines
 - Mechanism of action: Inhibition of 30s ribosomal subunit
 - Spectrum of activity:
 - Gram-positive bacteria: *Enterococcus* (including vancomycin-resistant enterococci), *Listeria*, *Staphylococcus* (including MRSA/CoNS), *Streptococcus*
 - Most gram-negative bacteria, including *Acinetobacter*, ESBL-producing Enterobacteriaceae, derepressed AmpC Enterobacteriaceae, CRE, and *Stenotrophomonas*
 - Anaerobes, including *Bacteroides* and *Clostridium*
 - Atypicals
 - Does not cover *Pseudomonas*, *Providencia*, or *Proteus*
 - PK
 - Wide volume of distribution: 7–10 L/kg
 - The intracellular distribution of tigecycline results in a decreased serum/tissue concentration ratio. This has led many clinicians to state that tigecycline is not the ideal drug for bloodstream infections. However, tigecycline has not been evaluated exclusively for the treatment of bloodstream infections. In a pooled analysis of eight

studies, patients with secondary bacteremia treated with tigecycline were compared with patients treated with other antibiotics. Overall, no significant differences in outcomes were seen. Despite these results, clinicians should exert caution with the use of tigecycline for bacteremia and should reserve tigecycline for pathogens when no other antibiotics are viable options.

- (3) Primarily biliary elimination
 - (4) Urinary elimination is 8%–11%. The low urinary elimination may limit tigecycline's role in treating UTIs. The use of tigecycline for treating multidrug-resistant UTIs has been reported only in case reports, with most reports showing treatment success. However, a recent evaluation of tigecycline for the treatment of KPC bacteriuria indicated a correlation with the subsequent development of tigecycline resistance. Without further data, tigecycline should not routinely be used for UTIs when other treatment options are available.
 - (5) Poor penetration into lung epithelial lining fluid, which is in contrast to high penetration into lung alveolar cells. This characteristic may partly explain the findings of a study evaluating tigecycline compared with imipenem for the treatment of hospital-acquired pneumonia. This study showed that tigecycline had a lower treatment success rate than imipenem. The difference in treatment success was mainly attributable to the significant differences in patients with ventilator-associated pneumonia. There was also a trend toward increased mortality in the subgroup of patients with ventilator-associated pneumonia.
 - (e) The FDA issued a safety warning in 2010 indicating a possible increased mortality risk associated with the use of the tigecycline compared with other drugs used to treat a variety of other serious infections. This was compiled using several phase III studies in which tigecycline had been proved noninferior to other standard treatments. Subsequently, several other meta-analyses were published with conflicting results regarding tigecycline's increased mortality risk.
 - (f) Given tigecycline's possible shortcomings, it seems prudent to avoid the routine use of tigecycline in infections when other treatment options are available. However, tigecycline may be one of the few remaining antibiotic options for treating carbapenem-resistant pathogens. When tigecycline must be used because of limited treatment options, clinicians should consider administering combination therapy.
 - (g) Resistance to tigecycline has been reported. Clinicians should seek confirmation from their microbiology laboratory regarding tigecycline sensitivity. Of note, CLSI currently has no recommendation for MIC breakpoint for tigecycline against *Acinetobacter* spp. The MIC breakpoint for sensitivity against Enterobacteriaceae is 2 mcg/mL or less.
- ii. Polymyxins:
- (a) Colistin (polymyxin E)
 - (1) Mechanism of action: A cationic cyclic decapeptide that functions by displacing calcium and magnesium from the outer cell membrane, hence changing the permeability of the cell membrane to allow insertion of the molecule into the cell membrane. Once the molecule is inserted into the cell membrane, it disrupts the cell membrane integrity and subsequently leads to cell death.
 - (2) Spectrum of activity: Covers only gram-negative bacteria, including CRE. Does not cover *Proteus*, *Providencia*, *Burkholderia*, *Serratia*, or *Stenotrophomonas*
 - (3) First used in the United States in the 1960s but fell out of favor because of reports of nephrotoxicity and neurotoxicity

- (4) Around 2000, with the emergence of CRE, colistin use was reconsidered, given the lack of treatment options.
- (5) Dosing challenges
 - (A) Different products provide different dosing recommendations.
 - (B) Colomycin injection is the brand primarily used in Europe. Dosed in international units (IU).
 - (C) Coly-Mycin is the brand primarily used in the United States. Dosing in colistin-based activity
 - (D) 3 million IU of colistin is equal to about 100 mg of colistin-based activity.
- (6) PK/PD
 - (A) All colistin products, regardless of the dosing units, are administered as colistimethate, which is a prodrug. Colistimethate is hydrolyzed to the active drug colistin.
 - (B) Colistimethate is excreted through renal clearance, whereas the active drug colistin is cleared by nonrenal pathways. Hence, renal dysfunction leads to a higher portion of colistimethate being present for hydrolysis into colistin, thus increasing the final active drug concentration.
 - (C) PD parameter for maximal activity is area under the curve/MIC ratio.
 - (D) In the 1960s, the dosing recommendations and PK/PD parameters were largely unknown because the methods for evaluations were drastically different from the current standards.
 - (E) Recent PK/PD evaluations show that traditional dosing methods are probably insufficient to reach adequate serum concentrations to maximize PD target attainment.
 - (F) Several studies have reported that a higher colistin dose is associated with significant improvements in clinical outcomes.
 - (G) The exact dosing regimen to be used has not been elucidated. However, one group of investigators, using PK modeling, proposed the following dosing recommendations:
 - All dosing with ideal body weight
 - All CrCl values calculated by the Jelliffe equation
 - Usual colistin concentration target: 2.5 mcg/mL
 - Loading dose: Colistin target x 2.0 x ideal body weight
 - Maintenance dose:
 - Not on renal replacement therapy: Daily dose = colistin target x (1.5 x CrCl + 30) divided every 8–12 hours
 - On intermittent dialysis: Daily dose of colistin on non-dialysis days = colistin target x 30
 - On continuous dialysis: Daily dose = colistin target x 192 divided every 8–12 hours
 - (H) Several ongoing investigations are evaluating the effects of high-dose colistin regimens and the utility of using a loading dose.
 - One study from South America is recruiting patients to evaluate the utility of a 200-mg loading dose.
 - One study reported a 300-mg loading dose regimen, followed by 150 mg every 12 hours. This study was non-comparative, but it reported high rates of clinical success.

- (7) Because the PK/PD of colistin is unclear and little is known regarding the optimal dosing regimen, colistin should be reserved for infections in which other treatment options are not available. In such cases, it may be prudent to administer combination therapy. Furthermore, many in vitro studies have shown synergy between colistin and other antimicrobials.
- (8) Resistance to colistin has been reported. In vitro studies also show that colistin resistance develops quickly, which may be another rationale for providing combination therapy. Clinicians should verify colistin susceptibility with their local microbiology laboratory.
 - (A) Routine monitoring of colistin concentrations is currently infeasible.
 - (B) According to PK data, an MIC of 2 mcg/mL or less should be considered sensitive.
- (b) Adverse reaction: Nephrotoxicity
 - (1) Nephrotoxicity
 - (A) 0%–45% reported in recent literature, depending on the definitions used for renal dysfunction
 - (B) In general, seems to be dose dependent
 - (C) Usually reversible, with few cases leading to a prolonged need for renal replacement therapy
 - (2) Neurotoxicity
 - (A) Ranging from paresthesia to apnea
 - (B) Incidence of 8%–27% reported in historical studies
 - (C) Mentioned only in case reports in the current era of colistin use
- (c) Polymyxin B:
 - (1) Mechanism of action, spectrum of activity, and adverse reactions similar to those of colistin
 - (2) Available in the United States but not in Europe and Australia
 - (A) PK/PD
 - (B) Administered as an active drug
 - (C) PD targets similar to those of colistin
 - Similar unknowns regarding best dosing regimen to achieve PD parameters
 - Manufacturer-recommended dosing: 1.5–2.5 mg/kg/day divided every 12 hours. Recommends renal dose adjustment, but recent studies suggest minimal renal clearance.
- iii. Ceftazidime/avibactam
 - (a) Avibactam is a new β -lactamase inhibitor recently approved by the FDA.
 - (b) Spectrum of activity: Broad gram-negative activity, including multidrug-resistant *Pseudomonas* and Enterobacteriaceae. Adding avibactam allows coverage against KPC-producing bacteria, together with coverage against other β -lactamases (OXA, CTX-M, AmpC). Minimal coverage against *Acinetobacter* spp., gram-positive, and anaerobes.
 - (c) FDA approved for the treatment of complicated intra-abdominal infection and complex UTIs. However, most clinicians will reserve its coverage for difficult-to-treat pathogens with minimal coverage options, such as KPC-producing Enterobacteriaceae.
 - (d) An in vitro study that included 120 KPC-producing pathogens showed good activity with ceftazidime/avibactam.
 - (e) No major adverse effects were seen with ceftazidime/avibactam in phase II and phase III studies.
 - (f) Currently, the average wholesale price for ceftazidime/avibactam is about \$900 per day with normal dosing.

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- iv. Combination therapy
 - (a) Several retrospective studies suggested that the use of combination therapy is warranted for the treatment of CRE, particularly a regimen involving colistin, tigecycline, and a carbapenem. Interpreting these studies is difficult. Many were noninterventional, hence leading to the evaluation of many treatment regimens. The increased ratio of the number of treatment regimens to the number of patients substantially increases the risk of spurious findings. If no optimal therapy exists for a patient, combination therapy may be considered. These therapies include scenarios in which the carbapenem MIC may be slightly elevated or in which therapies with suboptimal PK/PD (i.e., colistin and tigecycline) are used.
 - (b) A recent retrospective study that evaluated the role of combination therapy for carbapenem-resistant gram-negative pathogens showed that combination therapy with several agents, all of which had in vitro sensitivity, led to improvements in outcomes. In contrast, combination therapy with several agents, not all of which had in vitro sensitivity, did not lead to improvements.
 - (c) Several case reports recommend considering combining ertapenem with another carbapenem for the treatment of carbapenem-resistant pathogens. This approach takes advantage of the increased affinity for ertapenem seen in vitro with carbapenemases. Hence, administering ertapenem as a sacrificial carbapenem may allow a different carbapenem to exert its effects. However, this practice requires further testing; hence, it cannot currently be recommended.
 - 4. Multidrug-resistant *Pseudomonas*
 - a. Resistance mechanisms seen with *Pseudomonas aeruginosa* are unpredictable. The presence of several mechanisms, including β -lactamases, porinloss, efflux pump, and alteration of target proteins, complicates treatment options.
 - b. Clinical approach usually entails empiric coverage with a β -lactam, which has the best local in vitro activity against *Pseudomonas*, with or without a second antipseudomonal agent. Therapy could be de-escalated to a monotherapy with the narrowest spectrum on availability of AST results.
 - c. Ceftolozane/tazobactam is a novel β -lactam/ β -lactamase inhibitor antimicrobial with enhanced activity against *P. aeruginosa*.
 - i. Ceftolozane is a novel third-generation cephalosporin.
 - ii. Spectrum of activity: Gram-negative organisms, including *P. aeruginosa*. Activity includes coverage against ESBL and AmpC β -lactamase-producing organisms. Limited gram-positive and anaerobic coverage. Among multidrug-resistant and extended drug-resistant *Pseudomonas*, ceftolozane/tazobactam retains good activity, with its MIC of 90 mcg/mL still below the MIC breakpoint for resistant, as determined by the FDA.
 - iii. FDA approved for the treatment of complicated intra-abdominal infection and complicated UTI. However, clinically, its coverage will most likely be reserved for resistant pseudomonal infections.
 - 5. MRSA
 - a. MRSA is a significant cause of both community- and hospital-acquired infection.
 - b. Skin and soft tissue infections
 - i. Community-acquired MRSA often presents as a skin and soft tissue infection.
 - ii. Cutaneous infections and abscesses are best treated with adequate drainage.
 - iii. Antibiotics are usually not necessary unless the patient does not respond to drainage, has extensive disease, or has signs and symptoms of systemic infection.
 - iv. Antibiotic treatment choices for mild community-acquired MRSA cutaneous and skin infections include trimethoprim/sulfamethoxazole, clindamycin, and tetracycline.
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- c. MRSA bacteremia and endocarditis
 - i. Can be treated with either vancomycin or daptomycin
 - ii. In a study of patients with right-sided endocarditis, daptomycin was noninferior to vancomycin. Of interest, treatment response was poor with both therapies, with only about 40% in each group meeting that outcome. Daptomycin was dosed at 6 mg/kg in this study.
 - iii. Some experts recommend giving higher daptomycin doses (8–10 mg/kg) to optimize the PD target attainment for daptomycin. However, this approach requires further investigation. Daptomycin resistance in *S. aureus* has been reported. A correlation appears to exist between intermediate sensitivity to vancomycin, thought to be caused by a thickened cell wall—limiting penetration, and decreased susceptibility to daptomycin. Currently, the daptomycin MIC for MRSA is 1 mcg/mL or less.
 - iv. Several investigations have also evaluated daptomycin compared with vancomycin for MRSA bacteremia when the vancomycin MIC was greater than 1 mcg/mL. Although these investigations showed outcome benefit associated with daptomycin use, the studies have severe limitations, which may limit their applicability.
 - (a) Retrospective analyses
 - (b) Daptomycin was usually used as definitive therapy after an initial course of vancomycin.
 - (c) Daptomycin use in one study was associated with a significantly higher rate of infectious diseases consultation, which may have other treatment implications.
 - (d) Given study limitations, the routine use of daptomycin for MRSA infections when the vancomycin MIC is greater than 1 mcg/mL cannot be recommended.
 - (e) The 2011 IDSA guidelines for the treatment of MRSA state that the treatment of isolates with a vancomycin MIC of 2 mcg/mL or less should be determined by the patient's response to vancomycin, independent of the MIC.
- d. MRSA pneumonia. Community-acquired MRSA pneumonia can be treated with either vancomycin or linezolid. Clindamycin can be considered if the strain is susceptible.
 - i. Community-acquired MRSA infections may be associated with the presence of Panton-Valentine leukocidin, which is a two-component staphylococcal membrane toxin that targets leukocytes. This toxin has been linked with severe infections, necrotizing pneumonia, and abscess formation. Theoretically, clindamycin and linezolid, being ribosomal subunit and protein synthesis inhibitors, may attenuate the amount of toxin production.
 - ii. A recent randomized controlled study included patients with hospital-acquired pneumonia, health care-associated pneumonia, and ventilator-associated pneumonia who have a baseline respiratory culture positive for MRSA.
 - (a) Vancomycin was dosed by weight and adjusted locally according to trough levels.
 - (b) This was a noninferiority study with nested superiority criteria where the primary end point was clinical response at the end of the study.
 - (c) Clinical response was defined as resolution of signs of pneumonia with no further need for other antibiotics.
 - (d) Study met both the noninferiority and the superiority criteria with respect to clinical response and microbiological clearance.
 - (e) Study may have been confounded by less than 50% of patients reaching vancomycin target concentrations by day 3 and the vancomycin patients having a slightly higher rate of baseline bacteremia.
 - (f) No difference in mortality was seen.
 - (g) Many clinicians interpret the results from this study as suggesting that either vancomycin or linezolid can be considered for the treatment of MRSA pneumonia.

- e. Novel agents for the treatment of MRSA
 - i. Dalbavancin and oritavancin recently received FDA approval for the treatment of skin and soft tissue infections.
 - (a) Antimicrobial class: Lipoglycopeptide
 - (b) Spectrum of activity: Gram-positive pathogens including MRSA, vancomycin-resistant enterococci, vancomycin-resistant staphylococci, and drug-resistant *S. pneumoniae*
 - (c) PK and dosing: High protein binding and long half-life allow for extended-interval dosing.
 - (1) Dalbavancin is administered as a 1000-mg dose, followed by 500 mg 1 week later. In patients with a CrCl less than 30 mL/minute/1.73 m², the dose is reduced to 750 mg once, followed by 375 mg 1 week later. No dosage adjustments are needed if patients are on scheduled intermittent hemodialysis.
 - (2) Oritavancin was evaluated as a 1200-mg one-time dose. No dosage adjustments are needed for patients with mild to moderate renal dysfunction; however, it has not been evaluated in patients on scheduled intermittent dialysis.
 - (d) Studies
 - (1) In a noninferiority study, once-weekly dalbavancin was noninferior to twice-daily vancomycin followed by oral linezolid for the treatment of skin and soft tissue infections. In addition, fewer adverse drug effects occurred in the dalbavancin group.
 - (2) In a noninferiority study, an oritavancin one-time dose was found to be noninferior to twice-daily vancomycin for the treatment of skin and soft tissue infections. Similar rates of adverse effects were seen.
 - (3) Both studies were well designed, and each conformed to the FDA guidelines for the conduct of a noninferiority study for skin and soft tissue infections. However, long-acting antimicrobials pose additional challenges in hospitalized patients, including ensuring appropriate physician follow-up, reimbursements for inpatient administration, and ways to handle adverse drug reactions.
 - (e) Application. Place in therapy among critically ill patients is limited. May be suitable for critically ill patients transitioning to a long-term acute care facility.
 - ii. Tedizolid recently received FDA approval for the treatment of bacterial skin and skin structure infection.
 - (a) Antimicrobial class: Oxazolidinone
 - (b) Spectrum of activity: Gram-positive pathogens including MRSA, vancomycin-resistant enterococci, vancomycin-resistant staphylococci, drug-resistant *S. pneumoniae*, and linezolid-resistant gram-positive pathogens
 - (c) PK and dosing
 - (1) Bioavailability 91% – Can be administered as a parenteral solution or oral tablets
 - (2) Half-life: 12 hours
 - (3) Dosing: 200 mg once daily
 - (d) Studies: Tedizolid once daily for 6 days was compared with linezolid twice daily for 10 days for the treatment of acute bacterial skin and skin structure infection and was found to be noninferior.
 - (e) Application: Place in therapy among critically ill patients is limited. Studies are under way for the use of tedizolid in the treatment of hospital-acquired pneumonia.
 - iii. Ceftaroline
 - (a) Antimicrobial class: Fifth-generation cephalosporin
 - (b) Spectrum of activity: Enterobacteriaceae (similar to third-generation cephalosporins) and gram-positive pathogens, including MRSA, drug-resistant *S. pneumoniae*, and vancomycin-intermediate and vancomycin-resistant staphylococci

- (c) PK and dosing
 - (1) Activity against MRSA mediated through enhanced affinity to penicillin-binding-protein 2a
 - (2) Half-life: 2.7 hours
 - (3) Excretion: 88% urine
 - (4) Dosing:
 - (A) 600 mg intravenously every 12 hours is the FDA label-approved dosing. Reports of using 600 mg intravenously every 8 hours for severe infections
 - (B) Adjustments necessary for patients with renal impairment
- (d) Studies:
 - (1) Evaluated in a noninferiority trial compared with ceftriaxone, both in conjunction with clarithromycin, for the treatment of community-acquired bacterial pneumonia. Results indicated noninferiority, with numerically higher cure rates in those randomized to ceftaroline. Clinical response by day 4 of therapy was also higher in the ceftaroline group.
 - (2) Evaluated in a noninferiority trial compared with vancomycin plus aztreonam for the treatment of skin and skin structure infection. Ceftaroline cure rates were within the *a priori*-determined margin, thus satisfying the criteria for noninferiority.
- (e) Application:
 - (1) FDA approved for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia
 - (2) Despite its FDA approvals, the main role of ceftaroline is the availability of an additional agent with activity against MRSA. May be an option when vancomycin therapy is suboptimal and other treatment options may lead to unwanted adverse effects. May also be a reasonable option for the treatment of community-acquired pneumonia in institutions where community-acquired MRSA is common.

Patient Case

6. A 72-year-old woman with a history of end-stage renal disease is admitted to the medical ICU with signs and symptoms of sepsis. Blood cultures are obtained in which two of two bottles grow gram-positive cocci. The patient is initiated on vancomycin, and her tunneled dialysis catheter is removed. On day 4 of therapy, the blood cultures are finalized to be MRSA with the following antibiotic susceptibility results: oxacillin greater than 4 mcg/mL – R; vancomycin 2 mcg/mL – S; daptomycin 0.5 mcg/mL – S; and linezolid 1 mcg/mL – S. A transthoracic echocardiogram is obtained, which reveals echodensities on the mitral valve. The patient will be treated medically with antibiotics for 4–6 weeks. The patient's repeat blood cultures are currently no growth. Her vital signs and laboratory values are as follows: blood pressure 150/90 mm Hg, heart rate 88 beats/minute, temperature 100.2°F, WBC 11×10^3 cells/mm³, and lactate 1.1 mmol/L. Which is the most appropriate treatment regimen?
- A. Change vancomycin to linezolid 600 mg every 12 hours.
 - B. Add gentamicin and rifampin to vancomycin.
 - C. Change vancomycin to daptomycin 6 mg/kg every 48 hours.
 - D. Continue vancomycin, and target a trough level of 15–20 mcg/mL.

VII. IMMUNOCOMPROMISED PATIENTS

A. Febrile Neutropenia

1. Definition
 - a. Fever: A single temperature of 100.9°F (38.3°C) or greater orally or a temperature of 100.4°F (38.0°C) or greater orally for more than 1 hour
 - b. Neutropenia: Less than 500 neutrophils/mm³ or less than 500 neutrophils/mm³ during the next 48 hours
2. Patients with neutropenic fever admitted to an ICU should be considered high risk.
3. Initial therapy should include monotherapy with an intravenous antipseudomonal β -lactam (i.e., cefepime, piperacillin/tazobactam, meropenem, imipenem).
 - a. Most patients with an allergy to β -lactams tolerate cephalosporins and carbapenems.
 - b. Patients with type 1 hypersensitivity should be treated with either ciprofloxacin or aztreonam plus vancomycin.
4. Consider dual gram-negative therapy (fluoroquinolone or aminoglycosides) in patients with shock or if antimicrobial resistance is suspected.
5. Consider adding vancomycin to gram-negative therapy in patients with shock, suspected catheter-related infection, skin and soft tissue infection, and/or pneumonia. Gram-positive therapy can be discontinued in 48–72 hours if no evidence of gram-positive infections is discovered.
6. Modifications to initial antibiotic choices should be considered for patients with worsening clinical status or if patients' microbiological data warrant change.
7. Unexplained persistent fever in an otherwise clinically stable patient rarely warrants an escalation in therapy. Persistent fevers for 4–7 days after initiation of antibacterial agents should warrant consideration for empiric antifungal coverage in those who have persistent neutropenia.
8. Initial antimicrobials should be de-escalated or escalated in documented infections depending on in vitro susceptibility. Documented infections and unexplained fevers should be treated for a minimum of 14 days and until the absolute neutrophil count is greater than 500 cells/mm³.
9. Patients with hemodynamic instability should have their initial antibiotic regimen escalated to include coverage for resistant bacteria and fungi.
10. Hematopoietic growth factors should not be used for the treatment of febrile neutropenia. Prophylactic use of hematopoietic growth factors should be considered for patients with a high anticipated risk of febrile neutropenia (20% or greater).

B. Solid Organ Transplantation

1. Epidemiology
 - a. Hospital-acquired bacterial infections are the most common types of infections in SOT recipients.
 - b. 50%–75% of SOT recipients will experience an infection within the first year after transplantation.
 - c. Posttransplant infections may contribute to graft dysfunction and reduce long-term survival, and they have been associated with prolonged LOS and cost of care.
 - d. An analysis of 60,000 renal transplant recipients found that infections were the second leading cause of death.
2. General risk factors for infections
 - a. Excessive use of antibiotics before transplantation: With the use of prophylactic antimicrobials in the pretransplant period, many transplant recipients are experiencing resistant pathogens in the posttransplant period.
 - b. Infections are most common in the first 6 months after transplantation, with different pathogens presenting after various durations of immunosuppression. See Figure 4. OIs are rare in the first month after transplantation because the full effects of immunosuppression are not yet present. Fungal and viral infections experienced during the first month after transplantation are usually donor derived.
 - c. Duration of hospitalization after transplantation

- d. Renal dysfunction
- e. Several acute rejection episodes
3. General clinical approach for infectious diseases issues in critically ill SOT recipients
 - a. Be cognizant of the patient's transplant timeline, particularly with respect to possible OIs, pretransplant risk factors, immune status, intensity of immunosuppressive therapy, prophylactic regimens, and recent treatments of rejection.
 - b. Have a high clinical suspicion for OIs.
 - c. Severe infections sometimes warrant a reduction in maintenance immunosuppression. Consult with the transplant team regarding plans for maintenance immunosuppression.
 - d. Be aware of the many drug interactions between immunosuppressants and antimicrobials.

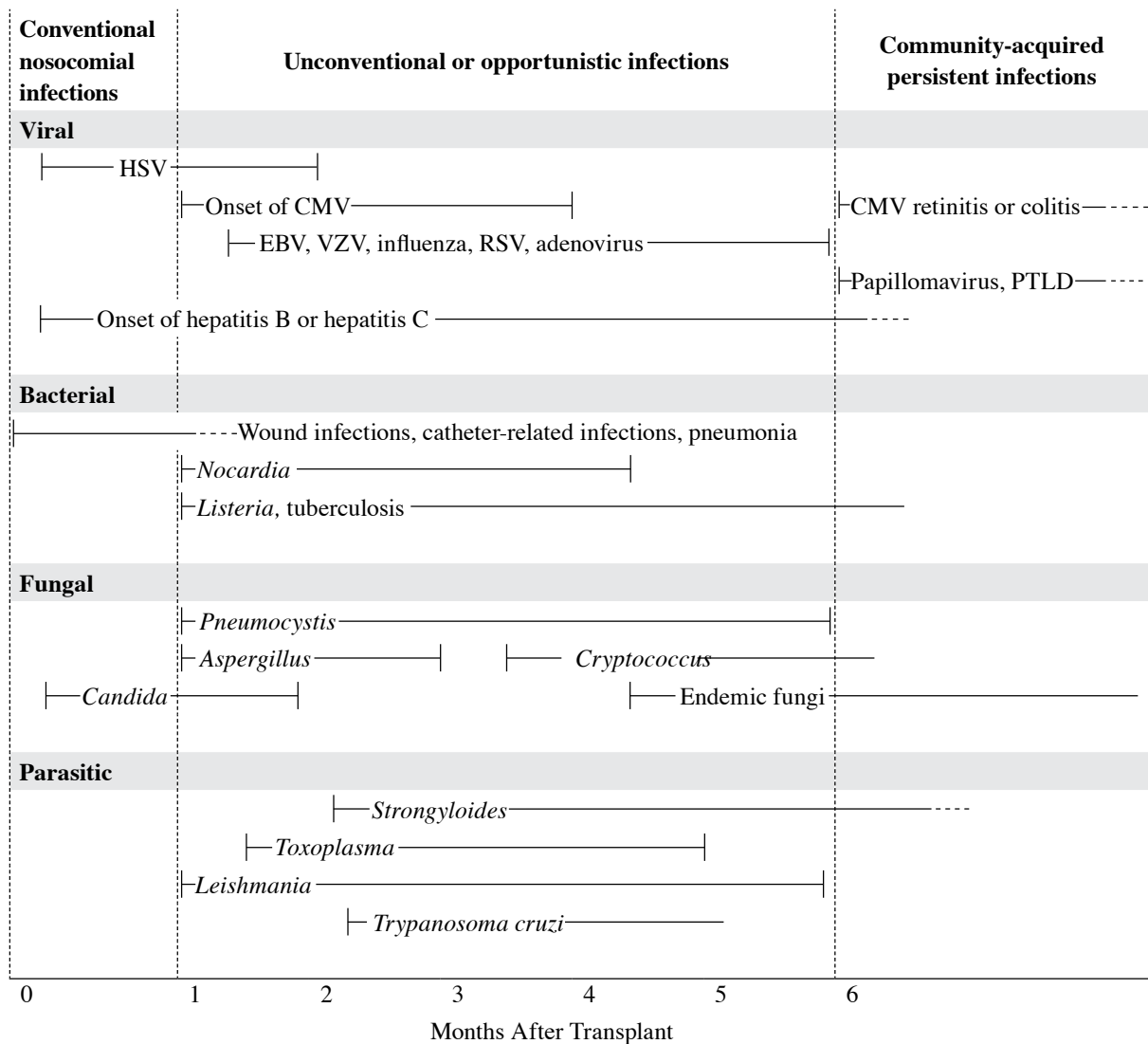


Figure 4. Usual sequence of infections after organ transplantation.^a

^aZero indicates the time of transplantation. Solid lines indicate the most common period for the onset of infection; dotted lines indicate periods of continued risk at a reduced level.

CMV = cytomegalovirus; EBV = Epstein-Barr virus; HSV = herpes simplex virus; PTLD = posttransplant lymphoproliferative disease; RSV = respiratory syncytial virus; VZV = varicella-zoster virus.

Reproduced with permission from: Baillie GM. Infectious disease concerns in solid organ transplantation. In: Schumock GT, Brundage DM, Dunsworth TS, et al., eds. Pharmacotherapy Self-Assessment Program, 5th ed. Book 2. Transplantation. Lenexa, KS: American College of Clinical Pharmacy, 2004:165-86.

VIII. HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNE DEFICIENCY SYNDROME IN CRITICALLY ILL PATIENTS

A. Diagnosis

1. Isolated CD4⁺ lymphopenia has occurred in critically ill patients without HIV disease.
 - a. Differential diagnosis of CD4⁺ lymphopenia
 - i. Idiopathic
 - ii. Common variable immunodeficiency
 - iii. Corticosteroid administration
 - iv. Circadian rhythm
 - v. Hematologic malignancies
 - vi. Critical illness
2. Patients with traditional HIV risk factors, isolated CD4⁺ lymphopenia, or AIDS-defining OIs who have not been given a diagnosis should receive HIV serologic testing. See Table 10 for AIDS-defining conditions.

B. Presentation for HIV-Associated Acute Illness

1. Changing prescribing patterns in highly active antiretroviral therapy (HAART) and improvements in care have changed the landscape of ICU admissions associated with HIV. Although the utility of ICU over time among HIV-positive patients has not decreased, the rationale for ICU admission has shifted from respiratory distress associated with pneumocystic pneumonia to other sepsis etiologies, neurologic disorders, and other end-organ dysfunctions.
2. See Table 11 for the management and prophylaxis of commonly occurring OIs in critically ill patients.

C. Management of HAART Therapy

1. Treatment-naïve patient
 - a. Initiation of HAART in an ICU may be deterred by factors such as lack of oral access, inability to assess the patient's willingness to commit to therapy, and high probability of interruptions in therapy because of surgical interventions.
 - b. Immune reconstitution inflammatory syndrome
 - i. Unexpected worsening of existing OI or unmasking of previously unrecognized illness associated with recent HAART initiation
 - ii. Recovery of immune response leading to a proinflammatory cytokine storm
 - iii. Risk factors
 - (a) Presence of disseminated disease or high antigen load
 - (b) High baseline HIV viral load
 - (c) Rapid response to antiretroviral therapy
 - iv. Evidence does not suggest that early administration of HAART (at the onset of an AIDS-defining OI) is associated with a higher incidence of immune reconstitution inflammatory syndrome.
 - v. In general, early and continued administration of HAART associated with improved outcomes, particularly in patients with OI. For patients with severe symptoms associated with immune reconstitution inflammatory syndrome (requiring vasopressors or intubation) consider the adjunctive use of prednisone.
2. Patient receiving HAART regimen
 - a. Considerations: Availability of drug formulations conducive to ICU administration; food requirements; dose adjustments associated with renal or hepatic impairment; new drug interactions; possible interruptions in therapy

- b. In general, if one of the antiretroviral therapies has to be discontinued, all of the therapies should be discontinued to decrease the promotion of resistance caused by the suboptimal suppression of viral replication. Exceptions: Nonnucleoside reverse transcriptase inhibitors (NNRTIs) have long half-lives (as long as 3 weeks); therefore, if NNRTIs are discontinued at the same time as other antiretrovirals with shorter half-lives, there will be a period of functional NNRTI monotherapy. May consider continuing antiretrovirals with shorter half-lives, if possible, for 1–2 weeks to minimize selection of NNRTI resistance.
 - c. Possible ICU drug interactions – See Table 12.
 - 3. HAART-associated adverse drug reactions
 - a. Newer generations of HAART regimens are generally well tolerated; however, many patients still receive older HAART therapy.
 - b. Many of the HAART-associated adverse effects have no specific treatment; therefore, early recognition and prompt discontinuation of the offending agent is crucial.
 - c. Lactic acidosis
 - i. Two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) remain the backbone of many HAART regimens.
 - ii. NRTIs are associated with a variety of mitochondrial toxicities.
 - iii. Older NRTIs, such as zidovudine, stavudine, and didanosine, have been associated with lactic acidosis.
 - iv. Symptoms: Fatigue, malaise, nausea, vomiting, abdominal pain, hepatomegaly
 - v. Management: Supportive therapy and discontinuing the potential offending agent
 - d. Abacavir hypersensitivity
 - i. Symptoms: Fever, rash, gastrointestinal (GI) symptoms
 - ii. Reaction associated with the presence of the *HLA-B*5701* allele, which has an 8% prevalence among whites in North America. Genetic screening for allele is recommended.
 - iii. Management: Supportive care and discontinuing agent, with rechallenge contraindicated because of the possibility of life-threatening hemodynamic compromise
 - e. Other HAART-associated significant adverse effects:
 - i. Nevirapine hypersensitivity: Rash (may progress to Stevens-Johnson syndrome), fever, hepatotoxicity
 - ii. Raltegravir-associated rhabdomyolysis
 - iii. Tipranavir-associated hepatotoxicity and intracranial hemorrhage
 - iv. Protease inhibitor-associated pancreatitis
- D. Management and Prophylaxis of HIV-Associated Infections: See Table 10.

Patient Case

7. A 46-year-old man is admitted to the medical ICU for diabetic ketoacidosis. The patient has a history of insulin-dependent diabetes, is HIV positive, and has cryptococcal meningitis. His current HAART regimen consists of atazanavir, ritonavir, tenofovir, and emtricitabine, which is continued on admission to the ICU. The patient's CD4⁺ count is 85/mm³. The patient's diabetic ketoacidosis is well controlled, and he is ready to be discharged from the ICU. Before discharge, the patient is noted not to be on any prophylaxis against OIs. Which prophylactic regimen would be most appropriate for the patient?
- A. Azithromycin 1200 mg once weekly and trimethoprim/sulfamethoxazole 1 double-strength (DS) tablet thrice weekly
 - B. Fluconazole 200 mg daily and trimethoprim/sulfamethoxazole 1 DS tablet daily
 - C. Azithromycin 1200 mg once weekly and fluconazole 200 mg daily
 - D. Fluconazole 200 mg daily and trimethoprim/sulfamethoxazole 1 DS tablet thrice weekly

Table 10. AIDS-Defining Conditions

Bacterial infections, multiple/recurrent (< 13 yr) Candidiasis: Bronchi, trachea, or lungs Candidiasis: Esophageal Cervical cancer: Invasive Coccidioidomycosis: Disseminated or extrapulmonary Cryptococcosis: Extrapulmonary Cryptosporidiosis: Chronic intestinal (for > 1 mo) Cytomegalovirus disease (other than the liver, spleen, or nodes) Cytomegalovirus retinitis (with loss of vision) Encephalopathy: HIV related Herpes simplex: Chronic ulcer(s) (for > 1 mo); bronchitis, pneumonitis, or esophagitis Histoplasmosis: Disseminated or extrapulmonary Isosporiasis: Chronic intestinal	Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex (< 13 yr) Lymphoma: Burkitt (or equivalent term) Lymphoma: Immunoblastic (or equivalent term) Lymphoma: Primary or brain <i>Mycobacterium avium</i> complex or <i>M. kansasii</i> : Disseminated or extrapulmonary <i>M. tuberculosis</i> : Any site (pulmonary or extrapulmonary) <i>Mycobacterium</i> : Other species or unidentified species; disseminated or extrapulmonary <i>P. jiroveci</i> pneumonia Pneumonia: Recurrent Progressive multifocal leukoencephalopathy <i>Salmonella septicemia</i> (recurrent) Toxoplasmosis of brain Wasting syndrome caused by HIV

Table 11. AIDS-Associated OIs and Their Respective Prophylactic and Treatment Options

OI/CD4 ⁺ Threshold for Prophylaxis	Prophylaxis Option	Treatment Option
<i>P. jiroveci</i> : < 200 cells/mm ³	Preferred: TMP/SMX ^b 1 DS PO daily <i>or</i> TMP/SMX ^b 1 SS PO daily Alternatives Dapsone ^a PO 100 mg/day Pentamidine 300 mg inhalation once monthly TMP/SMX 1 DS PO TIW Atovaquone PO 1500 mg/day	Preferred: TMP/SMX ^b 15–20 mg/kg PO/IV divided q6–8hr x 21 days <i>plus</i> prednisone 40 mg PO q12hr x 5 days; 40 mg/day x 5 days; 20 mg/day x 11 days (if Pao ₂ < 70 mm Hg or alveolar-arterial O ₂ gradient > 35) (IV methylprednisolone could be administered at 75% of dose) Alternatives: Pentamidine ^b IV 4 mg/kg/day Clindamycin 600–900 mg PO/IV q6–8hr + primaquine ^a PO 30 mg/day (base) Atovaquone 750 mg PO q12hr
Toxoplasmosis: < 100 cells/mm ³ and <i>Toxoplasma</i> IgG positive	Preferred: TMP/SMX 1 DS PO daily Alternatives: Dapsone ^a PO 50 mg/day + (pyrimethamine 50 mg PO + leucovorin 25 mg PO) once weekly TMP/SMX 1 DS PO TIW	Preferred: Pyrimethamine ^b 200 mg PO x 1; then 50–75 mg/day + sulfadiazine ^b 1000–1500 mg PO q6hr + leucovorin PO 10–20 mg/day x 6 wk Alternatives: Pyrimethamine ^b 200 mg PO x 1; then 50–75 mg/day + clindamycin 600–900 mg PO/IV q8hr + leucovorin PO 10–20 mg/day Pyrimethamine ^b 200 mg PO x 1; then 50–75 mg/day + atovaquone 1500 mg PO BID + leucovorin PO 10–20 mg/day
<i>Mycobacterium avium</i> complex: < 50 cells/mm ³	Preferred: Azithromycin 1200 mg once weekly <i>or</i> Clarithromycin 500 mg q12hr <i>or</i> Azithromycin 600 mg twice weekly Alternatives: Rifabutin ^c 300 mg/day	Preferred: At least two drugs: Clarithromycin 500 mg PO BID <i>or</i> azithromycin 600 mg/day <i>plus</i> ethambutol ^b PO 15–25 mg/kg/day Additional agents (consider depending on susceptibility testing, severe disease, or low CD4 ⁺ count) Rifabutin ^c PO 300 mg/day Amikacin ^b IV 10–15 mg/kg/day fluoroquinolones (moxifloxacin PO/IV 400 mg/day or levofloxacin ^b PO/IV 500 mg/day)

Table 11. AIDS-Associated OIs and Their Respective Prophylactic and Treatment Options (*continued*)

OI/CD4 ⁺ Threshold for Prophylaxis	Prophylaxis Option	Treatment Option
<i>Mycobacterium tuberculosis</i> : Primary prophylaxis not indicated	Latent infection treatment Preferred: Isoniazid (INH) PO 300 mg/day + pyridoxine PO 50 mg/day Alternatives: INH 900 mg PO twice weekly + pyridoxine 100 mg PO twice weekly	Active infection treatment Preferred: Rifampin ^c PO/IV 600 mg/day + INH PO 300 mg/day + pyrazinamide ^b PO 20–25 mg/kg/day + ethambutol ^b PO 15–25 mg/kg/day
Cryptococcosis: Primary prophylaxis not indicated Secondary prophylaxis may be considered	Secondary prophylaxis: Fluconazole 200–400 mg/day	Preferred: Induction therapy x 2 wk: Liposomal amphotericin IV 3–4 mg/kg/day + flucytosine ^b PO 25 mg/kg q6hr Alternatives: Induction x 2 wk: 1. Amphotericin B IV 0.7–1 mg/kg/day + flucytosine ^b PO 25 mg/kg q6hr 2. Amphotericin B lipid complex 3–4 mg/kg/day + flucytosine ^b PO 25 mg/kg q6hr 3. Liposomal amphotericin IV 3–4 mg/kg/day + fluconazole ^b 800 mg PO/IV daily Preferred: Consolidation therapy x 8 wk Fluconazole PO/IV 400 mg/day
<i>Cytomegalovirus</i> : Primary prophylaxis not indicated Secondary prophylaxis may be considered	Secondary prophylaxis: Valganciclovir ^b PO 900 mg/day	Preferred: Induction: Valganciclovir ^b PO 900 mg BID for 14–21 days <i>or</i> Ganciclovir ^b 5 mg/kg q12hr for 14–21 days Alternatives: 1. Foscarnet ^b IV 90 mg/kg q12hr or 60 mg/kg q8hr 2. Cidofovir IV 5 mg/kg/wk

^aShould not be used in patients with a glucose-6-phosphate dehydrogenase deficiency

^bRenal adjustments may be necessary.

^cMonitor for interactions with HAART.

BID = twice daily; DS = double strength; hr = hour(s); INH = isoniazid; IV = intravenous(ly); OI = opportunistic infection; PO = orally; SS = single strength; TIW = thrice weekly; TMP/SMX = trimethoprim/sulfamethoxazole.

Reproduced with permission from: Smith CL. HIV/infectious disease. In: ACCP Updates in Therapeutics® 2014: Pharmacotherapy Preparatory Review and Recertification Course. Lenexa, KS: American College of Clinical Pharmacy, 2014:580-621.

Table 12. Common Interactions Between Antiretrovirals and Commonly Used Medications in Critically Ill Patients

Agent	Antiretroviral	Interactions
Stress ulcer prophylaxis (proton pump inhibitors, histamine-2 receptor antagonists)	Rilpivirine: Contraindicated with proton pump inhibitors Atazanavir: Relatively contraindicated with proton pump inhibitors (administer no more than the equivalent of omeprazole 20 mg daily, and separate administration by at least 12 hr)	Decrease in antiretroviral concentrations
Triazole antifungals: Voriconazole, posaconazole, itraconazole	Protease inhibitors: Nonnucleoside reverse transcriptase inhibitors	Increase in antiretroviral concentration Decrease in antifungal concentrations
Antibacterials: Rifampin Clarithromycin Metronidazole	Protease inhibitors: Nonnucleoside reverse transcriptase inhibitors Protease inhibitors Nonnucleoside reverse transcriptase inhibitors Fosamprenavir, lopinavir, ritonavir	Decrease in antiretroviral concentration Increase in clarithromycin concentration Disulfiram reaction
Antiarrhythmics: Amiodarone Flecainide, propafenone, quinidine Diltiazem	Indinavir, ritonavir, tipranavir Lopinavir, ritonavir, tipranavir Atazanavir, fosamprenavir	Increased antiarrhythmic concentrations
Statins	Protease inhibitors Nonnucleoside reverse transcriptase inhibitors	Increase concentrations of statins – in decreasing order of interaction potential (lovastatin, simvastatin, rosuvastatin, atorvastatin, pravastatin)
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin	Protease inhibitors Nonnucleoside reverse transcriptase inhibitors	Increase in antiretroviral concentrations Decrease in anticonvulsant concentrations
Midazolam	Protease inhibitors Nonnucleoside reverse transcriptase inhibitors Cobicistat/elvitegravir	Increase in midazolam concentration
Methadone	Nonnucleoside reverse transcriptase inhibitors; fosamprenavir, ritonavir, lopinavir, nelfinavir, didanosine, saquinavir	Opioid withdrawal
Sildenafil	Protease inhibitors; delavirdine	Increase in sildenafil concentration
Warfarin	Delavirdine, efavirenz	Increase in warfarin concentration

IX. ANTIFUNGAL THERAPY**A. Amphotericin B**

1. Mechanism of action: Binds to ergosterol in the fungal cell membrane, which alters the membrane permeability, leading to ion leakage and fungal cell death
2. Spectrum of activity
 - a. *Candida* spp. (except for *C. lusitanae*), Blastomycetes, coccidioidomycosis, *Cryptococcus*, *Paracoccidioides*, histoplasmosis, aspergillosis, mucormycosis
 - b. Wide spectrum of activity allows its clinical use in many different systemic fungal infections.
3. Dose
 - a. Conventional amphotericin: 0.5–1.0 mg/kg/day
 - b. Lipid amphotericin: 3–5 mg/kg/day (higher doses have not been associated with improved outcomes)
4. Adverse effects
 - a. Renal toxicity
 - i. Decrease in glomerular filtration rate, which is associated with cumulative doses greater than 4–5 g
 - ii. Clinical manifestation
 - (a) Renal tubular acidosis
 - (b) Oliguria
 - (c) Azotemia
 - (d) Potassium, magnesium, phosphate wasting
 - iii. Prevention
 - (a) Avoid concomitant nephrotoxins.
 - (b) Avoid dehydration.
 - (c) Salt loading: 500 mL of normal saline before and after infusion of amphotericin
 - b. Infusion-related reactions
 - i. Mediated by cytokine release and prostaglandin synthesis
 - ii. Presentation: Fever, chills, nausea, vomiting, flushing, rigors
 - iii. Prevention
 - (a) Premedications – Administered 30–60 minutes before infusion
 - (1) Hydrocortisone 25–50 mg
 - (2) Ibuprofen 600 mg
 - (3) Acetaminophen 650 mg with diphenhydramine 50 mg
 - (4) Meperidine 50 mg if patient previously experienced rigors
 - (b) Use lower infusion rate on dose initiation.
 - c. Lipid amphotericin (liposomal amphotericin and amphotericin B lipid complex)
 - i. Amphotericin dissociates from lipid over time, which may limit its renal toxicity and infusion-related reactions.
 - ii. Premedication may still be necessary for amphotericin B lipid complex.

B. Triazole Antifungals

1. Mechanism of action: Inhibits the synthesis of ergosterol through blocking the CYP enzyme 14- α -sterol-demethylase. Inhibition of this enzyme leads to the accumulation of 14- α -methyl sterols on the fungal surface, which in turn leads to fungal cell death.
2. Fluconazole
 - a. Spectrum of activity:
 - i. *Candida* spp.
 - (a) *Candida krusei* is intrinsically resistant.

- (b) Variable sensitivity with *Candida glabrata*. Should not be used for *C. glabrata* unless antifungal susceptibilities are available. If *C. glabrata* is sensitive dosedependent, higher doses may be necessary (12 mg/kg/day).
 - (c) Good activity against all other pathogenic *Candida* spp.
 - ii. *Cryptococcus*
 - b. Dose
 - i. 6–12 mg/kg/day (400–800 mg/day)
 - ii. Available in intravenous and oral formulations
 - iii. Well absorbed orally with high bioavailability
 - iv. Primarily excreted by the kidneys – Renal dose adjustments are necessary.
 - c. Adverse effects: Minimal adverse effects and lowest propensity for drug interactions among triazoles
3. Itraconazole
- a. Spectrum of activity
 - i. *Candida* spp. – Has coverage similar to fluconazole with the exception of activity against *C. krusei*
 - ii. *Aspergillus*, *Blastomyces*, *Histoplasma*
 - b. Dose
 - i. 200–400 mg once daily
 - ii. Intravenous formulation no longer available
 - iii. Poor and erratic oral absorption. Improved with oral liquid formulation, maintaining high stomach acidity, avoidance of acid-suppressive therapy, and coadministration with acidic beverage
 - iv. Therapeutic drug monitoring may be necessary. Target: Itraconazole plus hydroxy-itraconazole concentration greater than 1 mcg/mL
 - v. Primarily used for fungal prophylaxis in immunocompromised patients and treatment of endemic fungi (histoplasmosis)
 - c. Adverse effects
 - i. GI upset, increase in liver function tests
 - ii. Drug interactions: CYP 3A4 and 2C9 inhibitor
4. Voriconazole
- a. Spectrum of activity
 - i. *Candida* spp. – Has coverage similar to fluconazole with the exception of activity against *C. krusei*
 - ii. *Aspergillus*, *Fusarium*, *Scedosporium*: Resistance against voriconazole has occurred with these pathogens.
 - b. Dose
 - i. Drug of choice for invasive aspergillosis
 - ii. 6 mg/kg every 12 hours x 2 doses as the loading dose, followed by 4 mg/kg every 12 hours
 - iii. Intravenous and oral formulations are available.
 - iv. Intravenously formulated in sulfobutyl-ether- β -cyclodextrin, which accumulates in renal dysfunction, although the clinical significance of this is unknown
 - v. Extensively metabolized by the liver, with 50% dose reductions recommended for patients with moderate to severe cirrhosis
 - vi. Genetic variations in CYP metabolism and high propensity for drug interactions lead to wide interpatient variability in concentrations.
 - vii. Therapeutic drug monitoring may be necessary. Target concentration: 1–5.5 mcg/mL.
 - c. Adverse reactions
 - i. Increase in liver function tests
 - ii. Visual hallucinations

- iii. Rash
 - iv. Nausea
 - v. CYP 3A4 and 2C9 inhibitor:
 - (a) Contraindicated with the use of rifampin, rifabutin, sirolimus, barbiturates, carbamazepine, and quinidine
 - (b) Significant dose reductions for cyclosporine and tacrolimus when coadministered with voriconazole
 5. Posaconazole
 - a. Spectrum of activity: Wide spectrum of activity, which includes *Candida* (similar to voriconazole), *Aspergillus*, *Zygomycetes*, and *Fusarium*
 - b. Dose
 - i. Oral suspension (immediate release): 200 mg every 6 hours. Oral suspension has extremely erratic absorption that is enhanced by coadministration with a high-fat meal and acidic food. In critically ill patients in whom coadministration with fatty meals and avoidance of acid-suppressive stress ulcer prophylaxis cannot be avoided, would recommend considering an alternative therapy or administration method (e.g., oral tablets or intravenous)
 - ii. Oral tablets (delayed release): 300 mg every 12 hours x 2 doses, followed by 300 mg once daily. Oral tablet is in an extended-release formulation, which cannot be crushed. Oral tablet absorption not as dependent on gastric pH and meal lipid content.
 - iii. Intravenous: 300 mg every 12 hours x 2 doses, followed by 300 mg once daily (intravenously formulated in sulfobutyl-ether- β -cyclodextrin, which accumulates in renal dysfunction, although the clinical significance of this is unknown)
 - iv. Therapeutic drug monitoring may be prudent, particularly when oral suspension is used. Target concentrations: Greater than 1.25 mcg/mL for treatment of invasive fungal infection.
 - v. Mainly used for fungal prophylaxis in immunocompromised patients and treatment when patient is not responding to other therapies
 - c. Adverse reactions
 - i. Increase in liver function tests
 - ii. Nausea/vomiting
 - iii. Drug interaction: CYP3A4 inhibitor
 6. Isavuconazole
 - a. Spectrum of activity: Wide spectrum of activity, including *Candida* (similar to voriconazole), *Aspergillus* (may retain activity for some species that are resistant to other azoles), *Zygomycetes*, and dimorphic fungi. Limited activity against *Fusarium*.
 - b. Dose
 - i. Intravenous or oral: 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) every 8 hours, after a 1116-mg (600 mg of isavuconazole) loading dose
 - ii. Isavuconazonium sulfate solution is readily water soluble, unlike posaconazole and voriconazole, and does not require stabilization with cyclodextrin.
 - c. Mainly PK advantages and safety benefits over voriconazole and posaconazole
 - i. Linear kinetics
 - ii. Oral bioavailability: 98%, not affected by food or acidity
 - iii. Fewer drug-drug interactions
 - iv. No QTc prolongation; in fact, associated with dose-dependent QTc shortening
- C. Echinocandins (caspofungin, micafungin, and anidulafungin)
1. Mechanism of action: Inhibition of glucan synthase, which is an enzyme responsible for the formation of 1,3- β -d-glucan. Inhibition of this enzyme leads to cessation of fungal cell wall formation.

2. Spectrum of activity: All *Candida* spp. and *Aspergillus*
 - a. In vitro, *C. parapsilosis* has a much higher MIC than other *Candida* spp. The clinical significance of this is unknown. Cases of breakthrough infections with *C. parapsilosis* during treatment with echinocandins have been reported. Several retrospective studies did not find worsened outcomes associated with echinocandin treatment of *C. parapsilosis*. The current IDSA guidelines on invasive candidiasis recommend using fluconazole for the treatment of *C. parapsilosis*.
 - b. Primarily used for invasive candidiasis, neutropenic fever, and invasive *Aspergillus* if patient cannot tolerate other therapies. Recent IDSA candidiasis guidelines recommend echinocandin as preferred initial therapy for both proven and empiric therapy.
 3. Dose (available only as an intravenous formulation)
 - a. Caspofungin: 70 mg once, followed by 50 mg once daily
 - b. Micafungin: 100 mg once daily
 - c. Anidulafungin: 200 mg once, followed by 100 mg once daily
 4. Adverse reactions
 - a. Well tolerated with minimal GI adverse effects
 - b. Minimal drug interactions
 - i. Avoid caspofungin coadministration with cyclosporine and tacrolimus.
 - ii. Avoid micafungin coadministration with nifedipine and sirolimus.
 - iii. Avoid administering anidulafungin with metronidazole (disulfiram reaction).
- D. Flucytosine
1. Mechanism of action: Converted by fungal enzymes to fluorouracil, which disrupts fungal RNA and DNA synthesis
 2. Spectrum of activity
 - a. *Candida* spp.
 - b. *Cryptococcus*: Treatment of choice (in conjunction with amphotericin) for *Cryptococcus*
 3. Dose
 - a. 37.5 mg/kg every 6 hours
 - b. Renal adjustments necessary
 - c. Well absorbed: Bioavailability 80%–90%
 - d. Available only as an oral formulation in the United States
 - e. Therapeutic concentrations: 25–100 mcg/mL
 4. Adverse reactions: Bone marrow suppression, particularly with supratherapeutic concentrations

Patient Case

8. A 66-year-old woman (height 66 inches, weight 75 kg) is admitted to the medical ICU for dehydration and acute kidney injury. The patient recently received an allogeneic bone marrow transplant and has not yet engrafted. She has been pancytopenic for 12 days. On day 5 of the medical ICU stay, the patient develops acute respiratory distress requiring intubation. Bronchoalveolar lavage is done, which eventually grows *Aspergillus fumigatus*, and the patient is given a diagnosis of invasive pulmonary aspergillosis. The patient's current medications include tacrolimus, corticosteroids, and fluconazole fungal prophylaxis. Her current relevant laboratory values are as follows: WBC 0.2×10^3 cells/mm³, lactate 1.5 mmol/L, and SCr 3.4 mg/dL. Which antifungal therapy is most appropriate?
 - A. Amphotericin 50 mg intravenously once daily
 - B. Isavuconazole load followed by 200 mg intravenously every 8 hours
 - C. Caspofungin load followed by 50 mg intravenously daily
 - D. Voriconazole load followed by 300 mg intravenously every 12 hours

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D

The CDC definitions for CAUTIs, which are used by the CMS reporting system, were recently updated. Because this patient had his urinary catheter removed for more than 24 hours before developing UTI symptoms, this case does not satisfy the definition of CAUTI (Answer D is correct; Answers A and C are incorrect). The current CDC CAUTI definitions do not consider the results of a urinalysis (Answer B is incorrect).

2. Answer: A

This patient presents with community-acquired meningitis. The high opening pressure is suggestive of a bacterial etiology, of which the most prevalent pathogen for this patient's risk factors and age is *S. pneumoniae*. Administering dexamethasone before initiating antibiotic therapy decreases mortality in patients with *S. pneumoniae* meningitis. (Answer A is correct) Awaiting laboratory and microbiologic test results analysis may cause inappropriate delays in therapy (Answer B is incorrect). In addition, although administering antimicrobials is a good idea, the beneficial effects associated with dexamethasone are diminished if administered after antimicrobials have been initiated. At the very least, corticosteroids should be administered concomitantly with antimicrobials (Answer C and D are incorrect).

3. Answer: D

The PNA FISH technology is designed to identify pathogens earlier. It performs well, with good sensitivity and specificity; hence, identification of *C. parapsilosis* should not require verification from culture (Answer A is incorrect). The drug of choice for the treatment of *C. parapsilosis* is fluconazole (Answer D is correct). Although echinocandin, voriconazole, and amphotericin would all cover *C. parapsilosis*, they all have a broader spectrum than is necessary, making them not the ideal choice (Answers A–C are incorrect).

4. Answer: A

Although PCT is a promising biomarker for the detection of bacterial infections, it must be interpreted within the context of the patient's clinical course. In this case, the patient has clear signs and symptoms of infection, together with signs of hypoperfusion. A low PCT should not be used to guide therapy discontinuation in this case, and antibiotics should be continued to cover the

most likely pathogens (Answer A is correct; Answer B is incorrect). Because the patient is admitted with presumed community-acquired pneumonia, the combination of ceftriaxone and azithromycin is appropriate right now (Answers C and D are incorrect).

5. Answer: B

This patient is being treated for an ESBL *E. coli* UTI, in which the source of the infection (urinary catheter) is removed. The patient also has signs of response to piperacillin/tazobactam with resolution of leukocytosis and fever. In this case, given the low inoculum of the infection, initial response, removal of source, and low MIC, continuing piperacillin/tazobactam is the best choice (Answer B is correct). Traditionally, it was widely believed that ESBL infections had to be treated with carbapenems. However, recent evidence suggests that β -lactam/ β -lactamase inhibitor combinations are a suitable option. In the era of antimicrobial stewardship, the preservation of carbapenem therapy should be regarded with high importance (Answer A is incorrect). This current culture has an MIC of 4 mcg/mL to cefepime, which, according to the updated CLSI guidelines, would be considered resistant (Answer C is incorrect). Because the patient is responding to the current therapy, combination therapy is unnecessary (Answer D is incorrect).

6. Answer: D

This patient is being treated for MRSA right-sided endocarditis, with the presumed source from her tunneled dialysis catheter. According to the IDSA guidelines for the treatment of MRSA, treatment with vancomycin of an isolate with an MIC of 2 mcg/mL or less should be determined by the patient's response to therapy, regardless of the actual MIC. This patient has responded to therapy with the presumed clearance of blood cultures and resolution of signs and symptoms of infection. Hence, continuing vancomycin and targeting a trough of 15–20 mcg/mL is the most appropriate choice (Answer D is correct). Linezolid is not indicated for the treatment of endocarditis (Answer A is incorrect). Adding gentamicin and rifampin is considered in the medical treatment of prosthetic valve endocarditis (Answer B is incorrect). Because the patient is responding to current vancomycin therapy, an escalation to daptomycin is inappropriate right now (Answer C is incorrect).

7. Answer: B

This patient is admitted to the ICU for an indication that is unrelated to the patient's underlying HIV. The assessment of which prophylactics are necessary against OIs depends on the patient's underlying disease, history, and CD4⁺ count. In this case, the patient has a CD4⁺ count less than 100/mm³ and a history of cryptococcal meningitis. Hence, prophylaxis should be administered for toxoplasmosis, *P. jiroveci*, and *Cryptococcus*. The best regimen for this patient is fluconazole 200 mg daily and trimethoprim/sulfamethoxazole 1 DS tablet once daily (Answer B is correct). The prophylaxis for *Mycobacterium avium* complex is indicated for patients with a CD4⁺ count of less than 50 cells/mm³, which is unnecessary at this point (Answers A and C are incorrect). Although trimethoprim/sulfamethoxazole 1 DS tablet thrice weekly is an option for prophylaxis, it is not the best choice against toxoplasmosis (Answer D is incorrect).

8. Answer B

This patient has invasive pulmonary aspergillosis. Usually, the treatment of choice is voriconazole. However, in this case, the patient has acute kidney injury with a CrCl less than 50 mL/minute/1.73 m². According to the package insert, voriconazole is contraindicated in this case because of the possibility of accumulation of cyclodextrin, the intravenous drug carrier for voriconazole. Although the clinical relevance of this accumulation is controversial, continued use of a contraindicated therapy is inappropriate when alternatives may be available (Answer C is incorrect). Isavuconazole is a new triazole that was found to be noninferior to voriconazole for the treatment of aspergillosis and has improved water solubility, which does not require it to be formulated with cyclodextrin (Answer B is correct). Conventional amphotericin may be a reasonable choice, but it will likely worsen the patient's acute kidney injury (Answer A is incorrect). Echinocandins are not the ideal therapies for invasive aspergillosis and should only be considered if there are no other treatment options (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

The prophylactic regimen for a patient without a β -lactam allergy who is undergoing cardiac surgery should be cephalosporin administered within 60 minutes of incision time, administered every 4 hours during surgery, and continued for no more than 48 hours. In this case, the patient has obesity disorder and weighs more than 120 kg; hence, the patient requires an initial dose of cefazolin 3 g (Answer C is correct). Given the patient's weight, administering cefazolin 2 g initially is inappropriate (Answers A and D are incorrect). Vancomycin is usually reserved for patients with a β -lactam allergy (Answer B is incorrect).

2. Answer: C

Although critical care pharmacists may not officially be part of many antimicrobial stewardship teams, many of their daily clinical activities constitute antimicrobial stewardship activities. These may include selecting the most appropriate treatment regimen and advocating the early de-escalation of antimicrobials. Even in the presence of a formalized antimicrobial stewardship team, these activities are often complementary to the formalized activities of the team (Answer C is correct). Given the wide variations in clinical practice, it may not be feasible to include an infectious diseases-trained pharmacist with every stewardship team. In that case, the activities and involvement of a critical care pharmacist may be even more crucial (Answer A is incorrect). The goal of an antimicrobial stewardship team is to optimize therapy through selecting the most appropriate therapy that would minimize adverse effects and unwanted selection of resistant or opportunistic infections. Although decreases in antimicrobial expenditures commonly occur, this is not the main goal of the team (Answer B is incorrect). Studies have shown that antimicrobial stewardship efforts in critically ill patients do not worsen outcomes. Given the aggressive empiric antimicrobial regimens commonly used in critically ill patients, antimicrobial stewardship should be instituted to minimize adverse effects and the emergence of resistance (Answer D is incorrect).

3. Answer: D

This patient presents with a health care-associated CNS infection, given the post-neurosurgical and device-related etiology of the infection. The most common pathogens

include MRSA and multidrug-resistant gram-negative organisms. In addition to neurosurgical management of the device (e.g., removal or revision), empiric antibiotic therapy is indicated, including therapy with agents having empiric activity against suspected pathogens and able to safely achieve relevant CSF concentrations. Cefepime and vancomycin are the most appropriate options listed with consideration of CNS-specific dosing (Answer D is correct). Ceftriaxone does not cover nosocomial-acquired gram negatives such as *Pseudomonas* (Answers A and B are incorrect). Piperacillin/tazobactam would be reasonable according to the spectrum of antibacterial activity; however, poor CNS penetration of tazobactam limits the utility of this agent for meningitis and other CNS infections (Answer C is incorrect).

4. Answer: D

The presence of the CTX-M gene detected on *E. coli* by rapid diagnostic testing usually signifies the presence of ESBL. This may be why the patient has not yet responded to piperacillin/tazobactam. The most appropriate action at this point is to broaden the coverage to cover for potential ESBL-producing *E. coli*. Carbapenems remain the drug of choice for ESBL-producing organisms, particularly in a patient who is hemodynamically unstable (Answer D is correct). Extended-spectrum β -lactamases are usually encoded on genes that carry resistance against other classes of antimicrobials; hence, resistance to other antimicrobials is common; therefore, adding either aminoglycosides or fluoroquinolones may not be appropriate (Answers B and C are incorrect). Although at times ESBLs may be covered by cefepime, it must be determined by final AST (Answer A is incorrect).

5. Answer: C

E. cloacae are AmpC β -lactamase-producing Enterobacteriaceae. The use of ceftriaxone or extended-spectrum penicillins (e.g., piperacillin and ticarcillin) may select out derepressed mutants, which are capable of causing the hyperproduction of AmpC β -lactamases. Derepressed mutants are capable of producing resistance against third-generation cephalosporins, monobactams, and extended-spectrum penicillins. In this case, the patient was taking 10 days of ceftriaxone before a new blood culture was growing lactose-positive gram-negative bacilli. Because lactose-positive gram-negative bacilli are usually Enterobacteriaceae, growing multidrug-resistant

pathogens such as *P. aeruginosa* and *Acinetobacter baumannii* is less likely. Hence, the most likely resistance mechanism in this patient is either selection of derepressed mutants or acquisition of a pathogen with ESBL. Both of these resistance mechanisms are adequately treated by a carbapenem. Hence, changing to a carbapenem pending final sensitivities is the most reasonable option (Answer C is correct). Both types of resistance mechanisms are capable of producing resistance against ceftazidime and piperacillin/tazobactam (Answers A and B are incorrect). Because the patient developed a new bacteremia while taking ceftriaxone, it is not reasonable to continue ceftriaxone alone (Answer D is incorrect).

6. Answer: B

The patient is only on day 4 of therapy from proven MRSA pneumonia. However, the patient developed a bacteremia with gram-positive cocci in pairs and chains despite receiving systemic vancomycin therapy. The most likely culprit is a vancomycin-resistant *Enterococcus* sp. The medical team has already discontinued vancomycin; therefore, the new therapy must cover both the MRSA pneumonia and the possibility of a vancomycin-resistant *Enterococcus* sp. Linezolid has good lung penetration and can adequately cover vancomycin-resistant enterococci (Answer B is correct). Daptomycin would provide adequate coverage for vancomycin-resistant enterococci, but because it is inactivated by lung surfactants, it is not a good option for the treatment of MRSA pneumonia (Answer A is incorrect). Ceftaroline covers MRSA and has good lung penetration; however, it covers only vancomycin-resistant *E. faecalis*, not *E. faecium*. Because, at this point, the speciation of the gram-positive cocci in pairs and chains is not available, ceftaroline is not the best choice (Answer C is incorrect). Tigecycline does cover MRSA and vancomycin-resistant enterococci; however, given its large volume of distribution and relatively low serum concentrations, it may not be the ideal choice for the treatment of bacteremia when other treatments are available (Answer D is incorrect).

7. Answer: B

The patient's history and clinical presentation suggest PJP. It is severe enough to warrant intubation, and the patient has a significant alveolar-arterial oxygen gradient. The usual drug of choice for such patients is trimethoprim/sulfamethoxazole, but because this patient has a sulfa allergy, this is not an option (Answer

A is incorrect). According to the HIV OI guideline, the second-line agent for the treatment of severe PJP is intravenous pentamidine. Because the patient had severe hypoxemia, adjunctive steroids should be administered (Answer B is correct). Atovaquone and primaquine/clindamycin regimens are usually reserved for patients with milder PJP. Furthermore, primaquine should not be administered to someone with a glucose-6-phosphate dehydrogenase deficiency (Answers C and D are incorrect).

8. Answer: B

This patient has febrile neutropenia with no recovery of neutrophils. According to the IDSA febrile neutropenia guidelines, when a source of infection is identified, the empiric antimicrobial therapy can be de-escalated to a more narrow-spectrum regimen according to the antibiotic susceptibility report. In this case, because the *E. coli* was pan-sensitive, it would be appropriate to de-escalate to a narrow-spectrum antimicrobial. The guidelines also specify that antimicrobial therapies should be continued for at least 14 days and until neutrophils are greater than 500 cells/mm³ (Answer B is correct). Although the patient continues to be febrile, an otherwise stable patient with continued fevers rarely requires additional antimicrobial therapy according to the guidelines. Hence, continuing more broad-spectrum therapy than necessary or adding other antimicrobials is unwarranted (Answers A, C, and D are incorrect).

NEUROCRITICAL CARE

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Learning Objectives

1. Identify pertinent pathophysiological and laboratory changes that acutely occur after neurological injuries and require therapeutic intervention.
2. Describe monitoring devices commonly used in neurocritical care patients that help with developing and optimizing treatment strategies.
3. Develop an evidence-based treatment strategy for neurocritical care patients that will optimize patient outcomes and reduce the risk of adverse drug effects and drug interactions.
4. Recommend a monitoring plan to assess response to therapeutic regimens and specific therapeutic goals for neurocritical care patients.
5. Reassess and develop new plans of care for neurocritical care patients according to therapeutic and adverse outcomes, and progress toward therapeutic goals.

Abbreviations in This Chapter

ADH	Antidiuretic hormone
AED	Antiepileptic drug
CNS	Central nervous system
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
CSWS	Cerebral salt-wasting syndrome
DIND	Delayed ischemic neurological deficit
ED	Emergency department
EEG	Electroencephalogram
GCS	Glasgow Coma Scale
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
ICU	Intensive care unit
INR	International Normalized Ratio
MAP	Mean arterial pressure
MRSE	Methicillin-resistant <i>Staphylococcus epidermidis</i>
PCC	Prothrombin complex concentrate
SAH	Subarachnoid hemorrhage
SCI	Spinal cord injury
SIADH	Syndrome of inappropriate antidiuretic hormone
TBI	Traumatic brain injury
VTE	Venous thromboembolism

Self-Assessment Questions

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

1. A 56-year-old woman is in her fourth day of hospitalization after her acute aneurysmal subarachnoid hemorrhage (SAH). She is oriented and following commands. Laboratory values reveal a serum sodium of 128 mmol/L. Other serum chemistry values include potassium (K) 3.9 mEq/L, chloride 103 mEq/L, bicarbonate (HCO_3) 27 mEq/L, blood urea nitrogen (BUN) 10 mg/dL, and serum creatinine (SCr) 1.0 mg/dL. Her urine output ranges from 1 to 2 mL/kg/hour, and her fluid balance has been +435 during the past 24 hours (currently receiving 0.9% sodium chloride at 125 mL/hour). Which is the best initial therapy for this patient's hyponatremia?
 - A. Tolvaptan 20 mg orally daily
 - B. 1.5% sodium chloride infusion at 125 mL/hour
 - C. Water restriction to less than 1.5 L/day
 - D. No treatment indicated right now
2. A 27-year-old woman is admitted with an acute ventriculoperitoneal shunt failure and associated infection. She has no significant medical history and no allergies to medications. A lumbar puncture is obtained that reveals a cerebrospinal fluid (CSF) white blood cell count (WBC) of 34×10^3 cells/mm³, red blood cell count (RBC) 1×10^3 cells/mm³, protein 78 mg/dL, and glucose 21 mg/dL. The cultures grow methicillin-resistant *Staphylococcus epidermidis* (MRSE). Her shunt is externalized. Despite 4 days of intravenous vancomycin (most recent vancomycin trough = 17.7 mcg/mL), the CSF continues to grow MRSE. Which is the most appropriate intraventricular antimicrobial regimen to initiate for this patient's refractory ventriculitis?
 - A. Give vancomycin 10 mg intraventricularly daily.
 - B. Give gentamicin 5 mg intraventricularly daily.
 - C. Give ampicillin 50 mg intraventricularly daily.
 - D. No antimicrobials should be given intraventricularly for this patient.

3. A 25-year-old man is admitted after a two-story fall from a ladder. His initial computed tomography (CT) scan of the brain reveals a large right temporal subdural hematoma, an overlying skull fracture, and a left temporal contusion. His post-resuscitation Glasgow Coma Scale (GCS) score is E1-M4-V1T. An intracranial pressure (ICP) monitor is placed with an opening pressure of 32 mm Hg and a cerebral perfusion pressure (CPP) of 53 mm Hg. Serum laboratory values include sodium (Na) 141 mEq/L, potassium (K) 3.6 mEq/L, blood urea nitrogen (BUN) 8 mg/dL, serum creatinine (SCr) 1.1 mg/dL, glucose 178 mg/dL, white blood cell count (WBC) 14.8×10^3 cells/mm³, pH 7.46, and Pco₂ 34. Which supportive care issues are most relevant to the appropriate treatment of a patient with a severe traumatic brain injury (TBI)?
- A. Avoid enteral nutrition for the first 5–7 days because of the lack of gastrointestinal (GI) tolerance in severe TBI.
 - B. Maintain CPP between 60 and 70 mm Hg to optimize perfusion and reduce complications.
 - C. Provide dextrose 5% or other dextrose-containing intravenous fluids to compensate for the patient's increased metabolic needs.
 - D. Initiate high-dose methylprednisolone therapy within 8 hours of injury to reduce cerebral edema.
4. A 69-year-old woman presents to the ED with a 30-minute history of difficulty with word finding and left upper extremity weakness. Her NIH Stroke Scale score is 13. A CT scan of the head reveals no acute abnormalities. The patient's home medications include lisinopril, carvedilol, warfarin, and atorvastatin. Her medical history includes hypertension, atrial fibrillation, and transient ischemic attacks (diagnosed 6 months ago). Serum laboratory values include Na 145 mEq/L, K 4.0 mEq/L, BUN 18 mg/dL, SCr 1.2 mg/dL, glucose 132 mg/dL, WBC 8.7×10^3 cells/mm³, hematocrit 38.9%, platelet count 355,000/mm³, and international normalized ratio (INR) 1.5. Her vital signs include blood pressure 167/98 mm Hg, heart rate 132 beats/minute, Sao₂ 98%, and respiratory rate 14 breaths/minute. Which is the most appropriate next step in this patient's care?
- A. Initiate aspirin 324 mg orally x 1.
 - B. Initiate alteplase 0.9 mg/kg intravenously (10% bolus dose, 90% infusion up to 90 mg maximum).
 - C. Initiate nicardipine to reduce blood pressure to systolic blood pressure (SBP) less than 140 mm Hg, followed by alteplase 0.9 mg/kg intravenously (10% bolus dose, 90% infusion up to 90 mg maximum).
 - D. Initiate vitamin K 10 mg intravenously x 1.
5. An 18-year-old man is admitted to the intensive care unit (ICU) after falling from a tree. Initial trauma screening reveals a C3–C4 fracture and dislocation with an incomplete spinal cord injury (SCI) at the corresponding levels (he has some sensory function bilaterally). The fracture has been reduced, and he arrives in the ICU 6 hours after injury. Which is the most appropriate statement related to initiating high-dose methylprednisolone therapy for this patient's SCI?
- A. High-dose methylprednisolone therapy may be used because he has an incomplete injury with some sensory function.
 - B. High-dose methylprednisolone therapy should be used because it will augment spinal perfusion.
 - C. High-dose methylprednisolone therapy should not be used because of the potential for adverse effects and questionable benefit.
 - D. High-dose methylprednisolone therapy should not be used because the patient is outside the treatment window.
6. A 27-year-old woman presents with fever, agitation, hypertension, and muscle rigidity. Her drugs-of-abuse screen is negative, and serotonin syndrome is a possible diagnosis. Which home medication is most likely to be a causative agent for serotonin syndrome?
- A. Buspirone
 - B. Levetiracetam
 - C. Cyproheptadine
 - D. Bupropion

7. A 58-year-old woman with a Hunt and Hess grade 4 SAH resides in your ICU. She is day 6 after her SAH. Her current medications include 0.9% normal saline at 100 mL/hour, nimodipine 60 mg per tube every 4 hours, norepinephrine 0.05 mcg/kg/minute (5 mcg/minute), famotidine 20 mg intravenously every 12 hours, docusate 250 mg per tube every 12 hours, and morphine as needed for headache. Current laboratory values include Na 144 mEq/L, K 4.1 mEq/L, SCr 0.6 mg/dL, serum osmolality 322 mOsm/L, and hematocrit 32.3%. Her blood pressure is 167/99 mm Hg, heart rate 133 beats/minute, respiratory rate 18 breaths/minute, Sao_2 99%, and central venous pressure 5 mm Hg. Her most recent transcranial Doppler velocities are mean middle cerebral artery 125/135 (right/left), with a corresponding Lindegaard ratio of 3.5/3.7 (right/left). Her ICP is currently 24 mm Hg. She has a Licox monitor placed in the hemisphere ipsilateral to her aneurysm, which currently shows a partial pressure of brain tissue oxygen (PbtO_2) of 14%. She is intubated and on the ventilator. Her GCS decreased from 10 to 8 during the past hour. Which treatment would be most appropriate for this patient?
- A. Verapamil 2.5 mg intra-arterially x 1
 - B. 3% sodium chloride 2.5 mL/kg intravenously x 1
 - C. 20% mannitol 0.25 g/kg intravenously x 1
 - D. 1 unit of packed RBCs
8. Which sedative is most desirable for a patient with a diagnosis of SAH and currently having vasospasm?
- A. Lorazepam 1 mg/hour
 - B. Midazolam 4 mg/hour
 - C. Morphine 2 mg/hour
 - D. Propofol 25 mcg/kg/minute

I. HYPONATREMIA

A. Epidemiology

1. Hyponatremia (sodium less than 135 mEq/L) is common in patients with neurological injury.
2. SAH 12%–43%
3. TBI 20%

B. Diagnosis/Pathophysiology

1. Laboratory tests (serum sodium) are needed to diagnose hyponatremia.
2. Urine sodium, urine osmolality, serum osmolality, and measurement of intravascular volume may also be helpful in determining the specific pathogenesis for hyponatremia.

C. Causes

1. Consideration of iatrogenic hyponatremia
2. Typically caused by an increase in salt-free water or loss of serum sodium

D. Differentiation Between Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and Cerebral Salt-Wasting Syndrome (CSWS) – Typically by intravascular volume

1. Measure intravascular volume using a central venous pressure catheter or similar invasive monitoring.
2. Monitor fluid balance, weights, skin turgor
3. Echocardiogram to estimate ventricular filling pressures

Table 1. Differential Diagnosis for SIADH and CSWS^a

	Serum Sodium (mEq/L)	Serum Osmolality (mOsm/L)	Urine Sodium (mEq/L)	Urine Osmolality (mOsm/L)	Intravascular Volume Status
SIADH	< 135	< 285	> 25	> 200	Euvolemia
CSWS	< 135	< 285	> 25	> 200	Hypovolemia

^aNote: Medications, particularly diuretics, may alter serum or urine measurements of osmolality or Na concentration.

CSWS = cerebral salt-wasting syndrome; SIADH = syndrome of inappropriate antidiuretic hormone.

E. Clinical Impact

1. Hyponatremia may result in increased brain edema and elevated ICP; therefore, serum sodium goals in neurocritical care patients tend to be higher than 135 mEq/L.
2. May cause neurological symptoms such as delirium, agitation, tremor, seizure, or coma

F. SIADH: Increased secretion of antidiuretic hormone ([ADH] or vasopressin) results in increased water retention at the renal distal tubules.

Box 1. Typical Causes of SIADH

Disease States	Medications
Traumatic brain injury	Selective serotonin reuptake inhibitors
Brain tumor	Tricyclic antidepressants
Stroke	Carbamazepine
Brain infection	Oxcarbazepine
Subarachnoid hemorrhage	Chlorpropamide
Intracerebral hemorrhage	Nicotine
Pneumonia/tuberculosis	Opioids
Lung cancer	Antipsychotic medications
	Nonsteroidal anti-inflammatory drugs

G. Treatment – Guidelines for the diagnosis and management of hyponatremia are available (Intensive Care Med 2014;40:320-31).

Table 2. Treatment Strategies for SIADH

	Fluid Restriction	Oral Na	Intravenous Na	Demeclocycline	Vasopressin (V)-Antagonists
Mechanism of action	Restriction of free water results in increased impact of insensible losses, permitting Na concentration to rise	Supplementation of Na	Supplementation of Na	Inhibition of ADH activity, possibly because of inhibition of aquaporin water channels	Inhibition of renal V1 vasopressin receptors (conivaptan V1 + V2 receptors; tolvaptan V1 only)
Dose	< 1500 mL/day	4–16 g/day (1 g = 17 mEq Na)	0.9%–3% at 0.5–1.5 mL/kg/hr	300 mg every 12 hr up to 1200 mg/day	Conivaptan: 20–40 mg IV daily Tolvaptan: 15–60 (Intensive Care Med 2014;40:320-31) mg PO daily
Efficacy	Modest, delayed (for 2+ days)	Modest, more effective for CSWS (for 2+ days)	Modest, more effective for CSWS (for 2+ days)	Modest, delayed (for 1 wk)	Modest, prompt for the first 24 hr
Common adverse effects	Thirst	Thirst, diarrhea	Fluid overload	GI upset, hepatotoxicity, photosensitivity	Thirst; conivaptan: infusion pain
Common considerations	Difficult to ensure adherence; caution for permitting hypovolemia in patients with cerebral perfusion needs such as SAH, TBI		≤ 2% sodium chloride may be given through peripheral IV	Chelation occurs with coadministered cations	Cost; drug-drug interactions are common

ADH = antidiuretic hormone; IV = intravenous(ly); PO = oral(ly); SAH = subarachnoid hemorrhage; TBI = traumatic brain injury.

1. Treatment of SIADH can be challenging in many neurocritical care patients such as those with SAH and TBI.
2. Treatment of choice is fluid restriction, which is typically not feasible in patients with SAH or TBI.
3. Priority on maintaining euolemia to optimize CPP, particularly when treating elevated ICP or cerebral vasospasm

H. Cerebral Salt Wasting Syndrome (CSWS)

1. Etiology is largely unknown, but speculation is typically focused on the increased secretion of natriuretic peptides, causing loss of sodium at the renal distal tubules.
2. Typical causes include TBI, SAH, and brain tumor.
3. Fludrocortisone 0.1–0.4 mg/day may be helpful in reducing sodium loss in CSWS (Arch Intern Med 2008;168:325-6).

I. Considerations for Rapid Correction of Hyponatremia

1. Recommended increase in serum sodium concentration is 0.5 mEq/L/hour.
2. Patients with chronic hyponatremia may need to be corrected more slowly because of the equilibration of brain electrolytes with chronic hyponatremic state (N Engl J Med 2000;342:1581-9).
3. Patients with acute hyponatremia may tolerate quicker correction.

$$\text{Na requirement (mmol)} = \text{total body water (0.6 x kg)}^a \times (\text{desired Na} - \text{current Na})$$

$$\text{Infusion rate (mL/hr)} = (\text{Na requirement} \times 1000) / (\text{infusion Na concentration} \times \text{time})$$

Figure 1. Common equations used for sodium correction in hyponatremia (N Engl J Med 2000;342:1581-9)

^a0.6 for men, 0.5 for women; infusion Na concentration in millimoles per liter and time in hours

4. Quicker correction in patients with severe symptoms (coma, seizures) may be prudent – Up to 1–2 mEq/L/hour for the first few hours.
5. Too rapid correction of serum sodium may result in central pontine myelinolysis; a routine approach should be to limit sodium increase to 12 mEq/L in the first 24 hours (Intensive Care Med 2014;40:320-31).

II. HYPERNATREMIA

A. Epidemiology

1. Hypernatremia (sodium greater than 150 mEq/L) is also common in patients with neurological injury.
2. SAH up to 22%
3. TBI up to 21%

B. Diagnosis/Pathophysiology: Laboratory tests (serum sodium) are needed to diagnose hypernatremia. Urine sodium, urine osmolality, urine volume, and serum osmolality may also be helpful in determining the specific pathogenesis.

C. Typical Causes

D. Consideration of Iatrogenic Hypernatremia Hypernatremia may be associated with increased acute kidney injury or other complications (Neurocritical Care 2015;22:184-191)

- E. Diabetes insipidus
 - 1. Decreased secretion of ADH or vasopressin results in decreased retention of water at the renal distal tubules.
 - 2. Characterized by voluminous (greater than 250 mL/hour), dilute urine output
- F. Treatment
 - 1. Hypotonic solutions for free-water replacement
 - a. Dextrose 5%–water
 - b. 0.45% sodium chloride
 - c. Water supplementation orally or per tube
 - 2. Vasopressin analogs
 - a. Supplementation of ADH to normal functional levels
 - b. Titrate therapy to normalized urine output, serum sodium correction, and urine-specific gravity.
 - c. Desmopressin
 - i. Intravenously or subcutaneously: 0.5–4 mcg every 8–12 hours (usual starting dose 1–2 mcg)
 - ii. Intranasally: 10–40 mcg/day divided into two or three doses (usual starting dose 10 mcg)
 - iii. Orally: 50–800 mcg divided into two doses (usual starting dose 50 mcg)
 - iv. May be dosed as needed depending on initial laboratory values
 - d. Patients after pituitary removal may more commonly require long-term therapy.
 - 3. Arginine vasopressin – Continuous infusion 1–15 units/hour (usual starting dose 1 unit/hour; titrate to urine output)
 - 4. Considerations for rapid correction of hypernatremia
 - a. Recommended decrease in serum sodium concentration is around 0.5 mEq/L/hour.
 - b. Too rapid correction of serum sodium may result in cerebral edema.
 - c. In general, neurocritical care patients should receive minimal amounts of dextrose or free water–containing fluids to avoid the risk of cerebral edema.

III. STATUS EPILEPTICUS

- A. Epidemiology – Accounts for 150,000 admissions in the United States annually
- B. Status Epilepticus – Continuous seizures for 5 minutes or more OR intermittent seizures with no regaining of consciousness in between for more than 5 minutes (N Engl J Med 1990;323:497-502)
- C. Refractory Status Epilepticus – Status epilepticus that persists after standard treatment (e.g., a benzodiazepine [emergency therapy] followed by another antiepileptic drug [AED] [urgent therapy])
- D. Super-Refractory Status Epilepticus – Seizures continuing despite adding additional AEDs and/or after initiating continuous infusion anesthetic agents
- E. Diagnosis/Pathophysiology – Diagnostic tests
 - 1. Laboratory tests often show electrolyte abnormalities (particularly Na, magnesium, and phosphorus).
 - 2. Electroencephalogram (EEG) monitoring is necessary to identify and characterize seizures.
 - a. Continuous monitoring is preferred in status epilepticus patients to capture intermittent or fluctuating seizure patterns (Neurocrit Care 2012;17:3-23)

- b. Typical recommended duration is at least 48 hours, and monitoring should be initiated as soon as possible after suggestion or diagnosis of seizure.

F. Causes

Table 3. Typical Etiologies of Status Epilepticus

Cause of Status Epilepticus	Approximate % of Patients
Epilepsy	33–55
Miscellaneous	12–24
Stroke	14–22
AED nonadherence	20
Drug withdrawal	10–14
Brain tumor	10
Metabolic	10
Traumatic brain injury	7
Drug toxicity	5
CNS infection	3

AED = antiepileptic drug; CNS = central nervous system.

G. Clinical Impact

1. Mortality rate ranges from 9% (primarily in patients with preexisting epilepsy/AED nonadherence) to 30% (in patients with a concomitant pathology such as TBI or stroke).
 - a. Mortality in nonconvulsive status epilepticus is about double that in seizures that are more overt.
 - b. Older adults have a higher mortality rate.
2. Discharge disposition: 14%–18% of patients presenting to the ED in status epilepticus ultimately have a neurological deficit.

H. Agent Selection (Neurocrit Care 2012;17:3-23. Epilepsy Currents 2016;16:48-61.)

1. First-line [emergent therapy]
 - a. Benzodiazepine therapy preferred
 - b. Lorazepam 0.1 mg/kg intravenously (max 4 mg/dose) OR
 - c. Midazolam 5–10 mg intramuscularly
2. Second-line therapy [urgent]
 - a. Typically, initiate an AED after benzodiazepine therapy if seizures persist or if a maintenance therapy must be started to prevent future seizures.
 - b. Valproate 20–40 mg/kg intravenously
 - c. (Fos)Phenytoin 18–20 mg/kg intravenously
 - d. Phenobarbital 20 mg/kg intravenously
 - e. Levetiracetam 1–3 g intravenously
3. Third-line therapy [refractory]
 - a. If seizures persist after first- and second-line therapy, refractory status epilepticus should be treated aggressively and in a timely manner.
 - b. Several AEDs are options for refractory status epilepticus, though limited data exist supporting any one agent or approach more than another.
 - c. Valproate 20–40 mg/kg intravenously (if not already given)
 - d. Midazolam high-dose infusion 0.5–2 mg/kg/hour (target burst suppression)

- e. Pentobarbital infusion (loading dose about 25 mg/kg total, continuous infusion 1–3 mg/kg/hour [target burst suppression])
- f. Propofol infusion 20 mcg/kg/minute (target burst suppression)
- g. Lacosamide 200–400 mg intravenously
- h. Topiramate 200–400 mg orally/nasogastrically
- i. Other AEDs listed earlier if not already given

I. Monitoring

1. Continuous EEG monitoring is necessary for all patients with SE.
2. Proactive monitoring of serum concentrations typically necessary for agents such as phenytoin and valproic acid to ensure adequate concentrations and mitigate risk of toxicity.

Table 4. Characteristics of Agents for Status Epilepticus

Antiepileptic Drug	Dosing	Common Adverse Effects	Considerations
Lorazepam	0.1 mg/kg IV (slow IV push); typically up to 8 mg total (max 4 mg/dose)	Sedation, hypotension	IV formulation contains propylene glycol
Midazolam intermittent	5–10 mg IM	Sedation, hypotension	Short duration with IV bolus
Diazepam	0.15 mg/kg IV (slow IV push); typically up to 10 mg total	Sedation, hypotension	IV formulation contains propylene glycol
Fosphenytoin	18–20 mg PE/kg IV (not to exceed 150 mg PE/min); may also give IM (if routine dosing)	Hypotension, arrhythmia	Several drug-drug interactions
Phenytoin	18–20 mg/kg IV (not to exceed 50 mg/min)	Hypotension, arrhythmia, phlebitis, purple glove syndrome	Several drug-drug interactions, IV formulation contains propylene glycol and ethanol
Valproic acid	20–40 mg/kg IV (not to exceed 6 mg/kg/min)	Hyperammonemia	Many drug-drug interactions, avoid in patients with TBI
Levetiracetam	1–3 g IV (not to exceed 5 mg/kg/min)	Sedation/paradoxical excitation, irritability	Renally eliminated, limited drug-drug interactions
Lacosamide	200–400 mg IV (typically for 15–30 min)	Dizziness, bradyarrhythmia	Limited drug-drug interactions
Topiramate	PO/enteral loading dose of 200 - 400 mg BID to QID x 2 days, tapering by 200 mg/day every 2 days	Metabolic acidosis	No IV formulation currently available
Phenobarbital	20 mg/kg (not to exceed 100 mg/min)	Sedation, hypotension, respiratory depression	IV formulation contains propylene glycol
Pentobarbital	10 mg/kg (typically for 15–30 min, depending on blood pressure); give additional 5- to 10-mg/kg boluses to full loading dose of 25–30 mg/kg; 1- to 5-mg/kg/hr infusion	Sedation, hypotension, respiratory depression, constipation, cardiac depression, immunosuppression	IV formulation contains propylene glycol; target is typically burst suppression; several drug-drug interactions

Table 4. Characteristics of Agents for Status Epilepticus (*continued*)

Antiepileptic Drug	Dosing	Common Adverse Effects	Considerations
Midazolam high-dose infusion	0.2 mg/kg bolus; 0.05–2 mg/kg/hr	Sedation, hypotension, respiratory depression	Potential tachyphylaxis, target is typically burst suppression
Propofol	1–2 mg/kg bolus; 20–200 mcg/kg/min, titrate by 5 mcg/kg/min	Sedation, hypotension, respiratory depression, propofol infusion syndrome	Target is typically burst suppression; provides 1.1 kcal/mL
Ketamine	0.5–3 mg/kg bolus; 0.5–10 mg/kg/hr	Excitation, hypertension, possible neurotoxicity, hallucinations	May be more effective in prolonged refractory status epilepticus

BID = twice daily; IM = intramuscular(ly); PE = phenytoin equivalents.

Patient Case

1. A 37-year-old man is admitted to the ICU after sustaining a traumatic subdural hematoma. On hospital day 2, his GCS score falls from E3-M6-V1T to E1-M5-V1T over 10 minutes, and his nurse notices facial twitching. An EEG is ordered. Current medications include fosphenytoin 200 mg phenytoin equivalents (PE) intravenously every 12 hours (6 mg PE/kg/day), famotidine 20 mg intravenously every 12 hours, heparin 5000 units subcutaneously every 8 hours, docusate 250 mg nasogastrically twice daily, and a supplemental vitamin infusion for potential alcohol withdrawal. Which is the best acute therapy to treat this patient's suspected seizure activity?
 - A. Fosphenytoin 20 mg PE/kg intravenously x 1
 - B. Valproic acid 20 mg/kg intravenously x 1
 - C. Lorazepam 4 mg intravenously x 1
 - D. Levetiracetam 1 g intravenously x 1

IV. CENTRAL NERVOUS SYSTEM INFECTION: INTRAVENTRICULAR ANTIBIOTIC ADMINISTRATION

- A. Case selection
 1. Recommended in adult patients with CSF shunt or ventriculostomy infections for difficult-to-eradicate pathogens or for patients who cannot undergo the surgical component of therapy
 2. Not recommended in neonatal or infant central nervous system (CNS) infection cases
- B. Appropriate dosing
 1. Intravenous plus intraventricular is probably superior to intravenous or intraventricular alone.
 2. Use preservative-free formulations.
 3. Do not use diluents containing dextrose.
 4. Do not use medications known to lower seizure threshold.
 5. Daily dosing is usually necessary; may need to adjust according to the amount of CSF drainage from external ventricular drain.

Table 5. Various Antimicrobials and Doses for Intraventricular Administration

Antimicrobial	Daily Dose/Volume (adults)	Approximate Osmolality (mOsm/kg)	Common Adverse Effects
Vancomycin	10–20 mg/1 mL NS	291	Headache, mental status changes, possible hyponatremia
Gentamicin	4–8 mg/1 mL NS	293	Seizures
Tobramycin	4–8 mg/1 mL NS	283	Seizures
Amikacin	30 mg/1 mL NS	383	Seizures
Polymyxin B	5 mg/1 mL NS	10	Hypotonia, seizures, meningeal inflammation
Colistimethate	10 mg/3 mL NS	367	Meningeal inflammation
Amphotericin B deoxycholate	0.5 mg/3 mL SWI	256 (in dextrose 5%)	Nausea, vomiting

NS = normal saline; SWI = sterile water for injection.

Pharmacotherapy 2009;29:832-45

V. INTRACRANIAL PRESSURE TREATMENT

A. General Concepts

1. Elevated ICP decreases tissue perfusion and tissue oxygenation and worsens neurological outcome.
2. Monro-Kellie doctrine: ICP equals cerebral blood volume (10%) plus CSF (10%) plus brain tissue (80%). Each of the therapies targeted at decreasing ICP acts on one or more of these components.

B. Treatment Thresholds

1. Recommendations are to treat sustained ICP greater than 20 mm Hg as measured by external ventricular drain, intraparenchymal catheter, or bolt.
2. Specific threshold may have interpatient variability.

C. Treatment Strategies (Neurocrit Care 2015 DOI 10.1007/s12028-015-0168-z)

1. Tier 0: Standard care, elevate head of bed to > 30 degrees
2. Tier 1: Osmotherapy, CSF drainage, correct Na concentrations, decrease PaCO₂ (32-35)
3. Tier 2: Na correction, sedation, decompressive surgery
4. Tier 3: Pentobarbital, hypothermia

D. Osmotherapy

Table 6. Comparison of Osmotherapy Agents

	Mannitol	Hypertonic Saline
Mechanism of action	Acute increase in cerebral blood flow results in cerebral vasoconstriction (because of autoregulation), leading to decreased cerebral blood volume Increase in serum osmolality creates osmotic gradient to pull extracellular fluid from brain Osmotic diuretic	Acute increase in cerebral blood flow results in cerebral vasoconstriction (because of autoregulation), leading to decreased cerebral blood volume Increase in serum osmolality creates osmotic gradient to pull extracellular fluid from brain
Typical dose	0.25–1 g/kg for 15 min (0.2-micron filter) Up to 1.6 g/kg if acute herniation	3%: 2.5–5 mL/kg for 15 min 7.5%: 1–2 mL/kg for 15 min 23.4%: 30 mL over 15 min
Monitoring values	Serum: Osmolality, Na, creatinine, K, osmolar gap Urine: Urine output	Serum: Osmolality, Na, creatinine, K
Adverse effects	Hyper/hyponatremia Hypokalemia Renal failure Hypovolemia Rebound cerebral edema (?)	Hypernatremia Hypokalemia Hyperchloremic acidosis Renal failure Central pontine myelinolysis (?)

1. Monitoring osmolar changes with osmotherapy
2. Traditional serum osmolality threshold was 320 mOsm/L when using mannitol.
 - a. Theory was that serum osmolality values greater than 320 were associated with renal dysfunction.
 - b. Osmolar gap appears to be a more appropriate and accurate method of evaluating renal dysfunction risk with mannitol.
 - c. Approximates the mannitol concentration
 - d. Goal osmolar gap is less than 20.
 - e. Calculation of osmolar gap

$$\text{Osmolar gap} = \text{Measured osmolality} - \text{Estimated osmolality}$$

$$\text{Osmolar gap} = \text{Measured osmolality} - [(2 \times \text{Na}) + (\text{BUN}/2.8) + (\text{glucose}/18)]$$

E. Metabolic Suppression

1. Mechanism of action: Suppression of electrical activity in brain (i.e., “burst suppression”) causes a reduction in cerebral metabolic rate of oxygen (CMRO₂).
2. Reduced CMRO₂ leads to decreased cerebral blood volume.
3. Pentobarbital sodium usually used in the United States (thiopental = Europe)
4. Risks may outweigh benefit, at least for certain conditions such as large hemispheric infarction.
5. Typical dose
 - a. 25–30 mg/kg intravenous loading dose. Usually given as 10 mg/kg x 1 dose, followed by 5 mg/kg every hour x 3 or 4 doses to avoid hypotension with large bolus dose
 - b. 1- to 5-mg/kg/hour infusion after loading dose

6. Titration
 - a. Titrated to goal ICP (usually less than 20 mm Hg)
 - b. Burst suppression (target usually is 2–5 bursts/minute) is surrogate for need of additional pentobarbital doses.
 - c. Bolus dose is required concomitantly with infusion titration because of its long terminal half-life and rapid redistribution out of the CNS.
 7. Monitoring
 - a. ICP
 - b. EEG and burst occurrence per minute
 - c. Serum concentrations do not correlate well with ICP response and should not be used to titrate infusion. May be useful when therapy has been discontinued as part of brain death examination (to rule out continued intoxication from pentobarbital).
 8. Adverse effects
 - a. Hypotension
 - i. Propylene glycol diluent
 - ii. Direct vasodilator
 - iii. Reduction in sympathetic tone because of metabolic suppression
 - iv. Cardiac depressant (particularly with high doses and duration greater than 96 hours)
 - b. Decreased GI motility
 - i. Difficulty with enteral nutrition
 - ii. Caloric needs are usually around 80%–90% of basal energy needs, so a lower flow rate for enteral nutrition is permissible.
 - iii. Ideally, would use a low-residual nutrition product because stooling is rare on pentobarbital infusion
 - c. Infection (particularly pneumonia)
 - d. Immunosuppression
 - e. Withdrawal seizures may be possible.
- F. Sedation – Mechanism of action: Decreased systemic oxygen delivery needs; reduced coughing, reduced agitation, decreased cerebral metabolic rate of oxygen
1. Propofol is typically preferred sedative – Quick onset, short acting, less accumulation with prolonged duration
 2. Benzodiazepines
 - a. Not preferred because of duration of action
 - b. Also associated with delirium and cognitive impairment
 - c. Potential for withdrawal effect, seizures
 3. Dexmedetomidine
 - a. Little evidence to support use in neurocritical care
 - b. Hypotension risk may be deleterious in specific patient types (e.g., aneurysmal SAH/vasospasm, TBI, SCI).
 - c. May be particularly helpful in patients with paroxysmal sympathetic hyperactivity
- G. Neuromuscular Blockade
1. Mechanism of action: Decreased systemic oxygen delivery needs; reduced coughing
 - a. Neuromuscular blockers have no intrinsic value for reducing ICP, but they may be helpful in select patients with specific issues that exacerbate ICP elevations.
 - i. Prevention of cough, ventilator dyssynchrony (both increase ICP)
 - ii. Control Pco_2 (increased Pco_2 may also raise ICP)

- b. Prevention of shivering during hypothermia
- c. Reduces intrathoracic pressure
- d. May be essential in patients requiring high positive end-expiratory pressure (increased intrathoracic pressure may increase ICP).
- 2. Various agents may be useful.
 - a. Depends on patient organ function, prescriber preference
 - b. Vecuronium (particularly if normal organ function)
 - c. Cisatracurium (particularly if end-organ dysfunction)
 - d. Avoid atracurium, if possible, because of hypotension risk.
 - e. Monitor by train-of-four (goal 1-2/4 twitches with no clinical evidence of neuromuscular function [e.g., over-breathing the ventilator rate]).

Patient Case

2. A 25-year-old man is admitted after a two-story fall from a ladder. The initial CT scan of his brain reveals a large right temporal subdural hematoma, an overlying skull fracture, and a left temporal contusion. His post-resuscitation GCS is E1-M4-V1T. An ICP monitor is placed with an opening pressure of 32 mm Hg; the CPP is 53 mm Hg. Serum laboratory values include Na 141 mEq/L, K 3.6 mEq/L, BUN 8 mg/dL, SCr 1.1 mg/dL, glucose 178 mg/dL, WBC 14.8×10^3 cells/mm³, pH 7.46, and Pco₂ 34. Which is the best initial therapy for this patient's elevated ICP?
 - A. Mannitol 20% 1 g/kg intravenously x 1
 - B. 23.4% sodium chloride 1 mL/kg intravenously x 1
 - C. Pentobarbital 10 mg/kg intravenously x 1
 - D. Midazolam 10 mg intravenously x 1

H. TBI Guidelines (J Neurotrauma 2007;24:S1-S95)

1. Seizure prophylaxis
 - a. Recommended as an option for prevention of early posttraumatic seizures (first 7 days after event)
 - b. Phenytoin most commonly recommended agent (because of support for use from prospective clinical trials) (N Engl J Med 1990;323:497-502)
 - c. Levetiracetam also commonly used, despite paucity of data
 - d. Valproic acid is as effective as phenytoin, but a trend toward increased mortality was observed in a prospective clinical trial, so it is not a first-line agent (J Neurosurg 1999;91:593-600).
 - e. Use of AEDs for prevention of late seizures (after 7 days) has not been proved to be effective (not recommended).
2. CPP modulation
 - a. CPP = mean arterial pressure (MAP) – ICP.
 - b. Surrogate for global cerebral perfusion
 - c. Recommended goal is 60–70 mm Hg.
 - d. Ideal CPP may have interpatient variability because of the patient's medical history and specific characteristics of the TBI.
 - e. Patients with a history of poorly treated hypertension may require higher CPP; monitor neurological status closely.
3. Fluid resuscitation with or without vasopressor therapy
 - a. Norepinephrine or phenylephrine is the preferred vasopressor for this indication.
 - b. Routine targeting of CPP greater than 80 mm Hg is no more effective than targeting of lower CPP and may result in increased complications (acute respiratory distress syndrome) and pulmonary edema.

-
4. Supportive care – Venous thromboembolism (VTE) prophylaxis
 - a. Patients with TBI have an increased risk of VTE because of:
 - i. TBI-related coagulopathy
 - ii. Delay in initiation of pharmacologic VTE prophylaxis
 - iii. Immobility
 - iv. Concomitant injuries (in the case of polytrauma)
 - b. Mechanical prophylaxis should be initiated as soon as possible.
 - c. Pharmacologic prophylaxis should be initiated after intracranial bleeding is stabilized.
 - i. Typically, 24–48 hours after event
 - ii. May depend on coagulopathy on admission, extension of bleeding on CT scan, and other factors
 - iii. Unfractionated heparin or low-molecular-weight heparin (LMWH) may be used for pharmacologic prophylaxis. LMWH may be preferred in patients with polytrauma, particularly long bone or pelvic fractures and in patients with SCI.
 5. Nutrition support
 - a. Initiating nutrition support within 48 hours improves immune competence and may improve neurological outcome (Crit Care Med 1999;27:2525-31)
 - b. Gastric feeding is not well tolerated in patients with TBI, particularly during the first 5–7 days and particularly in those with elevated ICP (causes decreased gastric motility). Post-pyloric feeding access should be established as soon as possible.
 - c. Metabolic needs are elevated after TBI (typically proportional to the severity of injury).
 - i. Patients with TBI typically require 120%–160% of basal metabolic needs.
 - ii. Metabolic cart/direct calorimetry can be used to better evaluate caloric needs.
 6. Prevention of stress-related mucosal bleeding
 - a. Patients with TBI have an increased risk of stress-related mucosal bleeding.
 - i. Hypotension associated with TBI or trauma
 - ii. Hypersecretion of acid associated with neurological injury (Cushing ulcers)
 - iii. Potential for coagulopathy
 - iv. Need for mechanical ventilation
 - b. Almost all patients with severe TBI should receive prophylaxis for stress-related mucosal bleeding.
 - i. Histamine-2 receptor antagonists (H₂RAs) have traditionally been the preferred agents.
 - ii. Proton pump inhibitors (PPIs) also raise gastric pH and permit hemostasis in areas of gastritis.
 - iii. Recent meta-analyses have suggested PPIs are superior to H₂RAs, but a well-powered clinical trial has not been completed in the ICU population or in the neuro ICU population.
 - iv. Which agent to select may depend on:
 - (a) Medications taken at home before admission
 - (b) Prescriber preference
 - (c) Presence of GI bleeding on admission
 - (d) Risk of Clostridium difficile infection
 7. Glycemic control
 - a. Hyperglycemia is associated with increased mortality in TBI.
 - b. Potential mechanisms
 - i. Glucose toxicity in neurons
 - ii. Surrogate for severity of injury
 - iii. Exacerbation of cerebral edema
 - c. Avoid administering dextrose 5% and other hypotonic glucose-containing fluids.
 - d. Glycemic goals
 - i. Prevent hyperglycemia (greater than 180 mg/dL)
 - ii. A range of 140–180 mg/dL seems reasonable.
-

- iii. Caution should be exercised with glucose values in low-normal range because of risk of hypoglycemia.
- iv. Hypoglycemia is associated with a worse outcome in TBI.
 - (a) Glucose obligate substrate for neurons
 - (b) Threshold for glucose needs may be altered in TBI.
 - (c) May increase seizure risk
- 8. Steroids
 - a. No role for high-dose methylprednisolone in the treatment of inflammation or edema associated with TBI.
 - b. Large, prospective, randomized clinical trial showed increased mortality in steroid group compared with placebo (CRASH) (Lancet 2005;365:1957-9)
- 9. Pharmacokinetic alterations
 - a. Altered volume of distribution: Patients with TBI have increased volume of distribution because of the following:
 - i. Fluid resuscitation
 - ii. Transient increased permeability of blood-brain barrier
 - b. Hepatic metabolism induction
 - i. TBI increases hepatic metabolic capacity (extent to which is likely proportional to severity of injury).
 - ii. Results in more effective clearance of hepatically metabolized medications
 - iii. Increased dosing requirement for commonly used agents such as phenytoin, midazolam
 - iv. Induction subsides over time (usually 1–3 months, but varies by patient).
 - v. Hypothermia during TBI may also reduce the induction of hepatic metabolism/cause metabolic rate of medications to be less than baseline.
 - c. Augmented renal clearance
 - i. Increase in glomerular filtration rate
 - ii. Fluid resuscitation
 - iii. Increased endogenous catecholamines and glucocorticoid response
 - iv. Results in more effective clearance of renally eliminated medications
 - v. Increased dosing requirement for commonly used agents such as vancomycin, aminoglycosides, β -lactams
 - vi. Augmented renal clearance tends to subside over time (usually after first 7 days, but varies by patient).

VI. PAROXYSMAL SYMPATHETIC ACTIVITY (I.E., “BRAIN STORMING”)

- A. Epidemiology
 - 1. About 8%–10% incidence in survivors of acquired brain injury
 - 2. Commonly associated with TBI (specifically diffuse axonal injury), but may occur with other CNS insults
- B. Diagnosis
 - 1. Typically, four or more symptoms (J Neurotrauma 2014;31:1515-20)
 - 2. Fever
 - 3. Tachycardia

4. Hypertension
5. Tachypnea
6. Dyspnea
7. Diaphoresis
8. Muscle rigidity
9. Common triggers
 - a. Pain
 - b. Bladder distension
 - c. Turning
 - d. Tracheal suctioning
 - e. Typically unprovoked (hence “paroxysmal”)
10. Pathophysiology largely unknown, but thought to be caused by somatosympathetic activation and heightened activity of brain stem after brain injury

Table 7. Preventive and Abortive Therapies for Paroxysmal Sympathetic Activity

Preventive Therapies	Abortive Therapies
Baclofen IT (titrated according to patient response)	Baclofen IT (titrated according to patient response)
Bromocriptine 1.25 mg PO/enterally twice daily (up to 40 mg/day)	Clonidine 0.1–0.3 mg PO/enterally three times daily
Clonidine 0.1–0.3 mg PO/enterally three times daily	Dantrolene 0.25–2 mg/kg IV every 6–12 hr
Gabapentin 100–300 mg three times daily (up to 4800 mg/day)	Dexmedetomidine
Propranolol 20–60 mg PO/enterally every 4–6 hr	Diazepam 5–10 mg IV
	Fentanyl 25–100 mcg IV
	Morphine 2–8 mg IV
	Propranolol 20–60 mg PO/enterally every 4–6 hr

Curr Treat Options Neurol 2008;10:151-7

VII. ACUTE ISCHEMIC STROKE

A. Epidemiology

1. Fifth leading cause of death and No. 1 cause of disability in the United States, with around 750,000 strokes in the United States annually
2. 85% of strokes in the United States are ischemic in nature.

B. Diagnosis/Pathogenesis

1. Diagnostic tests
 - a. Neurological examination
 - b. Vital signs
 - c. NIH Stroke Scale (greater than 25 is severe, range 1–42)
 - d. Imaging and other tests (Stroke 2013;44:870-947)
 - e. Noncontrast CT scan or magnetic resonance imaging (MRI) of the brain (to rule out bleeding)
 - f. CT angiography (if intra-arterial thrombolysis or thrombectomy is contemplated)
 - g. CT or MRI perfusion and diffusion imaging may be considered for patients outside the thrombolysis window.
 - h. Chest radiography (if lung disease is suspected)
 - i. Lumbar puncture (if SAH is suspected and CT scan is negative for blood)

- j. EEG (if seizures are suspected)
- 2. Laboratory tests
 - a. Blood glucose
 - b. INR, activated partial prothrombin time (consider thrombin time, anti-factor Xa [anti-Xa] activity for direct oral anticoagulants)
 - c. Complete blood cell count (CBC)
 - d. Tests for hypercoagulable state
- C. Causes
 - 1. Cardioembolic (29.1%)
 - 2. Large-artery atherosclerosis (16.3%)
 - 3. Lacunar infarcts (15.9%)
 - 4. Unknown (36.1%)
 - 5. Other (2.6%)
- D. Treatment Considerations (Stroke 2013;44:870-947)
 - 1. Thrombolysis: Alteplase 0.9 mg/kg (maximum 90 mg) within 4½ hours of symptom onset; 10% of total dose as intravenous bolus, followed by 90% as 60-minute intravenous infusion

Table 8. Typical Inclusion/Exclusion Criteria for IV Alteplase for Ischemic Stroke (exclusions are primarily based on the risk of systemic bleeding or hemorrhagic conversion of stroke)

Patient Selection Criteria	Contraindications
Onset of symptoms < 4½ hr from drug administration	Recent intracranial or intraspinal surgery
Baseline CT head excludes intracerebral hemorrhage (ICH) or other risk factors	Head trauma or stroke < 3 mo
Age > 18 yo	Active internal bleeding
<i>Vital signs and laboratory values:</i>	Symptoms suggest SAH
INR ≤ 1.7	Any history of ICH
Platelet count ≥ 100,000/mm ³	Intracranial neoplasm, arteriovenous malformation, or aneurysm
[note: recommendations are now to not delay thrombolysis in the case where INR and platelet count is unknown and there is no discernable reason to suspect an abnormal test]	Infective endocarditis
Blood glucose >50 mg/dL	Arterial puncture at noncompressible site < 1 wk
Blood pressure control (SBP < 185 mm Hg, DBP < 110 mm Hg) before alteplase administration	Acute bleeding diathesis
	Current use (<48 hrs) of novel anticoagulant agents with evidence of elevated sensitive laboratory tests
	<i>Additional exclusion criteria for 3- to 4½-hr window:</i>
	NIHSS > 25
	Current treatment with PO anticoagulants (regardless of INR)
	Evidence of ischemic injury > 1/3 of MCA territory

DBP = Diastolic blood pressure; NIHSS = NIH Stroke Scale (score).

Stroke 2013;44:870-947; N Engl J Med 2008;359:1317-29. Stroke 2016;47:581-641.

- 2. Permissive hypertension
 - a. Reduction in blood pressure outside thrombolysis or recanalization is reasonable within the first 24 hours after onset of stroke.
 - b. Cautiously to avoid hypotension or underperfusion of infarcted area (less than 15% blood pressure lowering)

- c. Resumption of home blood pressure medications is reasonable 24 hours after the onset of stroke.
- d. Recommended to treat blood pressure if it exceeds SBP greater than 220 mm Hg or diastolic blood pressure (DBP) greater than 120 mm Hg
3. Seizure prophylaxis. Use of AEDs for seizure prophylaxis is not indicated after ischemic stroke.
4. Mechanical thrombectomy and neuroendovascular interventions for ischemic stroke
 - a. Neuroendovascular devices may be used to remove or disrupt clot to facilitate recanalization.
 - b. No difference in safety outcomes when comparing usual care with usual care plus mechanical thrombectomy

Table 9. Overview of Mechanical Thrombectomy Studies in Patients with Ischemic Stroke

Study	Groups Compared	Efficacy
MR CLEAN	tPA ± stent retriever or intra-arterial thrombolytic (within 6 hr of symptom onset)	Increased likelihood of favorable outcome at day 90 (OR 1.67; 95% CI, 1.2–2.3)
EXTEND-IA	tPA ± stent retriever (within 6 hr of symptom onset)	Increased likelihood of independence at day 90 (adjusted OR 4.2; 95% CI, 1.2–12)
SWIFT PRIME	tPA ± stent retriever (within 6 hr of symptom onset)	Increased likelihood of independence at day 90 (RR 1.7; 95% CI, 1.2–2.3)
ESCAPE	tPA ± stent retriever (within 12 hr of symptom onset)	Increased likelihood of mRS improvement by 1 point (OR 2.6; 95% CI, 1.7–3.8) and lower mortality (OR 0.5; 95% CI, 0.3–0.8)

tPA = tissue plasminogen activator; mRS = modified Rankin Scale.

Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015;372:1009-18; Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;372:1019-30; Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med* 2015;372:2285-95.

E. Secondary prevention

1. Initiation of aspirin (325 mg x 1; then 81–325 mg/day), high-intensity statin, and intensive blood pressure regimen is necessary
 - a. Ideally, as soon as feasible after the onset of stroke
 - b. Aspirin should not be initiated within 24 hours of alteplase.
2. Control/modification of other disease states is often necessary.
3. Hypertension: Typical blood pressure goal is less than 140/90 mm Hg.
4. Atrial fibrillation
 - a. Rate or rhythm control
 - b. Anticoagulation (warfarin, direct oral anticoagulants)
 - c. Typically, anticoagulant therapy is delayed until 5–14 days after stroke to reduce the risk of hemorrhagic conversion.
 - d. Avoid using loading doses of warfarin.
5. Carotid artery stenosis: Stent versus endarterectomy (usually for patients with greater than 70% blockage and/or clinically evident symptoms)
6. Intracranial artery stenosis
7. Diabetes mellitus
8. Inherited or acquired hypercoagulable states

VIII. INTRACEREBRAL HEMORRHAGE

- A. Epidemiology. Around 50,000 cases in the United States annually
 1. Diagnosis/pathogenesis
 - a. Neurological examination
 - b. Vital signs
 - c. NIH Stroke Scale and/or GCS score
 2. Imaging and other tests
 - a. CT or MRI scan of the brain
 - b. CT angiography or contrast-enhanced CT (to help identify patients at risk of hematoma expansion and to evaluate for underlying structural lesions)
 - c. Medication history to identify agents that might produce coagulopathy
 - d. Laboratory tests
 - e. Blood glucose
 - f. INR
 - g. CBC
- B. Causes
 1. Chronic/poorly treated hypertension
 2. Oral anticoagulant use
 3. Cocaine/other stimulant use
 4. Ischemic stroke
 5. Chronic alcohol intake
 6. Brain tumor
 7. Arteriovenous malformation
 8. Amyloid angiopathy
- C. Clinical Impact – Death or major disability occurs in around 50% of patients.
- D. Treatment Considerations (Stroke 2010;41:2108-29)
 1. Coagulopathy reversal
 2. Prompt reversal is necessary. Reversal of laboratory values does not confirm hemostasis, especially with the newer oral anticoagulants.

Table 10. Anticoagulant Reversal Options

Anticoagulant	Reversal Agent and Dose	Adverse Effects
Warfarin	4f-PCC 25 units/kg (INR < 4), 35 units/kg (INR 4–6) or 50 units/kg (INR > 6) + vitamin K 10 mg IV Alternative: FFP 10–15 mL/kg + vitamin K 10 mg IV	Thrombosis, anaphylactoid reaction (vitamin K), pulmonary edema, or transfusion-related reaction (FFP)
PO factor Xa inhibitors ^a	4f-PCC 25–50 units/kg or activated 4f-PCC (FEIBA) 25–50 units/kg	Thrombosis; limited data for reversal, especially with FEIBA
PO DTIs	Idarucizumab (Praxbind) 5 g IV x 1; repeat dose may be necessary in patients with high DTI exposure or poor renal function If hemostasis is not achieved, consider 4f-PCC 25–50 units/kg or activated 4f-PCC (FEIBA) 25–50 units/kg	Idarucizumab approved in late 2015 – antibody specifically for dabigatran Thrombosis; limited data analyses show minimal efficacy for reversal with PCC and FEIBA

Table 10. Anticoagulant Reversal Options (*continued*)

Anticoagulant	Reversal Agent and Dose	Adverse Effects
PO antiplatelet agents	Platelet infusion (usefulness is uncertain) Does not appear to be beneficial in small, nonoperative, stable ICH	Pulmonary edema or transfusion-related reaction (FFP)
Unfractionated heparin	Protamine (1 mg of protamine for each 100 units of heparin infused within the past 2–3 hr)	Hypotension, hypersensitivity
Low-molecular-weight heparins	Protamine 1 mg for each 1 mg of enoxaparin (within 8 hr of last dose)	Hypotension, hypersensitivity

aReversal options have not been tested in patients with ICH and have variable degrees of coagulopathy reversal in experimental animal and human models.

DTI = direct thrombin inhibitor; 4f-PCC = 4-factor prothrombin complex concentrate; FEIBA = factor eight inhibitor bypassing activity; FFP = fresh frozen plasma.

Neurocritical Care 2016;24:6-46.

E. Blood Pressure Management

1. Prompt control of blood pressure is essential.
2. Historically, caution may have been used in rapidly reducing blood pressure in chronically hypertensive patients because of concerns regarding accommodations in cerebral autoregulation.

Table 11. Intravenous antihypertensive options

Agents	Dose	Considerations
Clevidipine	1-2mg/hr up to 21mg/hr	Half-life < 1min Formulated in lipid emulsion Tubing changes q12h
Esmolol	50mcg/kg/min up to 300mcg/kg/min	Bradycardia Duration 10-20min
Fenoldopam	0.1-1mcg/kg/min	Natriuresis
Hydralazine	10-20mg IV push	Reflex tachycardia Interpatient variability with response
Labetalol	10-20mg IV push or 1-2mg/min infusion	Bradycardia Duration of action 2-4 hours
Nicardipine	2.5-5mg/hr up to 15mg/hr	Duration of action 4-6 hours
Nitroglycerin	5mcg/min up to 200mcg/min	Tachyphylaxis Headache with higher doses More venodilation than arterial
Nitroprusside	0.5-2mcg/kg/min up to 10mcg/kg/min	Cyanide/thiocyanate toxicity with end-organ dysfunction

3. However, recent evidence suggests that the benefit of rapidly reducing the blood pressure (and thus reducing the risk of rebleeding) outweighs any concern for cerebral autoregulation issues and potential for ischemia.
4. INTERACT-2 – Large, prospective, randomized trial that compared levels of blood pressure control within 1 hour (N Engl J Med 2013;368:2355-65). SBP less than 140 mm Hg was as safe and effective as SBP less than 180 mm Hg (and may have had improved functional outcomes).
5. ATACH-2 – Large, prospective, multicenter, open label trial that compared levels of blood pressure control of 110-139 and 140-179 within 4.5 hours of ICH for 24 hours. There were 1000 patients enrolled and more than half were Asian. The trial was stopped early for futility as there was no difference in the primary outcome of death or disability. The intensive control arm had a significantly higher incidence of renal adverse effects (9% vs 4%). (N Engl J Med. 2016;375:1033-1043)

- F. Seizure Prophylaxis. Use of AEDs for seizure prophylaxis is not indicated after intracerebral hemorrhage (ICH).

Patient Case

Questions 3 and 4 pertain to the following case.

A 61-year-old man is admitted with acute onset of difficulty speaking, confusion, and right-sided weakness. His NIH stroke scale score is 20. A CT scan of the head reveals a right parietal ICH. The patient's home medications include hydroxychloroquine, ibuprofen as needed, warfarin, amlodipine, and donepezil. His medical history includes a deep venous thrombosis (1 year ago), hypertension, early dementia, and arthritis. Serum laboratory values include Na 140 mEq/L, K 3.6 mEq/L, BUN 27 mg/dL, SCr 1.8 mg/dL, glucose 289 mg/dL, hematocrit 36.7%, platelet count 245,000/mm³, and INR 2.8. His vital signs include blood pressure 163/101 mm Hg, heart rate 99 beats/minute, Sao₂ 97%, and respiratory rate 20 breaths/minute.

3. Which is the most appropriate initial therapy in addition to vitamin K for this patient's care?
 - A. Reinitiate amlodipine.
 - B. Give 6-pack infusion of platelets.
 - C. Give 4-factor prothrombin complex concentrate (PCC) 25 units/kg intravenously x 1.
 - D. Give recombinant factor VIIa (rfVIIa) 90 mcg/kg intravenously x 1.
4. For this 61-year-old patient with ICH, which is the most appropriate initial antihypertensive therapy?
 - A. Nitroprusside 0.5 mcg/kg/minute infusion to keep SBP less than 140 mm Hg
 - B. Nicardipine 5 mg/hour infusion to keep SBP less than 160 mm Hg
 - C. Labetalol 10 mg intravenously as needed to keep SBP less than 160 mm Hg
 - D. Esmolol 50 mcg/kg/minute infusion to keep SBP less than 180 mm Hg

Questions 5 and 6 pertain to the following case.

A 52-year-old woman is admitted to your ICU after a single-vehicle crash. She has many orthopedic injuries to her lower extremities and a subdural hematoma, which will require an emergency craniotomy for evacuation. Her home medications include metoprolol, rivaroxaban, lisinopril, and atorvastatin. Her medical history is significant for atrial fibrillation. Laboratory values obtained on admission were notable for hematocrit 31.2% and platelet count 577,000 mm³.

5. Which would be the most appropriate laboratory tests to obtain to evaluate the extent of anticoagulation from rivaroxaban?
 - A. INR
 - B. Anti-Xa activity level
 - C. Activated partial thromboplastin time
 - D. VerifyNow PRUtest measurement
6. Which would be the most appropriate therapy to reverse rivaroxaban before the emergency craniotomy for this patient?
 - A. 4-factor PCC 50 units/kg intravenously x 1
 - B. Vitamin K 10 mg intravenously x 1
 - C. Fresh frozen plasma 15 mL/kg intravenously x 1
 - D. rfVIIa 90 mcg/kg intravenously x 1

IX. SUBARACHNOID HEMORRHAGE

- A. Epidemiology
 1. Occurs in around 15 of 100,000 people in the United States
 2. 60%–70% female, typical age 40–60 years
- B. Diagnosis/Pathogenesis:
 1. Serial neurological examination
 2. Vital signs
 3. NIH Stroke Scale and/or GCS

Table 12. SAH Severity Scale Scores

	Score Range	Comments
Hunt and Hess	0 (no rupture) to 5 (moribund)	Best correlated with risk of mortality
World Federation of Neurological Societies (WFNS)	1 (GCS score 15, no deficit) – 5 (GCS score 3–6)	Integrates risk of mortality and motor dysfunction
Fisher	1 (no blood visualized) to 4 (diffuse SAH, ICH, or intraventricular hemorrhage present)	Best correlated with risk of vasospasm

GCS = Glasgow Coma Scale.

- C. Imaging (Stroke 2009;40:994-1025)
 1. CT scan of brain
 2. Lumbar puncture when CT scan of brain is negative for blood
 3. Digital subtraction (“conventional”) angiography
 4. May use CT angiography or magnetic resonance angiography if conventional angiography is not available.
 5. Transcranial Doppler, often daily during peak vasospasm risk period
- D. Medication History – To identify agents that might produce coagulopathy
- E. Laboratory and Other Tests
 1. INR
 2. CBC
 3. Troponin
 4. ECG (electrocardiogram)
 5. Echocardiogram
- F. Causes – Typically caused by cerebral aneurysm
 1. Modifiable risk factors for SAH
 2. Hypertension
 3. Smoking
 4. Illicit drug use
- G. Clinical Impact
 1. Sudden death: Around 20% of patients die before hospitalization.
 2. Vasospasm and delayed ischemic neurological deficits (DINDs)

-
- a. Presence of blood in subarachnoid space elicits a chemical meningitis-type inflammatory response and results in hemolysis of subarachnoid blood.
 - b. Vasospasm (persistent vasoconstriction) occurs, causing a reduction on distal cerebral blood flow.
 - i. Typical course is 3–14 days.
 - ii. Vasospasm risk peaks at around 7–10 days.
 - c. Several mechanisms of pathogenesis
 - i. Inflammatory infiltration
 - ii. Endothelin activation
 - iii. Liberation of hemoglobin results in the scavenging of nitric oxide.
 - d. Vasospasm is one of the main factors resulting in death or disability after acute SAH, aside from initial ictus.
- H. Treatment Considerations (Stroke 2012;43:1711-37)
- 1. Agents for preventing vasospasm or DINDs
 - a. Nimodipine (Br Med J 1989;298:636-42)
 - i. Lipophilic dihydropyridine calcium channel blocker
 - ii. “Cerebrovascular-specific”
 - iii. 60 mg orally or per tube every 4 hours x 21 days
 - iv. Only U.S. Food and Drug Administration (FDA) label-approved medication to reduce DINDs associated with SAH
 - v. Clinical trials did not show a large effect of nimodipine on the occurrence of vasospasm (though the effects of DINDs were still significantly less).
 - vi. Possibly neuroprotective
 - b. Statins
 - i. Preservation of nitric oxide balance as heme is liberated during SAH hemolysis.
 - ii. Phase II data with pravastatin and simvastatin
 - iii. Phase III trial (STASH) did not show benefit of applying statins in aneurysmal SAH (Lancet Neurol 2014;13:666-75; Stroke 2015;46:382-388).
 - iv. Abrupt withdrawal of statins in patients who were taking before SAH may result in a withdrawal effect and increase the risk of vasospasm.
 - c. Others?
 - i. Magnesium – No utility in attaining magnesium concentrations 3–4 mEq/L. Maintaining magnesium at normal concentrations (i.e., preventing hypomagnesemia) is advisable.
 - ii. Clazosentan – No utility in blocking endothelin-1
 - iii. Albumin – Not beneficial and may be associated with an increase in pulmonary edema
 - 2. Treatment of vasospasm
 - a. Intra-arterial therapies (see the following)
 - b. Triple-H therapy (hypertension, hypervolemia, hemodilution)
 - i. No longer recommended in the traditional format. Euvolemia is better than hypervolemia – Similar outcomes in clinical trials, less pulmonary edema
 - ii. Hemodilution has not been shown to be beneficial.
 - iii. Hyperperfusion therapy
 - (a) Better descriptor for the goal of therapy
 - (b) Vasospasm causes distal vasoconstriction to the point of ischemia.
 - (c) Maximizing cerebral blood flow mitigates ischemia.
 - iv. Contemporary therapy includes:
 - (a) Euvolemia
-

- (b) Vasopressors (blood pressure targets are ill defined but are also typically patient and symptom dependent)
 - (c) Inotropes (milrinone)
 - (1) Milrinone may be useful to improve cerebral perfusion, even in the context of normal cardiac output (Neurocritical Care 2012;16:354-362).
- 3. Seizure prophylaxis
 - a. Use of AEDs for seizure prophylaxis is controversial after SAH.
 - b. One small study suggests 3 days of prophylactic phenytoin after aneurysm clipping is helpful in reducing the seizure rate.
 - c. SAH guidelines permit prophylaxis, according to this study.
 - d. Some evidence suggests that phenytoin use in aneurysmal SAH is associated with worse outcomes and increased in-hospital complications.

X. INTERVENTIONAL ENDOVASCULAR MANAGEMENT

- A. Intra-arterial Therapies (Pharmacotherapy 2010;30:405-17)
 - 1. Administration technique
 - 2. Typically administered during cerebral angiography. Catheter advanced to vessels with lesion/vasospasm, and drug is infused locally (“super-selective infusion”)
 - 3. Calcium channel blockers
 - a. Typically used for cerebral vasospasm associated with SAH
 - b. Direct, local infusion typically results in immediate vasodilation.
 - c. Usually effective in proximal and distal vessels

Table 13. Typical Agents for Intra-arterial Use for Cerebral Vasospasm

Agent	Typical Dose	Adverse Effects
Nicardipine	2–10 mg (usually 1–2 mg), up to 5 mg/vessel	Systemic hypotension Increased ICP
Verapamil	1–20 mg (usually 5-10 mg)	Systemic hypotension Bradycardia Increased ICP
Milrinone	8 mg	Systemic hypotension
Papaverine	150–600 mg	Increased ICP Systemic hypotension Neurological deterioration Rebound vasospasm

ICP = intracranial pressure.

- B. Thrombolysis
 - 1. Most often used in patients with ischemic stroke
 - 2. Limited evidence to support combining with intravenously alteplase as a standard of care
 - 3. Current roles
 - a. Combination with mechanical thrombectomy
 - b. Rescue therapy in patients having received intravenously alteplase

- c. Large hemispheric infarction
 - i. Dose is not well defined.
 - ii. Typically applied until thrombus has resolved
 - iii. Alteplase less than 20 mg

Patient Case

Questions 7 and 8 pertain to the following case.

A 49-year-old woman presents to an urgent treatment center with the “worst headache of her life.” She is sent to your ED, where a CT scan of the head reveals a diffuse SAH. The patient takes no home medications and has an insignificant medical history other than a 20 pack-year history of smoking.

7. Which therapy is most appropriate to prevent ischemic complications from SAH?
 - A. Nimodipine for 21 days
 - B. Euvolemia and permissive hypertension for 14 days
 - C. Simvastatin for 14 days
 - D. Aminocaproic acid infusion for 48 hours
8. On hospital day 5, the patient has reduced alertness, and her GCS score decreases by 2 points. The digital subtraction angiography suggests cerebral vasospasm. Which treatment modality is best to initiate first?
 - A. 1 unit of packed RBCs to increase hemoglobin to 10 g/dL
 - B. Norepinephrine 0.05 mcg/kg/minute to increase MAP to 90 mm Hg
 - C. 0.9% sodium chloride boluses to increase central venous pressure to 14 mm Hg
 - D. Milrinone 0.375 mcg/kg/minute infusion to increase cardiac index to 5 L/minute/m²

C. Stent Deployment and Antiplatelet Agents

1. Intracranial stents often deployed in place of coils or to support coils for complex aneurysms
2. Intracranial circulation is different from coronary circulation.
 - a. Blood vessels are generally smaller and more tortuous.
 - b. Flow rate is lower.
 - c. Epithelialization of stent takes longer.
3. Dual antiplatelet therapy is typically used around the time of stent placement.
 - a. Clopidogrel plus aspirin
 - b. Current evidence suggests up to 3 months in duration (not 4 weeks like after percutaneous coronary intervention)
 - c. Platelet testing may be necessary in some individuals to evaluate their pharmacodynamic response to clopidogrel because up to 30% of patients have genetic polymorphisms that result in reduced platelet inhibition.
 - i. VerifyNow and other platelet function assays may be used to evaluate the pharmacodynamic response to clopidogrel
 - (a) Measured in platelet reactivity units (PRU)
 - (b) For clopidogrel VerifyNow testing, “therapeutic” range is not well defined, but consider range of 60-240
 - (1) < 60 associated with more bleeding events
 - (2) 240 associated with more thromboembolic events
 - d. No gold standard for platelet reactivity in this setting

- e. Patients may require higher/additional loading doses of clopidogrel peri-procedurally or if procedural thrombosis occurs.
- f. Prasugrel is not recommended in patients with high on-treatment platelet reactivity because of warnings about use in patients with a history of stroke – Increased bleeding.
- g. Ticagrelor may have a role in patients with a variable response to clopidogrel.

XI. ACUTE SPINAL CORD INJURY (Neurosurgery 2013;60(suppl 1):82-91)

- A. Epidemiology – Annual incidence of 15–40 cases per 1 million people in the United States
- B. Diagnosis/Pathogenesis
 - 1. Diagnostic tests
 - 2. Neurological examination
- C. Imaging (Neurosurgery 2013;60(suppl 1):82-91)
 - 1. CT scan of spine
 - 2. Many views of spine radiography are necessary when a CT scan is unavailable.
- D. Causes
 - 1. 40%–50% are caused by motor vehicle collisions.
 - 2. Falls (20%), violence (14%), recreational and work activities (9%)
- E. Clinical Impact
 - 1. Mortality
 - a. Ranges from 50% to 75% at the time of injury
 - b. Hospital mortality 4.4%–16%
 - 2. Morbidity
 - a. Paralysis and loss of sensation
 - b. Spasticity
 - c. Neurogenic shock
 - d. Orthostatic hypotension
 - e. Autonomic dysreflexia
 - f. Venous thromboembolism
 - g. Decubitus ulcers
 - h. Respiratory insufficiency
 - i. Bowel and bladder dysfunction
 - j. Sexual dysfunction
 - k. Treatment considerations
 - l. Neurogenic shock
 - i. Hypotension often occurs after injury (50%–90% of cervical spine injuries).
 - ii. May be associated with malperfusion of the spinal cord and worsened outcome
 - iii. Etiology of shock is decreased sympathetic nervous system outflow. Continues to be counterbalanced by parasympathetic outflow, which is not affected by SCI.
 - iv. Results in hypotension and bradycardia

F. Blood Pressure Management

1. Typical recommendations after acute SCI are to maintain MAP 85–90 mm Hg x 7 days to ensure adequate spinal perfusion.
2. Low quality evidence supports this recommendation, but it is included in the SCI guidelines as a treatment option. Hypotension should be avoided, especially in the first 2-3 days post-injury.
3. Often requires judicious fluid resuscitation and vasopressor support.
4. Persistent hypotension may be treated with fludrocortisone or midodrine.
5. Persistent bradycardia may be treated with pseudoephedrine, low-dose theophylline, or, in refractory cases, dopamine or transcutaneous pacing.
 - a. Goal heart rate is not well defined, but generally should aim for rate of 60-80 beats/minute where symptoms of bradycardia are absent.

G. VTE Prophylaxis

1. VTE occurs in 80%–100% of patients without pharmacologic prophylaxis
2. LWMHs are the drugs of choice for prophylaxis and should be initiated within the first 36 hours post-injury.
3. Duration of prophylaxis is typically about 8 weeks.

H. Role of High-Dose Methylprednisolone (Neurosurgery 2013;60(suppl 1):82-91; J Neurosurg 1998;89:699-706; JAMA 1997;277:1597-604; J Neurosurg 1992;76:23-31; N Engl J Med 1990;322:1405-11)

1. Controversial topic related to NASCIS-II and NASCIS-III trials
2. Methylprednisolone 30 mg/kg intravenously x 1, followed by 5.4 mg/kg/hour within 8 hours of injury for 24 (if started < 3 hrs after injury) or 48 (if started 3-8 hours after injury) hours
3. Both trials suggested a modest benefit in the first 6 weeks or 6 months (which often did not persist at 1 year) and a modest risk (primarily related to infection). Current guidelines do not support administering high-dose methylprednisolone.
4. NASCIS-II split enrolled population in half (those who received the drug before the median time to administration [8 hours] and those who did not).
 - a. Subgroup analysis may not have been powered to show benefit.
 - b. Reported motor and sensory scores from one side of the body, not both. The investigators later said there was no difference, but they have not allowed others to examine the raw data.
5. Consistently showed risk (GI bleeding, infection) and inconsistently showed benefit
6. Potential treatment effects may have been caused by early surgery or additional benefit of high-dose methylprednisolone therapy in combination with early surgery.
7. NASCIS-III used a functional independence measure (FIM) score to show how improvement in muscle strength might translate to improved outcome. Failed to show a difference in FIM score.
8. If a practitioner does choose to use high-dose steroids in SCI:
 - a. Must use methylprednisolone; no other steroids
 - b. Must use NASCIS-II or NASCIS-III dosing
 - c. Must give within 8 hours of injury

XII. BRAIN TUMORS**A. Epidemiology**

1. Primary brain tumors (from brain cells such as meninges and neural tissues)
2. 17,000–20,000 cases per year in the United States
3. Glioblastoma

4. Meningioma
 5. Pituitary adenoma
 6. Astrocytoma
 7. Metastases – Common neoplasms that result in spread to brain
 - a. Lung (40%–50%)
 - b. Breast (15%–20%)
 - c. Melanoma (5%–10%)
 - d. Colon (4%–6%)
 - e. Renal cell carcinoma
 - f. CNS lymphoma
- B. Diagnosis/Pathogenesis – Diagnostic tests
1. Contrast-enhanced MRI is the most common test.
 2. Biopsy is often necessary to elucidate the specific histology.
- C. Clinical Impact – Mortality is often high, depending on the nature and grade of the tumor.
- D. Treatment Considerations
1. Corticosteroids (and adverse drug reactions) for brain edema
 - a. Dexamethasone commonly used for vasogenic edema associated with tumor
 - i. Reduces peritumoral edema and symptoms associated with increased ICP. Temporarily reduces symptoms (neurological dysfunction, seizures, headache)
 - ii. Dose commonly 4-10 mg intravenously every 6 hours
 - b. May use other corticosteroids at comparable doses
 - c. Use of acid-suppressive agents may be helpful with concomitant steroid use to reduce the risk of GI complications (Wien Med Wochenschr 1988;138:97-101).
 - d. Consideration for glycemic control and gastric protection with prolonged use
 - e. Induction of phenytoin metabolism (because of increased metabolic rate)
 - f. Metabolism induced by phenytoin (because of increased cytochrome P450 [CYP] activity)
 2. VTE prophylaxis and treatment
 - a. High risk of VTE
 - b. Consider using combination pharmacologic/mechanical prophylaxis.
 - c. Enoxaparin is superior to warfarin for treatment of VTE in oncology patients.
 3. Seizure prophylaxis
 - a. Not typically indicated
 - b. AEDs often necessary (seizures may occur often) – Around 50% of patients with primary brain tumor present with seizure.
 - c. Phenytoin, carbamazepine, levetiracetam often recommended
 - d. Hepatic CYP enzyme-inducing agents, including phenytoin, should be used with caution because of possible drug interactions with chemotherapy.

XIII. CRITICAL ILLNESS POLYNEUROPATHY

- A. Epidemiology
 - 1. Exact incidence is unknown because of inconsistent monitoring and diagnosis.
 - 2. May be as high as 60% in patients with acute respiratory distress syndrome, 77% in long ICU stay (greater than 7 days), 80% in patients with multi-organ failure
- B. Diagnosis/Pathogenesis – Diagnostic tests
 - 1. Typically suspected when patients do not wean well from the ventilator or if their limbs are weak/flaccid
 - 2. Electrophysiological studies or muscle biopsy may provide a more precise diagnosis. Differential diagnosis includes evaluation for critical illness myopathy, Guillain-Barré syndrome, electrolyte abnormalities
- C. Causes
 - 1. The cause of critical illness polyneuropathy is unknown, but several hypotheses exist.
 - a. Mitochondrial dysfunction in critical illness may cause energy stress in vulnerable neurons.
 - b. Microcirculatory ischemia
 - c. Protein catabolism in severe critical illness/immobility may cause muscle wasting.
 - 2. Often associated with:
 - a. Sepsis
 - b. Multiorgan dysfunction
 - c. Hyperglycemia
 - d. Renal failure
 - e. Neuromuscular blockade
 - f. Duration of vasopressor or corticosteroid therapy
 - g. Duration of ICU stay
- D. Clinical Impact
 - 1. Limb and diaphragm weakness may persist for weeks to months.
 - 2. About 33% of patients with critical illness polyneuropathy ultimately cannot independently ambulate or breathe.
- E. Treatment Considerations
 - 1. No specific treatments have been shown to be effective.
 - 2. Intravenous immunoglobulin may play a role (Lancet Neurol 2008;7:136-44)
 - 3. Intensive glycemic control may reduce critical illness neuropathy.
 - 4. Passive mobilization/early physical therapy in the ICU
 - 5. Daily awakening/less time on the ventilator
 - 6. Limiting risk factors as much as possible

XIV. GUILLAIN-BARRÉ SYNDROME

- A. Epidemiology
 - 1. 1.11 cases per 100,000 person-years
 - 2. Men > women (almost 2:1)

- B. Diagnosis/Pathogenesis – Diagnostic tests
 1. Bilateral symmetric progressive weakness of limbs
 2. Generalized hyporeflexia or areflexia
 3. Nerve conduction studies may provide a more precise diagnosis.
- C. Causes
 1. Typically associated with *Campylobacter jejuni* infection. Also associated with Epstein-Barr virus, varicella-zoster, *Mycoplasma pneumoniae*, and potentially zika virus infections
 2. Swine flu vaccine in 1976 caused increased risk of Guillain-Barré syndrome.
- D. Clinical Impact
 1. Progressive weakness throughout 3–4 weeks
 2. 20% of patients remain severely disabled.
 3. Mortality rate around 5%
 4. Respiratory failure
 5. Autonomic dysfunction resulting in arrhythmia, hypertension, hypotension
 6. Neuropathic pain
- E. Treatment Considerations (N Engl J Med 1992;326:1123-9)
 1. Intravenous immunoglobulin versus plasma exchange
 2. Therapies are essentially equivalent.
 3. Plasma exchange: Five treatments throughout 2 weeks
 4. Intravenous immunoglobulin: 0.4 g/kg intravenously daily x 5 days
 5. Combination of therapies no better than single therapy alone
 6. Benefit of repeated treatments is unclear.
 7. Steroids are not particularly effective.
- F. Supportive Care
 1. VTE prophylaxis is imperative.
 2. Careful ventilation strategies to minimize barotrauma and prevent pneumonia
 3. Dysphagia is common, so enteral feeding access is necessary in most cases.
 4. Neuropathic pain is common; use opiates with caution to avoid respiratory depression.
 5. Euvolemia to minimize autonomic instability

XV. MYASTHENIA CRISIS

- A. Epidemiology
 1. Annual incidence of myasthenia gravis (MG) is 1 or 2 per 100,000.
 2. 15%–20% of patients with MG will develop myasthenia crisis within the first year of illness.
- B. Diagnosis/Pathogenesis
 1. Patients with myasthenia crisis typically present with respiratory failure caused by muscle weakness.
 2. Autoimmune disease targeting acetylcholine receptors at the neuromuscular junction
 3. Myasthenia crisis is usually preceded by a predisposing factor.
 - a. Respiratory infection
 - b. Emotional stress

- c. Aspiration
 - d. Changes in MG medication regimen
 - e. Other physiological stress (trauma, surgery)
- C. Treatment Considerations
1. Intravenous immunoglobulin versus plasmapheresis
 2. Intravenous immunoglobulin 0.4 g/kg/day x 3–5 days
 3. Plasmapheresis 20–25 mL/kg plasma x 5 exchanges every other day x 10 days
 4. Similarly effective; can choose according to patient risk factors, etc.
 5. Corticosteroids moderately effective
- D. Supportive Care – Consider discontinuing cholinergic therapies while the patient is acutely ill. May increase pulmonary secretions and complicate ventilator/ICU management.

XVI. SEROTONIN SYNDROME (Neurocrit Care 2014;21:108-13)

- A. Presentation
1. Autonomic hyperactivity (hypertension, tachycardia)
 2. Mental status changes
 3. Hyperthermia – Diaphoresis
 4. Neuromuscular abnormalities
 5. Rigidity
 6. Hyperreflexia and clonus

Table 14. Medications Associated with Serotonin Syndrome

Antidepressants	SSRIs (sertraline, fluoxetine, citalopram, paroxetine) Trazodone Nefazodone Buspirone Venlafaxine MAOIs (phenelzine)
Anticonvulsants	Valproic acid
Migraine agents	Sumatriptan
Antibiotics	Linezolid
Cough suppressants	Dextromethorphan
Herbal products	St. John's wort Tryptophan Ginseng
Antiemetics	Ondansetron Metoclopramide
Analgesics	Meperidine Fentanyl

MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor.

B. Treatment Considerations

1. Removal of precipitating drugs/factors
2. Control of agitation – Benzodiazepines
3. Control of autonomic hyperactivity – Hypotension treatment with direct-acting sympathomimetics
4. Control of hyperthermia
 - a. Cooling blanket
 - b. Sedation, neuromuscular paralysis, intubation
 - c. Avoid succinylcholine.
5. Serotonin-2a antagonist blocks serotonin receptors implicated with serotonin syndrome.
 - a. Cyproheptadine 12–32 mg/24 hours by mouth or per feeding tube. A 12-mg loading dose 2 mg every 2 hours as symptoms continue.
 - b. Chlorpromazine 50–100 mg intramuscularly

XVII. NEUROLOGICAL MONITORING DEVICES**A. ICP Monitors**

1. Goal ICP is typically less than 20 mm Hg.
2. Catheters are typically inserted under sterile conditions at the bedside.
3. Temporary catheters
 - a. Used primarily in the ICU
 - b. Ventriculostomy (aka external ventricular drain) – Diagnostic and therapeutic
 - i. Catheter inserted into frontal horn of lateral ventricle
 - ii. Transduces ICP, should be calibrated to zero routinely
 - iii. Higher infection rate compared with intraparenchymal catheter; insertion is more difficult (particularly with brain swelling)
 - iv. Permits drainage of CSF and intraventricular hemorrhage
 - v. Permits intraventricular drug administration
 - c. Intraparenchymal catheter
 - i. Wire that sits in brain tissue
 - ii. Transduces ICP
 - iii. Low infection rate, fewer complications with insertion
 - iv. Cannot calibrate the catheter, experience “drift” in ICP readings after prolonged use. May not be entirely accurate for duration of use.
 - d. Brain tissue oxygen monitor (Licox)
 - i. Intraparenchymal catheter
 - ii. Optimal location of placement is not well defined (injured vs. non-injured tissue).
 - iii. Transduces PbtO₂
 - (a) Goal PbtO₂ is usually greater than 20%.
 - (b) Concept similar to Svo₂ values systemically
 - iv. Desaturation shows increased ICP or reduced oxygen delivery.
 - v. Typically, will be used in combination with other monitoring modalities
 - e. Subarachnoid bolt
 - i. Single-lumen screw inserted through a burr hole into the subarachnoid space
 - ii. Transduces ICP
 - iii. Associated with increased CNS infection

4. EEG
 - a. Scalp electrodes are placed externally.
 - b. Permits evaluation of cortical electrical activity
 - c. Standard of care for seizure monitoring
5. Transcranial Doppler
 - a. Ultrasound of intracranial vessels
 - b. Used in monitoring for cerebral blood flow velocity or vasospasm
 - c. Threshold values
 - i. 125 cm/second may be suggestive of vasospasm.
 - ii. 200 cm/second typically suggestive of severe vasospasm
 - iii. Lindegaard ratio: Ratio of target blood vessel (usually middle cerebral artery) to carotid (internal carotid artery) transcranial Doppler values – Three suggestive of vasospasm
6. Bispectral Index (BIS) Monitor
 - a. Scalp electrodes are placed externally.
 - b. Uses EEG information to derive a number
 - c. BIS 0–100 (100 being completely wakeful)
 - d. Little correlation with BIS values and ICP control or extent of pharmacologic coma

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C

Answer C is correct because lorazepam is the agent of choice, as recommended by the status epilepticus guidelines. Answers A, B, and D are incorrect because phenytoin is less effective than lorazepam as the initial agent. Although valproic acid and levetiracetam have not been formally compared with lorazepam as the initial agent for status epilepticus, their use is supported by less clinically rigorous evidence.

2. Answer: A

Answer A is correct because mannitol is an agent of choice for treating elevated ICP according to the TBI guidelines. Clinical evidence supports the safety and efficacy of mannitol as a first-line therapy in this situation. Answer B is incorrect because although hypertonic saline is an option, the typical dose of 23.4% sodium chloride is 20–30 mL. Answers C and D (pentobarbital and midazolam) are not ideal selections for this patient because of the likelihood of hypotension.

3. Answer: C

Answer C is correct because warfarin is well reversed by 4-factor PCC products in a much more timely and complete manner than is vitamin K in the acute setting. Answer A is incorrect because although blood pressure control is important for this patient, amlodipine is unlikely to have timely effects immediately after ICH. Answer B is incorrect because platelets are minimally effective for reversing ibuprofen. Answer D is incorrect because rFVIIa is not recommended for reversal of warfarin because of thrombosis risks.

4. Answer: B

Answer B is correct because nicardipine is a recommended agent for reducing blood pressure after ICH, and the threshold for treatment is correct according to the INTERACT-2 study. Answer A is incorrect because although nitroprusside may be considered in this case, it is typically not recommended unless the SBP exceeds 220 mm Hg. In addition, this patient's renal dysfunction may increase the patient's risk of thiocyanate accumulation. Answers C and D are incorrect because although labetalol and esmolol are also effective at reducing blood pressure, the optimal SBP goal after ICH is less than 140 mm Hg.

5. Answer: B

Answer B is correct because the anti-Xa activity level is the laboratory value that best correlates with rivaroxaban activity. Answers A and C are incorrect because neither the INR nor the activated partial thromboplastin time is typically affected by rivaroxaban alone. Answer D is incorrect because the VerifyNow PRU test measurement is more specific to antiplatelet agents such as aspirin or clopidogrel.

6. Answer: A

Answer A is correct because the most consistent reversal effects, albeit with low-quality evidence, occur with 4-factor PCC. Answers B and C are incorrect because vitamin K and fresh frozen plasma have no effect on reversing factor Xa inhibitors. Answer D is incorrect because although factor VII may have some utility, reversal is incomplete, and factor VII is associated with an increased risk of thrombosis.

7. Answer: A

Answer A is correct because nimodipine is the only agent with an FDA indication for preventing ischemic complications related to SAH. Answer B is incorrect because prophylactic Triple-H therapy or variants thereof are not effective for preventing ischemic complications—rather, hyperperfusion therapies are used when vasospasm develops. Answer C is incorrect because clinical trials investigating the efficacy of statins for preventing vasospasm have failed. Answer D is incorrect because aminocaproic acid may in fact increase the risk of stroke in patients with SAH.

8. Answer: B

Answer B is correct because induction of hypertension with a vasopressor such as norepinephrine appears to improve cerebral perfusion. Titration of the infusion to MAP values that result in improvement of neurological symptoms is often necessary. Answer A is incorrect because data analyses are limited to support transfusing blood to a high hemoglobin (in fact, blood transfusion appears to be a risk factor for vasospasm). In addition, fluid resuscitation to hypervolemic levels is not beneficial. Answer C is incorrect because when hypervolemia is compared with euvolemia, neurological outcomes are no different, but patients receiving hypervolemia develop more pulmonary edema. Answer D is incorrect because milrinone is not first-line therapy for the treatment of vasospasm.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: B**

Answer B is correct because sodium supplementation is effective for treating hyponatremia. Although hypervolemia is no longer advocated, ensuring euvolemia is important. Answers A and C are incorrect because water restriction or tolvaptan is not desirable in a patient who is 4 days after ictus for SAH because of the importance of maintaining adequate cerebral perfusion. Hyponatremia may be deleterious in a patient with a new stroke such as SAH caused by cerebral edema, making Answer D incorrect.

2. Answer: A

Answer A is correct because vancomycin effectively covers MRSE, and the intraventricular dose of 10 mg daily is appropriate. Answer B is incorrect because gentamicin is less likely to be effective alone for MRSE and is more associated with seizures than other aminoglycosides. Answer C is incorrect because ampicillin (or other penicillins) should not be given by the intraventricular route because of the risk of seizures. Answer D is incorrect because this patient has a treatment-refractory, device-related CNS infection. In this instance, initiation of intraventricular antimicrobials may be considered.

3. Answer: B

Answer B is correct because the optimal CPP varies with each individual, but the typical recommended target range is 50–70 mm Hg. Patients with TBI have gastric intolerance but benefit greatly from early enteral nutrition, making Answer A incorrect. Answer C is incorrect because dextrose-containing fluids may increase cerebral edema in TBI. Answer D is incorrect because high-dose methylprednisolone therapy increases mortality in patients with TBI.

4. Answer: B

Answer B is correct because this patient meets the criteria for receiving alteplase and has no obvious contraindications. The more timely the administration of alteplase, the more likely the patient will benefit (and the less risk). Answer A is incorrect because aspirin should be initiated within the first 24–48 hours after stroke, but not necessarily immediately. Answer C is incorrect because the blood pressure may be slightly elevated (SBP less than 185 mm Hg, DBP less than 110

mm Hg) before alteplase administration or immediately after stroke in general (so-called permissive hypertension to ensure adequate cerebral perfusion). Nicardipine is not necessary for this patient at this point. Answer D is incorrect because reversal of warfarin with vitamin K is not recommended in the setting of an acute thrombosis in the brain.

5. Answer: C

Answer C is correct because current guidelines do not recommend high-dose methylprednisolone therapy because of the inconsistency of beneficial effects and the relatively consistent risk of adverse effects (GI bleeding, infection) shown in clinical trials. Answer B is incorrect because high-dose methylprednisolone does not augment spinal perfusion. Answers A and D are incorrect because although the NASCIS-III study showed some potential benefit for patients who received a bolus and a 47-hour infusion when it was initiated 3–8 hours after injury, particularly for incomplete injuries, the therapy is no longer recommended.

6. Answer: A

Answer A is correct because of the agents listed, buspirone is the only one that acts to increase CNS serotonin concentrations. Answers B–D would not be expected to increase CNS serotonin concentrations. Cyproheptadine is a potential therapeutic agent for patients with serotonin syndrome.

7. Answer: B

Answer B is correct because given this patient's change in neurological status, vital signs, and monitoring values, she is likely having a cerebral vasospasm with increased ICP. Therapy should be targeted at optimizing cerebral perfusion (fluid bolus or increase in MAP) and reducing ICP. Hypertonic saline will address both issues, causing an increase in intravascular volume to improve perfusion and possibly an increase in blood pressure while lowering ICP through osmotic effects. Answer A is incorrect because verapamil would need to be given super-selectively in the angiography suite. One possible adverse effect of verapamil is cerebral vasodilation, which might lead to increased ICP, and ICP would be undesirable in this patient right now. Answer C is incorrect because mannitol may act to decrease ICP,

but it would also cause diuresis, which is not desirable in a patient with ongoing cerebral vasospasm. Answer D is incorrect because although a blood transfusion may theoretically increase oxygen-carrying capacity to the brain (enhancing perfusion), blood transfusion may in fact cause a risk of cerebral vasospasm. In addition, it is unlikely to affect ICP.

8. Answer: D

Answer D is correct because propofol represents an almost-ideal agent for sedation with its quick onset and offset of activity and relative lack of dependence on organ function for clearance; however, boluses and large dose titrations should be avoided because of the risk of hypotension. Answers A and C are incorrect because long-acting sedating agents such as lorazepam and morphine are not desirable in patients with neurological injury because of their propensity to obscure the neurological examination for prolonged periods. Answer B is incorrect because midazolam (and other benzodiazepines) is associated with increased delirium. In addition, midazolam may accumulate when used for a prolonged period because of its long context-sensitive half-life.

MANAGEMENT OF PAIN, AGITATION, DELIRIUM, AND NEUROMUSCULAR BLOCKADE IN ADULT INTENSIVE CARE UNIT PATIENTS

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Learning Objectives

1. Develop a management strategy for the prevention and treatment of pain, agitation, and delirium (PAD) in an intensive care unit (ICU) patient with various comorbidities.
2. Discuss relevant pharmacokinetic and pharmacodynamic considerations of PAD medications as they pertain to disturbances in critical care physiology.
3. Identify relevant adverse effects, drug interaction, and drug withdrawal syndromes in the management of PAD.
4. Evaluate patients in the ICU for PAD using a validated screening tool.
5. Construct a plan for the management of delirium.
6. Identify the long-term effects of critical illness in adult ICU patients.
7. Create a management strategy for PAD-related medications that are continued beyond ICU discharge.
8. Describe a treatment and monitoring plan for critically ill patients receiving neuromuscular blockade.

Abbreviations in This Chapter

ARDS	Acute respiratory distress syndrome
BPS	Behavioral Pain Scale
CAM-ICU	Confusion assessment method for the intensive care unit
CPOT	Critical-Care Pain Observation Tool
GABA	γ -Aminobutyric acid
ICDSC	Intensive Care Delirium Screening Checklist
ICP	Intracranial pressure
ICU	Intensive care unit
NMBA	Neuromuscular blocking agent
PAD	Pain, agitation, and delirium
PRIS	Propofol-related infusion syndrome
RASS	Richmond Agitation Sedation Scale
SAS	Sedation-Agitation Scale
SAT	Spontaneous awakening trial
SBT	Spontaneous breathing trial
SCCM	Society of Critical Care Medicine
TOF	Train of four

Self-Assessment Questions

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

1. P.J. has been receiving propofol 50–60 mcg/kg/minute and fentanyl 75–100 mcg/hour for 4 days. She has no significant medical history. Laboratory results today show that liver function tests have increased to 5 times baseline, lactate is increased to 5 mmol/L, and triglyceride concentration is 450 mg/dL. No new medications have been added. Given these laboratory values, which complication would be most appropriate to address?
 - A. Deep venous thrombosis (DVT)
 - B. Critical illness-induced polyneuropathy
 - C. Intensive care unit (ICU) delirium
 - D. Propofol-related infusion syndrome (PRIS)
2. T.I. is a 35-year-old man admitted to the ICU for severe alcohol withdrawal. His medical history is otherwise unknown. Laboratory values are within normal limits on admission. He has been receiving a lorazepam infusion 6–8 mg/hour for active alcohol withdrawal. On day 4, his blood pressure is 130/75 mm Hg, oxygen saturation is 98% on 2 L of oxygen, blood urea nitrogen (BUN) is 50 mg/dL, and serum creatinine (SCr) is 2.0 mg/dL; he has a new anion gap of 20 mEq/L, an osmolar gap of 18 mmol/L H₂O, and a fractional excretion of sodium of 0.2. Which is the most likely cause for his clinical presentation?
 - A. Acute respiratory distress syndrome (ARDS)
 - B. Propylene glycol toxicity
 - C. Delirium tremens
 - D. Acute tubular necrosis
3. R.B. is a 25-year-old man admitted to the ICU for acute pancreatitis and sepsis. He is intermittently agitated on hydromorphone 2 mg/hour and midazolam 6 mg/hour (Richmond Agitation-Sedation Scale [RASS] score of -1 to +2) and is not oxygenating adequately after adjustments on the ventilator. The physician would like to initiate therapeutic paralysis. Which is the next best step in the treatment of this patient?

- A. Spontaneous awakening and breathing trials
 - B. Cisatracurium infusion
 - C. Intermittent vecuronium
 - D. Sedate the patient to a “deeply sedated” clinical state
4. P.V. is a 70-year-old woman (weight 50 kg, decreased from 60 kg 2 months ago) admitted to the ICU in ARDS. She has a history of cirrhosis and is currently fluid overloaded (net positive 5 L). She has been on a continuous infusion of fentanyl and propofol for 5 days. Which pharmacologic factor would best be considered with respect to her analgesics or sedatives?
- A. Risk of PRIS in patients with ARDS
 - B. Unpredictable clearance of fentanyl
 - C. Enzymatic induction of fentanyl by propofol
 - D. Hypocalcaemia secondary to extended use of propofol
5. L.B. is a 38-year-old woman intubated in the neurosurgery ICU for 72 hours receiving propofol. The nurse is requesting medications for “severe agitation and hallucinations.” Her heart rate and blood pressure have steadily increased since admission, and a chart review reveals years of chronic pain while receiving oxycodone and tramadol at home. Her laboratory values are normal, but she is not tolerating enteral-route medications. Which is the most appropriate recommendation at this time?
- A. Quetiapine as needed for agitation
 - B. Fentanyl infusion
 - C. Lorazepam as needed for agitation
 - D. Hydromorphone patient-controlled analgesia
6. S.P. has just been intubated in the ICU and is in severe alcohol withdrawal. He has a history of frequent delirium tremens and alcohol withdrawal seizures. Which medication is most appropriate to begin initial management of pain, agitation, and delirium (PAD) in this patient?
- A. Dexmedetomidine
 - B. Phenytoin
 - C. Fentanyl
 - D. Midazolam
7. H.F., a 65-year-old man admitted to the ICU from home for aspiration pneumonia requiring intubation, is initiated on levofloxacin and metronidazole. Other medications include fentanyl and dexmedetomidine infusions as well as amiodarone and quetiapine given enterally, which are home medications. His last RASS was -2, and he has intermittent agitation. Vital signs and laboratory values are normal, and corrected QT (QTc) is 500 milliseconds. The team has implemented nonpharmacologic delirium management measures. Which is the most appropriate recommendation at this time?
- A. Increase quetiapine for agitation, and monitor QTc.
 - B. Change levofloxacin and metronidazole to piperacillin-tazobactam.
 - C. Discontinue amiodarone and quetiapine because of his prolonged QTc.
 - D. Give lorazepam as needed for agitation.
8. S.V., a 70-year-old woman with a history of hypertension, is transferred from the floor to the ICU for worsening pneumonia and new-onset hypoactive delirium. She has been nil per os (NPO) since admission 3 days prior. She remains febrile (temperature 102°F [38.89°C]) with decreased urine output; other vital signs and laboratory values are within normal limits. Her medications include ceftriaxone, heparin, and hydrochlorothiazide. Which best represents the most important set of considerations regarding her delirium?
- A. Dementia and sleep disorder
 - B. Undetected alcohol withdrawal
 - C. Adrenal insufficiency
 - D. Dehydration and untreated infection

I. PAIN, AGITATION, AND DELIRIUM (PAD) IN THE INTENSIVE CARE UNIT

A. Background

1. The Society of Critical Care Medicine (SCCM) published updated guidelines for the management of PAD in adult ICU patients in 2013. These guidelines, together with recently published research, help guide ICU clinicians in the challenging task of optimizing patient comfort and outcomes while avoiding the complications of under- or oversedation. The PAD guidelines were written by a 20-member multidisciplinary, multi-institutional task force, each member of which with extensive expertise in the overall management and associated outcomes of PAD. Rigorous research has developed our understanding of the assessment tools and medications used for PAD, the prevention and treatment methods used for PAD, and the long-term effects of the ICU environment on patients and caregivers. Recommendations for specific ICU populations such as burn, neurologic, neurosurgical (including traumatic brain injury), and cardiac populations may need specialized consideration.
2. Specific management concepts to highlight within the updated PAD guidelines:
 - a. A renewed focus on the assessment, prevention, and control of pain in the ICU. Patients continue to report inadequate pain control as their primary concern during their ICU stay.
 - b. Target a lighter level of sedation or implement a strategy of daily interruption of sedation.
 - c. Assess a level of wakefulness as assessed by the patient's ability to follow commands.
 - d. Routine assessment for delirium and recommendations for methods of delirium prevention
3. The 2013 PAD guidelines used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method to develop each recommendation for both descriptive and actionable questions. Only important or critical outcomes were considered when reviewing the evidence, and only critical outcomes were assessed for each recommendation.
 - a. Each guideline statement and recommendation was ranked according to the quality and strength of the evidence and was denoted "A" (high quality; randomized controlled trials), "B" (moderate quality; randomized controlled trials with significant limitations or high-quality observational studies), or "C" (low quality; observational studies).
 - b. A *strong* recommendation is worded as "we recommend" and is denoted with a "1," showing that most task force members believed the benefits of the intervention significantly outweighed the risks and would likely pursue the action.
 - c. A *weak* recommendation is worded as "we suggest" and is denoted with a "2," showing that most task force members believed the benefits of the intervention likely outweighed the risks, but the task members were not confident about the trade-off.
 - d. A *no recommendation* could also be stated because of either lack of evidence or lack of consensus among the reviewers and would be denoted with a zero.

- B. Pharmacy Intervention – Pharmacists provide unique and valuable insight into the management of PAD in the ICU. Much of the management for PAD involves medications with complex pharmacologic profiles, allowing many opportunities for pharmacy expertise on the critical care team. As the management of PAD in the ICU continues to evolve, pharmacists should seek avenues for contributing to the critical care community through development of hospital protocols and assessing for quality improvement; providing education for medical, pharmacy, and nursing colleagues; and/or doing research on pertinent questions surrounding the management of PAD in the ICU.

II. PAIN IN THE INTENSIVE CARE UNIT

A. Introduction

1. More than half of ICU survivors report severe pain as the most traumatic memory of their ICU stay. Recent data show that 50%–80% of ICU patients report pain as “uncontrolled” during their ICU stay, similar to research from 2 decades ago.
2. Both short- and long-term negative sequelae are related to uncontrolled pain in the ICU. Assessing pain in the ICU is challenging, particularly in patients who cannot effectively communicate. If patients cannot adequately communicate their degree of pain but retain motor activity, medications should be titrated according to validated behavioral pain scales.

B. Incidence and Causes of Pain: Pain may occur in any type of ICU patient, and considerations for pain management often require an individualized approach to optimize treatment. The interdisciplinary team should complete a comprehensive review of all variables such as acute and chronic pain, routine nursing care that may cause discomfort, and procedural-based pain.

1. Common causes of pain in the ICU include, but are not limited to, acute trauma, injury or burns, postoperative pain, exacerbation of chronic pain, heart disease, ischemia, acute or chronic underlying disease state pain such as cancer pain, pancreatitis, or other abdominal pathology.
2. Less discernible causes of pain may include those from either routine nursing care or the provision of life-sustaining measures: presence of an endotracheal tube and endotracheal tube suctioning, wound care, tube or Foley insertion, immobility, bed repositioning, bathing, medication administration, and physical and occupational therapy. Other examples of painful invasive procedures include intravenous line placement, scoping procedures, chest tube placement or removal, paracentesis, lumbar puncture, biopsies, and fracture reductions.

C. Short- and Long-term Consequences of Pain in the ICU

1. Acute pain can invoke a stress response, resulting in a hypercatabolic state, decreased tissue perfusion, and impaired wound healing. Uncontrolled pain decreases a patient’s immune response to infection by suppressing natural killer cell activity and neutrophil function.
2. Long-term studies (12 months post-ICU stay) report detrimental physiologic and psychological function in patients who recall significant pain during their hospitalization, particularly in patients admitted with a traumatic injury.
 - a. Health-related quality of life is decreased in up to 20% of patients.
 - b. Chronic pain is reported in up to 40% of patients.
 - c. Posttraumatic stress disorder is reported in 5%–20% of patients.

D. Assessment of Pain

1. The gold standard for assessing pain remains the patient’s self-report of pain. Several scenarios in the ICU make the self-reporting of pain challenging for clinicians (e.g., mechanical ventilation, presence of sedation and/or delirium). SCCM currently recommends two validated behavioral pain scales to be done in a repetitive and routine manner: the Behavioral Pain Scale (BPS) (Table 1) and the Critical-Care Pain Observation Tool (CPOT) (Table 2).
 - a. Assessment scales should be used routinely in all ICU patients (+1B recommendation). Most nursing protocols assess pain every 4–6 hours while the patient is awake. In addition, it is important to reassess the degree of pain within about 30 minutes to 1 hour after administering an “as-needed” pain medication to determine the appropriateness of the pain medication or dose.
 - b. Pain scores should be documented in the medical chart and then used to help formulate daily titrations in pain medications.

- c. The PAD guidelines recommend that patients be treated within 30 minutes of a “significant pain” score. A BPS greater than 5 or a CPOT score of 3 or greater is indicative of pain.
2. Using vital signs alone is not recommended for assessing pain in the ICU patient. Abnormal vital signs such as tachycardia and hypertension are appropriate for use as a prompt to further investigate the need for pain control.
3. Further research is needed to determine the effectiveness of a preprocedural pain assessment tool and the ways in which this assessment will affect analgesic administration. A recent study by Puntillo et al. in 2014 found the procedures most likely to double the patient’s pain intensity score (from preprocedure to during-procedure scoring) were chest tube removal, wound drain removal, and arterial line insertion. This study found that higher-intensity pain and pain distress before the procedure were associated with a high risk of increased pain during the procedure (Am J Respir Crit Care Med 2014;189:39-47).
4. A recent study by Kanji et al. found that the CPOT is a valid pain assessment in noncomatose, delirious adult ICU patients who are not able to reliably self-report the absence or presence of pain (Crit Care Med 2016;44:943-7).

Table 1. Behavioral Pain Scale (BPS)^a

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

^aA BPS score > 5 indicates significant pain.

Adapted with permission from: Lippincott Williams & Wilkins/Wolters Kluwer Health. Payen J, Bru O, Bosson J, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 2001;29:2258-63.

Table 2. Critical-Care Pain Observation Tool (CPOT)^a

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 eyelids tightly closed	Grimacing	2

Table 2. Critical-Care Pain Observation Tool (CPOT)^a (*continued*)

Indicator	Description	Score	
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movement	0
	Slow, cautious movements; touching or rubbing the pain site; seeking attention through movements	Protection	1
	Pulling tube, trying to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension Evaluation by passive flexion and extension of upper extremities	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 (intubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: Blocking ventilation, alarms often 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
Total, range			0–8

^aA CPOT score ≥ 3 indicates significant pain.

Adapted with permission from: Lippincott Williams and Wilkins/Wolters Kluwer Health. Gelinas C, Fillion L, Puntillo K, et al. Validation of the Critical-Care Pain Observation Tool in adult patients. *Am J Crit Care* 2006;15:420-7.

E. Treatment of Pain in the ICU

1. In a patient whose pain is inadequately controlled in the ICU, intravenous opioids are considered first-line treatment for nonneuropathic pain (+1C recommendation). Non-opioids should be considered for mild to moderate pain or used in conjunction with opioids to reduce opioid dosing requirements.
2. Preprocedural pain management should be considered in all ICU patients. One study reported that up to 60% of patients did not receive preprocedural systemic pain medication for common procedures and wound care in the ICU, although 89% of patients received a topical anesthetic for central venous catheter placement (*Am J Crit Care* 2002;11:415-29).
 - a. Preprocedural pain management with both nonpharmacologic and pharmacologic therapies is recommended for procedures that may cause pain (+2C recommendation). If a medication is deemed necessary, the timing of administration should be in accordance with the onset of the specific analgesic medication. The American Society for Pain Management Nursing (ASPMN) published recommendations for preprocedural pain management in 2011. The ASPMN recognizes both the psychological and the physical elements of procedural pain and agrees with combining nonpharmacologic and pharmacologic methods. Examples of nonpharmacologic options recommended by ASPMN include relaxation and breathing techniques, imagery, massage, music, thermal measures, and positioning (*Pain Management Nursing* June 2011(12):95-111).
 - b. Preemptive analgesia for chest tube removal is a “strong” recommendation by SCCM, together with nonpharmacologic relaxation techniques (+1C recommendation).

3. Postoperative thoracic epidural anesthesia/analgesia is recommended for patients undergoing abdominal aortic aneurysm treatment. Thoracic epidural anesthesia is “suggested” for traumatic rib fractures in the ICU.
4. Pharmacotherapy for pain
 - a. Intravenous opioids on an as-needed, scheduled, or continuous infusion basis are recommended to treat pain in the ICU. The pharmacokinetics of different opioids may vary; thus, opioids should be chosen according to patient comorbidities and individual needs (Table 3). Fentanyl is the most commonly used intravenous opiate in American adult ICUs.

Table 3. Opiates Commonly Used in the ICU

Drug	Metabolic/Drug Interaction Considerations	Usual CI Starting Dose ^a	Drug-Specific Adverse Effects ^b	Drug Accumulation Factors
Fentanyl	3A4 major substrate	12.5–25 mcg/hr; 0.35–0.5 mcg/kg	Muscle rigidity	Hepatic failure; high volume of distribution; high lipophilicity; unpredictable clearance (long context-sensitive half-time) with prolonged infusion
Morphine	Glucuronidation	1–2 mg/hr	Hypotension, bradycardia from histamine release	Hepatic failure; active metabolite (3-morphine glucuronide) accumulates in renal failure
Hydromorphone	Glucuronidation	0.25–0.5 mg/hr	Overdose effects from dosing errors (high-potency opiate)	Hepatic failure
Methadone	3A4 and 2B6 major substrates		QTc prolongation, serotonin syndrome	Long half-life; hepatic and renal failure will delay clearance
Remifentanyl	Blood and tissue esterases	Loading dose: 1.5 mcg/kg CI: 0.5–15 mcg/kg/hr	Chest wall rigidity; rebound pain on discontinuation	

^aUsual starting dose in the ICU for pain management in an opiate-naïve patient^bOther common significant adverse effects for all opiates to be considered: Constipation, respiratory depression, bradycardia, hypotension, altered mental status.

CI = continuous infusion

- i. General mechanism of action of opiates: Bind to mu-opioid receptors in the central nervous system (CNS)
- ii. Commonly used intravenous opioids in the ICU: Fentanyl, morphine, hydromorphone, remifentanyl, and methadone
- iii. Tolerance: May quickly develop to all opiates, particularly when given as a continuous infusion. On switching to a different intravenous or oral opiate, equianalgesic dosing may be difficult to estimate, and low starting doses should be considered.

- iv. Significant adverse effects: Decreased respiratory drive: This may be a desired effect in some ICU scenarios; however, a depressed respiratory drive is a critical negative implication during the ventilator weaning process; decreased blood pressure and heart rate, constipation, gastrointestinal (GI) intolerance, altered sensorium.
- v. GI intolerance and constipation: A bowel regimen should be initiated on day 1 unless contraindicated, with assessment for efficacy every 24–48 hours. GI intolerance in the ICU can result in increased time on mechanical ventilation, delayed time to attaining nutritional goals, and prolonged ICU stay. Constipation may also contribute to agitation.
- vi. Altered mental status: Opiates may induce a sedative effect as well as an altered sensorium in some patients. Unless contraindicated, clinicians should consider tapering the opiate dose in an altered patient who has adequate pain control.
- vii. Patient-controlled analgesia: In alert and clinically stable patients, use of patient-controlled analgesia may be considered to titrate to the patient's perceived level of pain. Patient-controlled analgesia may also be useful on discontinuation of continuous infusion opiates.
- b. Fentanyl
 - i. Pharmacokinetics: Hepatic metabolism, cytochrome P450 (CYP) 3A4 substrate. Quick onset and short duration of action; lacks a pharmacologically active metabolite. Highly lipophilic, high volume of distribution and protein binding; maintains a three-compartment model; continuous infusion dosing may lead to prolonged and unpredictable clearance (prolonged context-sensitive half-time).
 - ii. Many dosage forms: Injectable (intravenous, intramuscular, intrathecal, epidural), transdermal, transmucosal, nasal spray. Different dosage forms should not be converted on a 1:1 mcg basis; use specific manufacturer recommendations if converting. Injectable form of fentanyl is most commonly used in the ICU setting. The fentanyl patch is not generally appropriate for use in the ICU because of its latent onset (about 12 hours) and erratic/increased absorption in a febrile patient.
 - iii. Adverse effects: Respiratory depression, bradycardia, hypotension, CNS depression, constipation, ileus, risk of serotonin syndrome when used with other serotonergic agents
- c. Morphine
 - i. Pharmacokinetics: Hepatic metabolism by glucuronidation to two major active metabolites, morphine-3-glucuronide (45%–55%) and morphine-6-glucuronide (10%–15%). The glucuronide metabolites of morphine are both renally eliminated; accumulation can occur with the chronic use of morphine or in patients with decreased renal function. Morphine-3-glucuronide does not have analgesic activity, but adverse effects may include seizure activity or agitation. Morphine-6-glucuronide does have analgesic activity by the mu-receptor and may cause additive sedation and respiratory depression if accumulation occurs. Continuous morphine infusions are rarely used for analgesia in the ICU setting because of the concerns with the active metabolites.
 - ii. Dosage forms: Injectable (intravenous, subcutaneous, intrathecal, epidural) and oral. Intravenous-to-oral conversion is not a 1:1 mg ratio.
 - iii. Adverse effects: Histamine release may cause significant hypotension; bradycardia, respiratory depression, CNS depression, constipation, ileus.
- d. Hydromorphone (Dilaudid)
 - i. Pharmacokinetics: Hepatic metabolism by glucuronidation to an inactive but potentially neurotoxic metabolite. Low volume of distribution, highly water soluble, and relatively low protein binding.
 - ii. Dosage forms: Injectable (intravenous, subcutaneous) and oral; intravenous-to-oral conversion is not a 1:1 mg ratio.
 - iii. Adverse effects: CNS alterations (e.g., abnormal dreams, aggressive behavior, altered thinking), respiratory depression, hypotension, constipation

- e. Remifentanyl (Ultiva)
 - i. Research primarily done in Europe; limited reported use in U.S. adult ICUs for ongoing analgesic use.
 - ii. Dosage form: Injectable only
 - iii. Pharmacokinetics: Clearance by blood and tissue esterase; clearance not dependent on organ function. Fast onset and short duration of action with little to no accumulation. High volume of distribution, high protein binding.
 - iv. Adverse effects: Respiratory depression, hypotension, bradycardia, constipation
 - v. Rebound pain: Quick offset (5–10 minutes) may lead to rebound pain and withdrawal symptoms, and additional pain medication may be needed if remifentanyl is interrupted or discontinued.
 - vi. Benefit in adult ICUs: Decreased time on mechanical ventilation with short-term use (72 hours or less)
 - vii. Cost (AWP): 1 mg = \$55.16; 5 mg = \$234.74.
- f. Methadone
 - i. Pharmacokinetics: Phase I hepatic metabolism to inactive metabolites. Many drug interactions: major substrate of CYP 3A4, 2B6. Moderate inhibitor of CYP2D6, weak inhibitor of CYP3A4. Longer-acting opiate with variable duration of action (12–48 hours); may accumulate quickly in patients with hepatic failure or patients receiving hemodialysis. Animal studies have found that the d-isomer of methadone works as both a partial mu-agonist and an N-methyl-d-aspartate receptor antagonist (the l-isomer is a full mu-agonist). These properties of the d-isomer are thought to decrease the tolerance effect to other opioids. Methadone is currently marketed as the racemic mixture. On initiating oral methadone, steady state and peak analgesic effect may not be reached for 3–5 days; oversedation and respiratory depression may occur if titrated too quickly.
 - ii. Dosage forms: Injectable (intravenous, intramuscular, subcutaneous) and oral. Not a milligram-per-milligram conversion.
 - iii. Adverse effects: Dose-dependent QTc prolongation, altered mental status, respiratory depression, confusion, dizziness, arrhythmias, constipation, risk of serotonin syndrome when used with other serotonergic agents
- 5. Non-opioid adjunctive pain medications should be considered in combination with opioids to reduce opioid requirements. Clinically stable patients may tolerate a conversion from opiates to non-opiate medications.
 - a. Local and regional anesthetics such as bupivacaine
 - b. Acetaminophen (Tylenol)
 - i. Total daily acetaminophen doses should be considered from all acetaminophen combination products, with a maximum total daily dose of 4 g. Decreased total daily dosing should be considered in patients with significant liver disease.
 - ii. Intravenous acetaminophen: Dose reduction recommended if the creatinine clearance (CrCl) is 30 mL/minute/1.73 m² or less or with continuous renal replacement therapy (every 8 hours); contraindicated in severe hepatic disease. The cost of the intravenous formulation of acetaminophen is considerably higher than that of the oral or rectal formulations.
 - c. Intravenous or oral nonsteroidal anti-inflammatory medications: Ibuprofen, ketorolac. Use with caution in critically ill patients with renal or hepatic dysfunction. May increase the risk of acute renal failure, bleeding, or GI adverse effects.

- d. Ketamine (Ketalar) has been used for analgesia and sedation in the ICU, primarily in the pediatric population. Published data for the use of ketamine in adults for analgesia and/or sedation are limited to case reviews, and long-term cognitive effects of ketamine are not known. Data from animal studies suggest a significant decline in cognitive function after continued use of ketamine.
 - i. Called a “dissociative anesthetic,” providing analgesic activity at subanesthetic doses. It is a schedule III controlled substance and works primarily as an N-methyl-d-aspartate receptor antagonist. Ketamine is void of the constipation, respiratory depression, and hypotensive effects that plague the opiate class.
 - ii. May decrease dose requirements of concurrently administered opioids
 - iii. Other uses include rapid sequence intubation, refractory pain syndromes, cancer pain, neuropathic pain, asthma (bronchodilatory effects), refractory seizure activity, and depression.
 - iv. Dosing range is varied; usual starting dose for analgesia or sedation is 0.1 mg/kg/hour. Reviews of ketamine use in adult ICUs report a dosing range of 0.1–2.5 mg/kg/hour and a range in duration of 3 hours to 9 days.
 - v. Significant adverse effects: Mild to severe emergence reactions (e.g., confusion, excitement, irrational behavior, hallucinations, delirium) in around 12% of patients, enhanced skeletal muscle tone, tachycardia, hypertension, hypotension
- 6. Anticonvulsants are recommended in the PAD guidelines together with opioids for confirmed neuropathic pain. Anticonvulsants have not been studied extensively in the ICU population. There is a potential for significant adverse effects and drug interactions, requiring close monitoring and follow-up. If the patient is discharged home on an anticonvulsant for neuropathic pain, follow-up should be documented and the primary care provider notified.
 - a. Gabapentin (Neurontin)
 - i. Suggested starting dose range: 300–600 mg/day divided two or three times daily; requires renal adjustment.
 - ii. Pharmacokinetics: Renally excreted, dose adjusted for reduced CrCl
 - iii. Adverse effects: May be severe, including CNS depression, paresthesias, and asthenias
 - b. Carbamazepine (Tegretol)
 - i. Suggested starting dose range: 50–100 mg twice daily; use with caution in patients with hepatic impairment, and adjust for a CrCl less than 10 ml/minute/1.73 m² or with hemodialysis.
 - ii. Pharmacokinetics: Strong inducer of many CYP enzymes, substrate of CYP3A4. Closely monitor for drug interactions.
 - iii. Adverse effects: Somnolence, severe skin reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis), pancytopenia, syndrome of inappropriate antidiuretic hormone
- F. Analgosedation Method in the ICU: This method of sedation advocates the use of opiate medications before prescribing an anxiolytic/hypnotic medication to provide patient comfort in the ICU unless anxiolytics are otherwise indicated. The PAD guidelines give the analgosedation method of sedation a +2B level of recommendation. Providing pain relief early in the ICU stay may decrease the agitation associated with pain and/or general discomfort while minimizing the use of alternative medications commonly used for agitation (e.g., benzodiazepines). The guidelines recognize that current data using analgosedation are primarily limited to open-label trials, using remifentanyl as the analgesic, and mostly conducted in Europe, where critical care staffing and management practices differ from those in the United States. Despite these limitations, it remains notable that studies using the analgosedation method found a significant decrease in benzodiazepine dosage requirements when opiates were the primary medications used for discomfort and agitation. This is a positive step in decreasing the untoward adverse effects of the benzodiazepine class of sedatives. There is a potential for high cumulative doses of opiates with the analgosedation method, necessitating daily monitoring of their adverse effects (e.g., respiratory depression, altered mental status, GI slowing).

Patient Case

Questions 1 and 2 pertain to the following case.

T.O. is a 70-year-old man just admitted to the ICU with multiple fractures after a motor vehicle accident. His medical history includes hypertension. He is now agitated after intubation. His laboratory values are normal, and his vital signs include blood pressure 175/95 mm Hg and heart rate 110 beats/minute.

1. Which grouping of initial sedatives is most appropriate at this time?
 - A. Fentanyl infusion and midazolam infusion
 - B. Propofol infusion and fentanyl as needed
 - C. Midazolam as needed and fentanyl as needed
 - D. Fentanyl infusion and propofol infusion
2. After 2 weeks in the ICU, T.O. is being prepared for chest tube removal. He is currently receiving a fentanyl drip with adequate pain control. Which is the best pain management regimen for chest tube removal?
 - A. Give intravenous acetaminophen 15 minutes before chest tube removal.
 - B. Make no change in pain treatment because his current pain regimen is adequate.
 - C. Increase his pain medication infusion dose by 50% the morning of his chest tube removal.
 - D. Give fentanyl 50 mcg injectable 15 minutes before chest tube removal.

III. AGITATION IN THE INTENSIVE CARE UNIT

- A. Agitation in the ICU – Maintaining patient comfort for the duration of an ICU stay can be extremely challenging, requiring significant resources and daily discipline from the nursing, medical, and pharmacy team. Ongoing research has improved our understanding of the consequences of either under- or overtreating agitation in the ICU, and clinicians should continue to apply this knowledge to their daily selection and titration of medications. Treatment of a patient who presents with agitation must always begin with attempts to identify and correct the etiology of the agitation. Common causes of agitation in the ICU include pain, delirium, hypoxia, hypoglycemia, dehydration, and drug or alcohol withdrawal. Close inspection of significant patient variables will also help determine the appropriate sedative:
 1. Pain control
 2. Substance abuse and smoking history
 3. Neurologic function: Baseline and acute mental status, history of seizure activity, dementia, psychiatric history
 4. Clinical variables: Blood pressure, heart rate, respiratory rate
 5. Comorbidities (baseline and acute): Cardiac, renal, hepatic, gastric, pulmonary, pancreatic
 6. Home medication use: Any medication from which a patient could withdraw: Benzodiazepines, opioids, antidepressants, other γ -aminobutyric acid (GABA) receptor agonists
- B. Primary Medications for the Treatment of Agitation – Include propofol, dexmedetomidine, and benzodiazepines (usually lorazepam and midazolam) (Table 4). Benzodiazepines are first-line agents for status epilepticus, alcohol withdrawal, benzodiazepine dependence or withdrawal, and need for deep sedation or amnesia and with the use of neuromuscular blockade. Other indications for benzodiazepines may exist, which must be scrutinized throughout the ICU stay.

Table 4. Sedatives for Patients on Mechanical Ventilation in the ICU

Drug	Onset and Duration	Precautions for Use	CYP Substrate (major)	Usual Dose	Significant Adverse Effects
Propofol	Onset: 1 min Duration: short term: 0.5–1 hr; long term > 7 days: variable; 25–50 hr has been observed (depends on depth and time on sedation)	Hypotension, bradycardia, hepatic/renal failure, pancreatitis	2B6	5–50 mcg/kg/min; 0.3–3 mg/kg/hr	Hypotension, respiratory depression, bradycardia, PRIS
Dexmedetomidine	Onset: 5–10 min (with LD) 1–2 hr (without LD) Duration: 1–2 hr	Hepatic failure; symptomatic bradycardia	2A6	LD: 0.5–1 mcg/kg (optional) MD: 0.2–0.7 mcg/kg/hr	Hypo/hypertension, bradycardia
Lorazepam	Onset: 5–20 min Duration: 4–8 hr; prolonged with continuous infusion	Delirium, renal failure	N/A	Intermittent: 1–4 mg IV every 4–6 hr	Oversedation, propylene glycol toxicity
Midazolam	Onset: 3–5 min Duration: 2–6 hr, prolonged with continuous infusion	Hepatic failure, end-stage renal failure or dialysis, delirium	3A4 (active metabolite)	0.02–0.1 mg/kg/hr	Oversedation

CI = continuous infusion; IV = intravenously; LD = loading dose; MD = maintenance dose; N/A = not applicable; PRIS = propofol-related infusion syndrome

- C. SCCM provides the following statement in the PAD guidelines regarding sedation in the ICU: “We suggest that sedation strategies using non-benzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred to sedation with benzodiazepines (either midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated adult ICU patients” (+2B recommendation).” SCCM further states that “benzodiazepine use may be a risk factor for the development of delirium in adult ICU patient” (level B quality of evidence). Two randomized studies evaluated the differences in clinical outcomes while adult ICU patients were receiving sedation with either a benzodiazepine or a non-benzodiazepine strategy. Heterogeneity occurred among the findings of these two studies (see No. 1 and No. 2 below), which may be partly because of differences in study design.

1. The MENDS study compared the sedative effects of lorazepam and dexmedetomidine in medical and surgical adult ICU patients (n=103). Dexmedetomidine had more “delirium-free + coma-free” days than lorazepam (7 vs. 3 days, $p=0.01$), and the prevalence of “delirium or coma” was lower in the dexmedetomidine group (87% vs. 98%, $p=0.03$). The assessment of “delirium-free + coma-free” was the most appropriate outcome to evaluate as compared with “delirium without coma,” given that delirium cannot be assessed for in patients with coma. More patients were within 1 point of their RASS goal with dexmedetomidine (67%) than with lorazepam (55%), $p=0.008$, but there was no difference in mechanical ventilator-free days, ICU length of stay, or 28-day mortality. This study has been critiqued because both groups received continuous infusions of sedatives without additional bolusing, whereas in clinical practice most practitioners would bolus lorazepam before increasing the infusion rate. Additionally, patients were not required to have a spontaneous awakening trial (SAT). (JAMA 2007;298:2644-53).

2. The SEDCOM study compared the sedative effects of midazolam with those of dexmedetomidine in medical and surgical adult ICU patients (n=366). The prevalence of delirium was lower in the dexmedetomidine group (54%) than in the midazolam group (76.6%), $p<0.001$. Median time to extubation was shorter in the dexmedetomidine group (3.7 days) than in the midazolam group (5.6 days), $p<0.01$; however, the times in target sedation range, ICU length of stay, and mortality were no different between the two groups. This study did allow bolus dosing of study drugs, and patients were required to have an SAT if safety criteria were met (JAMA 2009;301:489-99).
- D. Clinical Outcome Differences Among Sedative Agents in Medical and Surgical ICU Patients: A recent meta-analysis, "Benzodiazepine versus Nonbenzodiazepine-Based Sedation for Mechanically Ventilated Critically Ill Adults," reviewed trials from 1996 to 2013 (Crit Care Med 2013;41:S30-8):
1. Studies from this review contained the following criteria: (1) randomized controlled parallel-group design; (2) medical and surgical adult ICU patients on mechanical ventilation receiving intravenous sedation; (3) patients receiving a non-benzodiazepine (propofol 1% or dexmedetomidine) compared with a benzodiazepine (lorazepam or midazolam); and (4) patients having predefined outcomes. Excluded cardiac surgery and obstetric patients.
 2. Four primary outcomes from six randomized trials were reported in the review (1235 patients):
 - a. ICU length of stay (all six studies reported): ICU length of stay was longer in a benzodiazepine strategy than in a non-benzodiazepine-based strategy (mean difference 1.6 days; 95% confidence interval [CI], 0.72–2.5; $p=0.0005$).
 - b. Duration of mechanical ventilation (four studies reported): Longer duration of mechanical ventilation in a benzodiazepine-based strategy than in a non-benzodiazepine-based strategy (mean difference 1.9 days; 95% CI, 1.7–2.09; $p=0.00001$)
 - c. Delirium prevalence (two studies reported): No difference in delirium prevalence between a benzodiazepine and a non-benzodiazepine-based strategy (relative risk [RR] 0.98; 95% CI, 0.76–1.27; $p=0.94$)
 - d. Short-term (45 days or less) all-cause mortality (four studies reported): No difference in risk of death between a benzodiazepine and a non-benzodiazepine-based strategy (RR 0.98; 95% CI, 0.76–1.27, $p=0.94$)
 3. A multicenter, randomized study, MENDS 2: Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Septic Patients with Acute Respiratory Failure, is currently being conducted to compare propofol and dexmedetomidine to determine the best sedative medication to decrease delirium and improve survival and long-term brain function in septic patients.
- E. Propofol (Diprivan)
1. SCCM suggests using a non-benzodiazepine (propofol or dexmedetomidine) for sedation to improve clinical outcomes in mechanically ventilated patients (+2B recommendation). Throughout the past decade, propofol has been increasingly used worldwide for sedation in the ICU. Propofol's short duration of action, lack of accumulation, and relatively clean adverse effect profile at low to moderate doses makes it an appealing alternative.
 2. Mechanism of action: General anesthetic by potentiation of the GABAA receptor; may inhibit *N*-methyl-D-aspartate receptor activity at high doses. Propofol decreases cardiac β -adrenergic responsiveness and attenuates β -adrenergic signal transduction in cardiac myocytes, resulting in direct cardiac depressive effects.
 3. Pharmacokinetics: Hepatic conjugation; clearance may be prolonged (from minutes to hours) in patients with severe hepatic impairment or cirrhosis or with long-term infusions as it redistributes from fat and muscle to plasma. Highly lipophilic pharmacokinetics and a large volume of distribution lead to extensive tissue distribution. Propofol maintains a three-compartment linear model: plasma, rapidly equilibrating

- tissues (e.g., major organs), slowly equilibrating tissues (e.g., fat deposits). Substrate of CYP 2B6, 2C9, 2C19, and 3A4; pharmacokinetic studies of healthy volunteers show a 25% increase in propofol plasma concentrations when given with midazolam, a weak CYP 3A4 and 2C9 inhibitor.
4. Lipid formulation considerations: Standard propofol is a 1% (10 mg/mL) lipid emulsion containing 1.1 kcal/mL (0.1 g of fat per 1 mL of propofol); this should be accounted for when calculating nutritional intake (e.g., propofol at 50 mcg/kg/minute in a 70-kg patient would provide around 500 calories per day contributed by fat). Propofol contains 0.005% disodium edetate (EDTA) to decrease the rate of microorganism growth, which is known to chelate trace metals, including zinc. Zinc supplementation should be considered in patients at high risk of zinc deficiency (sepsis, burns, large-volume diarrhea) if propofol is used for more than 5 days. Strict aseptic technique must be followed when handling propofol; manufacturers recommend discarding propofol bottles and changing intravenous tubing every 12 hours to decrease the risk of contamination.
 5. Dosing range for ICU sedation: Usual starting dose 5–10 mcg/kg/minute, titrated every 5–10 minutes to goal sedative effect. Abrupt discontinuation of propofol is not recommended because of its rapid clearance (5–10 minutes).
 6. Data: In a multicenter European trial (PRODEX), Jakob et al. compared propofol (n=249) with dexmedetomidine (n=251) for sedation in prolonged mechanical ventilation. Patients in both groups were treated with daily sedation interruption trials and spontaneous breathing trials (SBTs), and pain was treated with fentanyl boluses. Proportion of time in target RASS (0, -3) without rescue therapy was the same in the propofol group (65%) as in the dexmedetomidine group (65%). There was no difference in median time on mechanical ventilation in propofol (5 days) versus dexmedetomidine (4 days), $p=0.24$. Patients' ability to communicate discomfort was better in the dexmedetomidine group. Rates of hypotension and bradycardia were similar between the two groups. Critical illness polyneuropathy was more common in the propofol group (n=11) than in the dexmedetomidine group (n=2), $p<0.02$. The composite outcome of agitation, anxiety, and delirium occurred in propofol (29%) versus dexmedetomidine (18%) ($p=0.008$) (JAMA 2012;307:1151-60).
 7. Adverse effects: Bradycardia and hypotension (may be more common or severe in patients with cardiac dysfunction, intravascular volume depletion, or low systemic vascular resistance); respiratory depression, hypertriglyceridemia, pancreatitis with or without hypertriglyceridemia, PRIS
 8. PRIS: This is a rare but life-threatening complication of propofol, usually occurring at doses greater than 50 mcg/kg/minute for 48 hours or more. The mechanism of PRIS may include alterations in the liver metabolism of the lipid emulsion, leading to an accumulation of ketone bodies and lactate and/or disruptions in the mitochondrial respiratory chain and inhibition of oxidative phosphorylation. Patients with urea cycle disorders may experience alterations in propofol metabolism within 24–48 hours of propofol use. Consider avoiding in patients with acute liver failure, or pancreatitis, because the symptoms of PRIS may be difficult to distinguish from the underlying disease state abnormalities. PRIS carries a high mortality rate, and propofol should be discontinued immediately if symptoms are present.
 - a. Clinical characteristics of PRIS: Metabolic acidosis, acute renal failure, cardiovascular collapse, cardiac arrhythmias including Brugada-like syndrome, rhabdomyolysis, myoglobinemia, myoglobinuria, hyperkalemia, hypertriglyceridemia, elevated creatine kinase concentrations
 - b. Risk factors for PRIS or other adverse effects of propofol: Neurologic injury, sepsis, use of vasoactive medications, high-dose propofol, acute liver failure

F. Dexmedetomidine (Precedex)

1. SCCM suggests that in adult ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal, dexmedetomidine infusions rather than benzodiazepine infusions should be administered for sedation to reduce the duration of delirium (+2B recommendation). Dexmedetomidine is considered a weak sedative with opiate sparing analgesic properties. Although ICU surveys report low use of dexmedetomidine compared with other sedatives, clinical outcomes research of dexmedetomidine has shown favorable results.
2. Mechanism of action: Highly selective and dose-dependent α_2 -adrenoceptor agonist in the CNS. Dexmedetomidine provides a hypnotic and sedative effect by inhibition of norepinephrine release from the locus coeruleus; dexmedetomidine also produces a weak antinociceptive effect by way of inhibition of neuronal transmission through presynaptic C-fibers and release of substance P, and hyperpolarization of postsynaptic α receptors in the dorsal horn of the spinal column. Dexmedetomidine does not directly affect respiratory drive; therefore, intubation is not required with use. Dexmedetomidine is considered a weak sedative and would not be appropriate for use when deep sedation is required (e.g., in a patient requiring neuromuscular blockade). Both anterograde amnesia and retrograde amnesia have been described in a small proportion of patients (20%–50%) in adult and pediatric studies. A benzodiazepine may be required if full amnesia is desired because of the clinical scenario.
3. Pharmacokinetics: Hepatic by glucuronidation and renal excretion. Onset with loading dose 15–20 minutes; onset without loading dose greater than 20 minutes to 1 hour; terminal half-life = 3 hours (may be significantly prolonged in hepatic impairment). Highly protein bound 94%.
4. Clinical effects: Sedation and weak opiate-sparing antinociceptive effects.
5. Dosing for ICU sedation: Optional loading dose 0.5–1 mcg/kg intravenously for 10 minutes, followed by 0.2–0.7 mcg/kg/hour. The loading dose may initially cause severe tachycardia and hypertension, but it can then quickly lead to significant bradycardia and/or hypotension secondary to receptor saturation. Because of these untoward hemodynamic effects, the loading dose is rarely administered in clinical ICU practice on initiation of dexmedetomidine, and the drip is usually initiated at 0.2–0.4 mcg/kg/hour. For the maintenance infusion dose, randomized trials have safely used dexmedetomidine at higher than manufacturer-recommended doses, up to 1.5 mcg/kg/hour. Clinical efficacy with doses greater than 1.5 mcg/kg/hour remains unclear. Other routes of administration have been described for dexmedetomidine, including intramuscular, subcutaneous, epidural, and intranasal.
6. Duration of use: Although the package insert recommends a therapy of 24 hours or less, randomized trials have used dexmedetomidine for up to 5–7 days; thus, ICU clinicians often administer dexmedetomidine for longer than 24 hours. Safety beyond 7 days of use has not been well established.
7. Data: The Dexmedetomidine to Lessen ICU Agitation (DahLIA) study was a double-blind placebo-controlled, parallel-group randomized clinical trial in 15 ICUs in Australia and New Zealand in which 39 patients were randomized to dexmedetomidine and 32 patients to placebo. At 7 days, dexmedetomidine increased ventilator-free hours compared with placebo (median, 144.8 hours vs. 127.5 hours, 95% CI 4 to 33.2 hours, $p=0.01$). Patients in the dexmedetomidine group had decreased time to extubation as compared with placebo (median 21.9 hours vs. 44.3 hours, 95% CI 5.3 to 3.1 hours, $p<0.001$). An accelerated resolution of delirium was found in the dexmedetomidine group as compared with placebo (median, 23 hours vs. 40 hours, 95% CI 3 to 28 hours, $p=0.01$). However, propofol use was common in both groups after randomization (72% in the dexmedetomidine group vs. 88% in the placebo group (median cumulative dose 980 mg (IQR 280-3050) vs. 5390 mg (IQR 1880-10803), $p<0.001$).
8. Adverse effects: Tachycardia, bradycardia, hypertension, hypotension, dry mouth. Should generally be avoided in patients with acute decompensated heart failure or advanced heart block.
9. Other potential uses in the ICU: Procedural sedation, palliative care pain and anxiety control, adjunct to opiates for sickle cell crisis, adjunct to benzodiazepines or propofol for alcohol withdrawal, bridge to extubation while tapering off longer-acting sedatives and/or opiates, to provide sedation and anxiolysis during noninvasive mechanical ventilation

G. Lorazepam (Ativan)

1. Pharmacokinetics: Benzodiazepine that binds to the postsynaptic GABA_A receptor, undergoes hepatic clearance by conjugation to inactive compounds; moderate to high volume of distribution and high protein binding. Onset of action is 15–30 minutes, slower than more lipophilic benzodiazepines (e.g., midazolam). Duration of action of intermittent dosing is 4–8 hours. As a continuous infusion, clearance of lorazepam decreases in an unpredictable fashion, and prolonged sedation may occur.
2. Effects: Anxiolysis/sedation, anticonvulsant, muscle relaxant. Maintains anterograde amnesia properties; however, studies report that patients who received benzodiazepines in the ICU may maintain delusional versus factual memories.
3. Dosing range: 1–4 mg every 4–6 hours intermittent dosing is recommended before using continuous infusion; accumulation and prolonged awakening times with continuous infusion of lorazepam may occur because of prolonged duration of action.
4. Data: Carson et al. studied the number of days on mechanical ventilation in medical ICU patients receiving intermittent lorazepam (n=64) compared with continuous infusion propofol (n=68); each group underwent daily interruption of sedation if the fraction of inspired oxygen (F_{IO₂}) was less than 80%. Median time on mechanical ventilation was 9 days in the lorazepam group versus 4.4 days in the propofol group, p=0.006; ICU length of stay was 12.7 days in the lorazepam group versus 8.6 days in the propofol group (p=0.05); no difference in hospital mortality. Delirium was not assessed in this study (Crit Care Med 2006;34:1326-32).
5. Propylene glycol toxicity: Because of its insolubility, injectable lorazepam is diluted in propylene glycol. Propylene glycol toxicity can occur with lorazepam infusions for more than 48 hours, particularly at doses of 6–8 mg/hour or greater, and can manifest as new-onset renal failure, respiratory failure, metabolic acidosis, and altered mental status. Most hospitals cannot measure quantitative levels of propylene glycol, therefore surrogate markers of propylene glycol toxicity such as an elevated osmolar gap (>10) and elevated anion gap with new metabolic acidosis are recommended for monitoring. If these metabolic abnormalities are present while on a lorazepam infusion, the lorazepam should be discontinued.
6. Other adverse effects: Paradoxical agitation, confusion, prolonged duration of sedative action, respiratory depression, hypotension, bradycardia

H. Midazolam (Versed)

1. Pharmacokinetics: Benzodiazepine that binds to the postsynaptic GABA_A receptor; undergoes phase I hepatic metabolism to an active glucuronidated metabolite, α_1 -hydroxymidazolam, which is then renally excreted. A short- to medium-acting benzodiazepine in patients with normal renal and hepatic function. CYP3A4 substrate. Midazolam is highly lipophilic, has a large volume of distribution, and is highly protein bound.
2. Clearance: Clearance of midazolam or its metabolite is significantly altered if either hepatic (primary drug accumulation) or renal (active metabolite α -hydroxymidazolam accumulation) functions are significantly impaired. Continuous renal replacement therapy partly clears the active metabolite but does not effectively clear the parent compound and is therefore not recommended as a method for definitive midazolam clearance (Am J Kidney Dis 2005;45:360-71). High lipophilicity and a large volume of distribution may lead to significant drug accumulation and a depot effect in the ICU patient. In general, clearances of midazolam infusions have wide interpatient variability in the ICU, and emergence times may be significantly prolonged.
3. Effects: Anxiolysis/sedation, anticonvulsant, muscle relaxant. Maintains anterograde amnesia properties.
4. Dosing range: 1–4 mg every 2–4 hours intermittently or as needed should be considered before initiating continuous infusion. Older adult patients may tolerate only 1–2 mg per dose.

5. Data: In a multicenter European trial (MIDEX), Jakob et al. compared midazolam (n=251) with dexmedetomidine (n=249) for sedation in prolonged mechanical ventilation. Patients in both groups were treated with daily sedation interruption trials and SBTs, and pain was treated with fentanyl boluses. There was no difference in the primary outcome: proportion of time in target RASS (0, -3) without rescue therapy in the midazolam group (56%) versus the dexmedetomidine group (60%). Median time on mechanical ventilation was lower in the dexmedetomidine group (5 days) than in the midazolam group (6.8 days), $p=0.03$. Patients in the dexmedetomidine group were more arousable, more cooperative, and better able to communicate discomfort or pain to clinical staff than were patients in the midazolam group. Hypotension occurred more often in the dexmedetomidine group (20.6%) than in the midazolam group (11.6%; $p=0.007$); and bradycardia was more common in the dexmedetomidine group (14.2%) than in the midazolam group (5.2%; $p<0.001$). The two treatment groups showed no difference in neurocognitive adverse events after 48 hours of follow-up, including agitation, anxiety, and delirium (JAMA 2012;307:1151-60).
 6. Adverse effects: Paradoxical agitation and prolonged duration of sedative action, respiratory depression, hypotension, bradycardia
- I. Amnestic Effects of Sedatives: Lorazepam, midazolam, and propofol all produce anterograde amnesia. This may be a beneficial effect of these drugs in certain ICU settings.
- J. Titration of Sedation in the ICU
1. Titration of medications using a sedation protocol to a goal level of sedation is arguably one of the most salient clinical practice standards within ICU care. This titration practice has consistently been shown to decrease time on mechanical ventilation, decrease ICU length of stay, and decrease rates of tracheostomy, which may all result in faster physical and cognitive rehabilitation time.
 - a. The goal level of sedation should be reassessed daily, documented, and communicated clearly to the nursing and medical staff because the goal may change throughout a patient's ICU stay.
 - b. Level of sedation should be assessed every 2–4 hours throughout the day and evening. Consider assessing every 4 hours during nighttime sleeping hours to minimize sleep interruption.
 - c. The two validated sedation scales currently recommended by the PAD guidelines are the RASS (Table 5) and the Riker Sedation-Agitation Scale (Table 6).
 2. Recommended methods for titration of medications include either (1) titration to a “light” versus “deep” level of sedation, unless clinically contraindicated, or (2) daily SAT (+1B recommendation). The PAD guidelines detail an important distinction for “light” sedation as not solely a number on a sedation scale but as a level of purposeful interaction and ability to follow commands:
 - a. Patients should receive sedation only if required.
 - b. Sedatives should be titrated to allow patient responsiveness and awareness, as shown by patients' ability to purposefully respond to a combination of any three of the following actions on request: open eyes, maintain eye contact, squeeze hand, stick out tongue, and wiggle toes. A numerical score on a sedation scale may not fully represent a patient's ability to follow purposeful commands.
 3. Data: In a multicenter, prospective, longitudinal Australian and New Zealand Study, Shehabi et al. evaluated 251 medical/surgical patients that were ventilated and sedated ≥ 24 hours. Within 4 hours of commencement of ventilation, deep sedation occurred in 191 (76.1%) of patients and in 171 (68%) of patients at 48 hours. Early deep sedation was an independent predictor of time to extubation (HR 0.90, 95% CI 0.87-0.94, $p<0.001$), hospital death (HR 1.11, 95% CI 1.02-1.20, $p=0.01$), and 180-day mortality (HR 1.08, 95% CI 1.01-1.16, $p=0.026$) (JAMA 2012;307:1151-60).

4. In a single center, nested cohort study within the Awakening and Breathing Controlled (ABC) randomized trial, Seymour, et al. evaluated 140 patients in which hourly doses of benzodiazepines and propofol during the daytime (7 a.m. to 11 a.m.) and nighttime (11 p.m. to 7 a.m.) for 5 days) were measured. Greater daytime benzodiazepine doses were independently associated with failed SBT and extubation and subsequent delirium in adjusted models ($p < 0.02$ for all). A failed SBT ($p < 0.01$) and delirium ($p = 0.05$) were associated with nighttime increases in benzodiazepine doses (Crit Care Med 2012 40:2788-96).
- K. SAT Paired with SBT: The daily coordination of an SAT completed before an SBT is a method of weaning sedation before attempts at breathing trials in order to maximize a patient's chances of weaning from mechanical ventilation. This pairing of an SAT before an SBT is becoming recognized as an important component to ICU care and management of sedation. Important safety screens are incorporated into the daily SAT because studies have shown that the SAT is not appropriate for all ICU patients. If a patient does not pass the safety screen and does not undergo the SAT, this should not preclude the appropriate titration of sedatives to a goal level of sedation throughout the remainder of the day:
 1. SAT safety screen (criteria may vary; published trial protocols have had variations): If any are present, discontinue the protocol and repeat in 12–24 hours or according to hospital protocol:
 - a. Current RASS > 2 ; or goal for deeper sedation (e.g., RASS -3 to -5)
 - b. Active seizures requiring a continuous infusion of a sedative to control
 - c. Active alcohol withdrawal requiring a continuous infusion of a sedative to control
 - d. $\text{FiO}_2 \geq 70\%$ (these criteria are not consistently present among published trial protocols)
 - e. Neuromuscular blockade
 - f. Myocardial ischemia in previous 24 hours or ongoing myocardial ischemia
 - g. Intracranial pressure (ICP) > 20 mm Hg or need for control of ICP
 2. If pass SAT safety screen, begin SAT: Hold continuous sedative and analgesic infusions. Bolus opioids are recommended for breakthrough pain. Continuous opioid infusions allowed to continue while stopping sedatives if presence of active pain. If the patient “passes” the SAT, continue to the SBT safety screen.
 3. SAT failure (if any are present, discontinue the protocol, and repeat in 12–24 hours or according to hospital protocol):
 - a. Anxiety/agitation/pain present (e.g., RASS greater than +1 for 5 minutes or more)
 - b. Respiratory rate greater than 35 breaths/minute for 5 minutes or more
 - c. Oxygen saturation $< 88\%$ for 5 minutes or more
 - d. ICP greater than 20 mm Hg
 - e. Acute cardiac ischemia or arrhythmia
 - f. Respiratory or cardiac distress (e.g., heart rate increase of 20 beats/minute or greater, heart rate less than 55 beats/minute, use of accessory muscles, abdominal paradox, diaphoresis, or dyspnea)
 4. If SAT fails: Consider giving patient bolus opioids first (up to 3 doses in 1 hour) before restarting infusion. Reinitiate sedation infusion, if necessary, at half the previous dose and titrate to goal. Determine the reasons for SAT failure. Repeat SAT steps in 12–24 hours or according to hospital protocol.
 5. SBT safety screen (if any are present, discontinue the protocol; repeat in 12–24 hours or according to hospital protocol):
 - a. Agitation
 - b. Oxygen saturation less than 88%, $\text{FiO}_2 > 50\%$
 - c. PEEP (positive end expiratory pressure) ≥ 7.0 cm H_2O
 - d. Myocardial ischemia in previous 24 hours
 - e. Increasing vasopressor requirements
 - f. Lack of inspiratory efforts
 6. SBT: If a patient tolerates the SBT for 30 to 120 minutes, consider extubation.

7. SBT failure:
 - a. Respiratory rate > 35 breaths/minute (for more than 5 minutes) or less than 8 breaths/minute
 - b. Oxygen saturation < 88% for more than 5 minutes
 - c. ICP > 20 mm Hg, mental status change
 - d. Acute cardiac ischemia or arrhythmia
 - e. Respiratory distress (use of accessory muscles, abdominal paradox, diaphoresis, and dyspnea)
 8. If SBT fails: Put the patient on prior ventilator settings. Repeat bundle in 12–24 hours or according to hospital protocol.
- L. Sedation Protocol Compared with the Paired SAT-SBT Protocol: Studies comparing a standard sedation protocol with daily pairing of a SAT with SBT have shown decreased days on mechanical ventilation, days in the ICU, and decreased rates of delirium when the SAT is paired with the SBT.
1. The ABC trial included 336 mechanically ventilated patients from four tertiary care hospitals. Patients were randomized to patient-targeted sedation protocol plus the SBT (“usual care” control group) or to daily SAT paired with the SBT (intervention group). Both groups were deeply sedated on enrollment (RASS -4), and both groups had been admitted for 2.2 days before enrollment. In the intervention group, patients who passed the safety screen underwent an SAT: sedatives and analgesics used for sedation were discontinued, and analgesics used for active pain were continued. Patients “passed” their SAT if they opened their eyes to command or tolerated being off sedation for at least 4 hours without meeting failure criteria. The mean ventilator-free days was 11.6 days in the usual care control group versus 14.7 days in the SAT plus SBT group ($p=0.02$). The time to discharge was 12.9 days in the control group versus 9.1 days in the intervention group ($p=0.01$). Self-extubations were higher in the intervention group, but there was no difference in self-extubations requiring reintubation between groups. Rates of delirium assessed by the confusion assessment method for the intensive care unit (CAM-ICU) were no different between groups (74% vs. 71%).
 2. The first study evaluating the ABCDE (Awakening and Breathing Coordination, Delirium Monitoring/Management, and Early Mobility) Bundle compared clinical outcomes in patients before ($n=146$) and after ($n=150$) bundle-protocol implementation; 187 patients were on mechanical ventilation. The bundle protocol consisted of a daily-paired SAT/SBT, delirium screening with the CAM-ICU every 8 hours, and an early mobility protocol. The “before” bundle patients were enrolled from February to October 2011; the “after” bundle patients were enrolled from October 2011 to April 2012. There were some differences in patient type on admission, including more elective admissions in the post-bundle group (39 vs. 30), more cardiothoracic surgery patients in the post-bundle group (20 vs. 6), more surgical patients in the pre-bundle group (21 vs. 11), and more patients coming from an outside hospital in the pre-bundle group (9 vs. 1). The post-bundle group had more median ventilator-free days (24 vs. 21 days, $p=0.04$), less delirium at any time (49 vs. 62%, $p=0.03$), and less percentage of ICU days with delirium (33.3 vs. 50%, $p=0.003$).
 3. The SLEAP investigators from the Canadian Critical Care Trials Group studied the outcomes of patients receiving a daily sedation protocol alone versus patients receiving a daily sedation protocol plus a daily sedation interruption (Crit Care Med 2015;43:557-66; Crit Care Med 2015;43:2180-90; JAMA 2012;308:1985-92). From January 2008 to July 2011, 430 patients were enrolled from 16 tertiary care medical and surgical ICUs. Only opiate and benzodiazepine infusions were allowed in the study. According to the sedation-alone protocol, the RASS goal was -3 to 0, and the Sedation-Agitation Scale (SAS) goal was 3 or 4. Nurses assessed sedation levels on an hourly basis and titrated medications every 15–30 minutes to achieve sedation goals. If patients were oversedated in either group (SAS 1 or 2; RASS -4 or -5), infusions were discontinued. According to the sedation protocol with daily sedation interruption, nurses stopped benzodiazepine and opiate infusions once a day and assessed hourly for wakefulness (e.g., a light SAS or RASS score, plus ability to follow at least three commands).

- a. Clinical outcomes (published 2012): There was no difference in the primary outcome of time to successful extubation between the two groups (7 days in both groups). There was a significant difference in time to extubation in the prespecified surgical/trauma group between sedation protocol with daily sedation interruption and sedation protocol alone (6 vs. 13 days; hazard ratio [HR] 2.55; 95% CI, 1.40–5.44). No difference in time to extubation was detected between groups among medical ICU patients (9 vs. 8 days; HR 0.92; 95% CI, 0.72–1.18). However, significantly lower daily doses of both benzodiazepines and opiates boluses and continuous infusions were used in the sedation protocol–alone group than in the sedation protocol plus interruption group. Although the sedation protocol suggested to target lights sedation, the actual mean RASS/SAS was not reported for either group making it unclear how deeply sedated either group was.
 - b. Delirium outcomes (published 2015): Delirium by the Intensive Care Delirium Screening Checklist (ICDSC) was diagnosed in 53.8% of patients in the study; there was no difference in delirium in the sedation protocol–alone group versus the protocol plus daily sedation interruption group. Patients who had delirium had a longer duration of mechanical ventilation, longer ICU and hospital stay, longer use of restraints, higher rates of tracheostomy, and higher incidence of unintentional device removal. Patients with delirium received almost the twice the mean dose of midazolam equivalents/patient/day (104 mg vs. 57 mg), higher fentanyl equivalents/patient/day (1497 mcg vs. 1150 mcg), more frequent use of anticholinergics (18 vs. 8.6%), and more frequent use of trazadone or zopiclone (17.7 vs. 9.8%) than did patients who were not delirious. Patients who developed delirium had a higher incidence of alcohol and cigarette use than did patients who did not develop delirium.
 - c. Recall in ICU survivors (published 2015): The SLEAP investigator study did patient interviews on days 3, 28, and 90 post-ICU discharge to determine differences in recall between the sedation-alone protocol group and the protocol plus daily sedation interruption group. There were no differences in type of recall between the sedation strategies. Delusional memories were common at day 28 (70% of patients) but were unrelated to the presence of delirium or the total dose of benzodiazepines or opiates. Patients with no recall had received lower total doses of benzodiazepines than had patients with recall. Emotional memories such as panic and confusion declined over time.
- M. The PAD guidelines suggest using objective measures of brain function (e.g., auditory evoked potentials, Bispectral index) as an adjunct to subjective sedation assessments in adult ICU patients concomitantly receiving an NMBA (+2B); the guidelines also recommend that “electroencephalogram monitoring be used to monitor nonconvulsive seizure activity in adult ICU patients with either known or suspected seizures or to titrate electrosuppressive medication to achieve burst suppression in adult ICU patients with elevated intracranial pressure (+1A).”

Table 5. Richmond Agitation-Sedation Scale (RASS)

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

Table 5. Richmond Agitation-Sedation Scale (RASS) (*continued*)

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

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Table 6. Riker Sedation-Agitation Scale

7	Dangerous agitation	Pulling at ETT, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting ETT
5	Agitated	Anxious or mildly agitated, trying to sit up, calms down to verbal instructions
4	Calm and cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
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

ETT = endotracheal tube

Adapted with copyright permission from: Lippincott Williams and Wilkins/Wolters Kluwer Health. Simmons LE, Riker RR, Prato BS, et al. Assessing sedation during intensive care unit mechanical ventilation with the Bispectral Index and the Sedation Agitation Scale. *Crit Care Med* 1999;27:1499-504.

N. Acute Withdrawal Syndrome of Long-term Analgesia and/or Sedation in the ICU

1. Patients who have been receiving high doses of continuous infusion sedation and/or analgesia in the ICU for an extended period may be at risk of sedative or analgesia withdrawal as dose tapering begins. In a retrospective review of adult trauma/surgical ICU patients, 32% of patients experienced either sedative or opiate withdrawal soon after discontinuing these medications. The patients in this study had been in the ICU for 20 days or more and were receiving higher mean daily analgesic and sedative doses than were the non-withdrawal patients (fentanyl 6.4 mg vs. 1.4 mg; lorazepam 38 mg vs. 11 mg). The withdrawal patients in this study were also more likely to have received an NMBA (*Crit Care Med* 1998;26:676-84).
2. The risk factors and incidence of sedation or analgesia withdrawal in adult ICU patients have not been well characterized; however, these are important considerations in the long-term ICU patient receiving high doses of these medications. Use of longer-acting agents given orally or by feeding tube has been described to assist in the transition off long-term continuous infusions. The medical indication and dosing plan for using oral medications to taper off continuous infusions should be clearly documented in the medical chart on patient discharge from the ICU.

Patient Cases

3. A 48-year-old man with cirrhosis and now hepatorenal syndrome was intubated for respiratory distress. He has been receiving midazolam 1 mg/hour and fentanyl 75 mcg/hour for 2 days; his RASS (-4 to -5) and pain score have been negative for 24 hours. Oxygen requirements have decreased, and vital signs are normal. Which is the most appropriate change in his medications?
 - A. Discontinue midazolam; give as-needed lorazepam for agitated RASS score.
 - B. Decrease midazolam; give as-needed fentanyl for agitated RASS score.
 - C. Discontinue midazolam; initiate propofol drip.
 - D. Change midazolam to dexmedetomidine drip.
4. T.L. is a 55-year-old woman intubated for respiratory distress for severe pneumonia. She is receiving fentanyl 50 mcg/hour and dexmedetomidine 1.0 mcg/kg/hour. Her home medications are confirmed to include esomeprazole 20 mg daily, lorazepam 1 mg three times daily, and citalopram 10 mg daily. The nurse reports intermittent agitation with tachycardia and a negative pain score. Which is the most appropriate recommendation?
 - A. Increase fentanyl drip for agitated RASS score.
 - B. Reinitiate lorazepam and citalopram.
 - C. Give fentanyl boluses as needed for agitation.
 - D. Increase dexmedetomidine.

IV. DELIRIUM IN THE INTENSIVE CARE UNIT

- A. Delirium is an acute and fluctuating disturbance in consciousness resulting in the inability to receive, process, store, or recall information. In the ICU, delirium may present as hyperactive (agitated and restless), hypoactive (flat affect, apathy, lethargy, decreased responsiveness), or mixed hyper/hypoactive states. Most common in the ICU are mixed and hypoactive states of delirium. Two screening tools are currently recommended by the PAD guidelines: (1) the CAM-ICU and (2) the ICDSC. Both the CAM-ICU and the ICDSC require a RASS (-3) or a SAS (3) or more alert to be completed.
 1. The CAM-ICU assesses four features: (1) acute change or fluctuation in mental status from baseline, (2) inattention, (3) altered level of consciousness, and (4) disorganized thinking. If features 1 *and* 2 plus feature 3 *or* 4 are present, the patient is considered positive for delirium. Detailed training is available at www.icudelirium.org.
 2. The ICDSC consists of eight items, evaluated during an 8- to 24-hour period. The eight symptoms are level of consciousness, inattention, disorientation, hallucinations-delusions-psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep-wake cycle disturbances, and symptom fluctuation. A point is given for any symptom that is present during the previous 24 hours; a score of 4 or higher indicates the presence of delirium.
- B. Background – 30%–80% of ICU patients reportedly develop delirium, depending on the severity of illness and the diagnostic method, yet assessment for delirium is still not routine in most U.S. ICUs. During a patient's hospitalization, the presence of delirium is associated with difficulty in weaning mechanical ventilation and longer duration of mechanical ventilation, increased use of physical and chemical restraints, longer duration of ICU stay, and additional stress to family and friends who may not understand the course of delirium.

Delirium is also associated with up to a 3-fold increase in mortality, increase in cognitive decline, delay in cognitive recovery, and increased likelihood of being discharged to a nursing home. Two studies found that a longer duration of delirium was independently associated with worse activity of daily living scores and worse cognitive impairment scores at 3 and 12 months post-ICU discharge (Crit Care Med 2014;42:369-77; N Engl J Med 2013;369:1306-16). A recent retrospective study reported increased difficulty in the weaning of mechanical ventilation when delirium was detected in patients during the first spontaneous weaning trial compared with in patients who did not have delirium (Respirology Nov 2015;1-8).

1. The underlying pathophysiology of delirium is not well understood; however, it may involve a complex set of factors:
 - a. Cerebral hypoperfusion and alterations in cerebral blood flow
 - b. Degradation of the blood-brain barrier, causing influx of inflammatory cytokines and microvascular thrombosis
 - c. Depletion in central neurotransmitters (e.g., dopamine, norepinephrine, serotonin)
 - d. Depletion in acetylcholine
 - e. Medication withdrawal
2. Risk factors for delirium: A recent systematic review of studies from 2001 to 2013 described 11 variables identified as risk factors for developing delirium in the ICU, extracting from only a strong or moderate level of evidence (Crit Care Med 2015;43:40-7):
 - a. Age
 - b. Preexisting dementia
 - c. History of baseline hypertension
 - d. Sedative-associated coma
 - e. APACHE II (Acute Physiology and Chronic Health Evaluation II) score
 - f. Delirium on the previous day
 - g. Emergency surgery
 - h. Mechanical ventilation
 - i. Organ failure
 - j. (Poly)trauma
 - k. Metabolic acidosis
3. Other reported risk factors or precipitants:
 - a. Infection
 - b. Dehydration or malnutrition
 - c. Sleep deprivation
 - d. Centrally acting medications (benzodiazepines, opiates, anticholinergics)
 - e. Lack of exposure to sunlight
 - f. Lack of personal interaction
 - g. Physical restraints or insertion of catheters or tubes
4. Medication-induced altered mental status – Although the development of delirium is considered multifactorial, any patient who presents with a change in mental status should have his or her medications and medication doses immediately scrutinized as part of the initial workup for delirium. Several classes of medications have long been recognized for their effects on mental status and cognitive function, in or out of the ICU. These medications have the potential to affect a patient's level of consciousness or course of delirium at any point in the patient's hospital stay. Anticholinergics, benzodiazepines, opiates, antipsychotics, antispasmodics, anticonvulsants, corticosteroids, and others should be used with caution in a hospitalized patient, with close monitoring of the patient's cognitive adverse effects. Because renal and hepatic function may fluctuate throughout an ICU stay and affect the clearance of these medications, doses must be thoughtfully titrated. Research on the degree of impact these medications have on the overall course of sedation and delirium in the ICU is difficult to characterize, and research is undergoing.

Given the multifactorial nature of delirium in the ICU, clinicians should be leery of solely assigning blame to medications but should remain vigilant when assessing the need and doses of the aforementioned medications.

- a. **Benzodiazepines:** The PAD guidelines state “benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients (B).” Of interest, research directed at finding an independent association between the use of benzodiazepines and the development of delirium in the ICU including a recent meta-analysis, a randomized trial, and a systematic review has yielded mixed results (Crit Care Med 2015;43:40-7; Crit Care Med 2015;43:557-66; Crit Care Med 2013;41:S30-8). Recently, investigators used more appropriate statistical analysis for a fluctuating illness such as delirium (e.g., Markov monitoring was used to determine the probability of a daily transition to delirium while assuming this was independent of the patient history beyond the prior day) in addition to more frequent delirium monitoring to examine the use of benzodiazepines and the transition from an awake state without delirium to delirium, or from coma to delirium by the next day (Intensive Care Med 2015;41:2130-7). This study found that a midazolam equivalent dose of just 5 mg/day increased the odds of developing delirium the next day by 4%, and the use of benzodiazepine infusions was an independent risk factor for the transition to delirium in the study population. However, there was a large difference in the daily dose of benzodiazepines between the continuous infusion (daily median dose 99 mg) as compared with the intermittent dosing group (daily median dose 4.1 mg), making one wonder if the risk factor for the transition to delirium was indeed the cumulative dose and not the method of administration. As the data evolve, the scrutiny of benzodiazepine use should persist for ICU clinicians. Routine strategies to preferentially use a non-benzodiazepine sedative (e.g., propofol or dexmedetomidine) and to avoid benzodiazepine infusions unless clinically indicated in addition to diligent performance of daily SATs to discontinue as soon as possible should be used.
- b. **Anticholinergics:** These medications are known for their sedating and altering effects on mentation and should be avoided or used with extreme caution in the ICU setting. One proposed mechanism for delirium is a decline in acetylcholine concentrations; therefore, any medication that may further inhibit the activity of acetylcholine could worsen the patient’s mental status. A prospective cohort study of 1,112 critically ill patients was conducted to determine if anticholinergic exposure increased the probability of transitioning to delirium. On 6% of ICU days, transition from “awake and without delirium” to “delirium” occurred. A nonsignificant increase in the probability of transitioning to delirium the following day resulted from a one unit increase in the Anticholinergic Drug Scale (odds ratio, 1.05; 95% CI 0.99-1.10). The dose of the medication was not evaluated to determine the effects on the transition to delirium, and it was not evaluated if patients were already delirious and remained delirious while receiving anticholinergic medications (Crit Care Med 2015;43:1846-52).
- c. **Systemic corticosteroids:** The neuropsychiatric effects of systemic steroids in various clinical settings have been described for more than 50 years. Common symptoms include mania, depression, mood lability, anxiety, insomnia, delirium, and psychosis. The incidence of these symptoms varies greatly depending on the clinical setting, dose of steroid, and patient’s underlying medical history. Reported risk factors for neuropsychiatric effects secondary to steroids include a daily prednisone dose equivalent to 40 mg or greater, hypoalbuminemia, underlying psychiatric disorder, and blood-brain barrier damage (Curr Opin Organ Transplant 2014;19:201-8). Although steroids are commonly used in the ICU for various indications and at various doses, significant research directed at the neuropsychiatric effects of steroids in the critically ill population is lacking. In a secondary analysis of a multicenter observational study of adult medical and surgical ICU patients with acute lung injury (n=330), Schreiber et al. found a significant and independent association between the use of systemic corticosteroids and the transition to delirium from a non-comatose, non-delirious state within 24 hours of corticosteroid administration (odds ratio [OR] 1.52 [1.05–2.21], p=0.03). Delirium

was documented on one or more days in 83% of patients, with a median duration of 7 days. There was no significant association in prednisone-equivalent dose and transition to delirium. Schreiber et al. recognize that a direct causal relationship could not be determined between corticosteroid use and delirium from this observational study; however, they believe that the study adds valuable data toward our understanding of risk factors for delirium in the ICU (Crit Care Med 2014;42:1480-6). A second study that investigated steroids and transition to delirium in a mixed medical and surgical ICU population (n=1112) found no association between steroid use and a transition to delirium. The median prednisone equivalent dose was 50 mg (Crit Care Med 2015;43:e585-8).

5. Outcomes of sedation-related versus illness-related delirium: A single-center study using propofol and fentanyl timed its CAM-ICU assessments before and after a daily sedation interruption protocol. Rapidly reversible delirium was defined as delirium while patients were receiving sedation that resolved within 2 hours after performing an SAT. This type of delirium was rare (12% of the 102 patients), but these patients has a prognosis that was similar to patients who did not have delirium. The large majority of patients (75%) has persistent delirium, delirium that did not resolve with cessation of sedatives, a higher risk of death, and longer length of stay. (Am J Respir Crit Care Med 2014;189:658-65). Patients can have both sedation-related and illness-related delirium, and additional research in this area is needed to clarify the differences in short- and long-term outcomes.
- C. Monitoring for Delirium: SCCM provides a grade 1B strong recommendation for routine monitoring in all ICU patients for delirium, using either the CAM-ICU or the ICDSC. The PAD guidelines summarized their review of five delirium assessment scales used for adult ICU patients. The two scales with the highest psychometric (e.g., validity and reliability) scores were the CAM-ICU and the ICDSC. Both scales were designed for patients in the ICU either on or off mechanical ventilation, and both showed high sensitivity and specificity when tested against the American Psychiatric Association's criteria for delirium.
1. Delirium should be assessed at least every 8-12 hours and documented in the medical chart; results should be discussed with the medical team. Because these assessment scales cannot distinguish between sedation-related and disease-related causes of delirium, delirium assessments should ideally be timed both before and after SATs with appropriate time allowed for drug clearance (www.icudelirium.org, Am J Respir Crit Care Med 2014;189:658-65). If this timing is not feasible and a patient screens positive for delirium while receiving ongoing analgesia or sedation, an SAT should be conducted if the patient passes the safety screen to assist in ruling out a medication-induced cause of delirium.
 2. If a patient's delirium score is positive, the medical team should correct possible etiologies (e.g., decrease sedative doses, if safe), decrease ongoing risk factors, address inciting factors (e.g., metabolic derangements, infection, withdrawal), and try nonpharmacologic treatment and preventive measures when appropriate.
- D. Prevention of Delirium: With a lack of data supporting the use of pharmacologic agents to prevent delirium, the PAD guidelines focus their recommendations on nonpharmacologic prevention methods when feasible, particularly for patients at high risk of delirium. Preventive efforts may help avert 30%–40% of new-onset delirium cases, particularly in older adults. Recommended nonpharmacologic strategies include:
1. Early mobilization (+1B recommendation)
 2. Decreasing nighttime disturbances to optimize a sleep environment: Cluster patient care activities and medication administration to daytime and evening to help normalize sleep patterns; control light and noise; consider earplugs at night in patients without delirium (+1C recommendation).
 3. Decrease the use of benzodiazepines and anticholinergics in patients at risk of delirium; use the lowest effective doses of any sedating medication (e.g., opiates, antipsychotics).

- E. Sleep in the ICU: Uninterrupted sleep (ideally 4 hours or more) is vital for an adequate immune response to illness, to maintain normal metabolic and hormonal balance, and to help decrease delirium and/or agitation. Disturbances in the ICU such as multiple alarms and frequent physical interruptions (e.g., examination, turning, laboratory tests, medication administration) make it challenging for patients to maintain the slow-wave sleep cycle needed for optimal immune function. Sleep research in the ICU is ongoing, and more information will be forthcoming regarding its effects in the critically ill patient. Currently, the PAD guidelines strongly recommend promoting sleep in adult ICU patients by optimizing patients' sleep environments (+IC recommendation):
1. To avoid waking patients at night, pharmacists should ensure that medications are scheduled during the daytime and evening hours, if possible—particularly orally or subcutaneously administered medications.
 2. Sleep protocols should seek to cluster patient care activities (e.g., vital sign checks, radiology tests, laboratory checks, sedation assessments) around nighttime sleeping hours unless clinically indicated in a specific patient population.
- F. Treatment of Delirium: The cause of delirium may be multifactorial, and identifying and correcting the underlying etiology is the first step in management. Patients can also progress to alcohol withdrawal or withdrawal from other chronic medications/substances and present with hyperactive delirium. The PAD guidelines state that "There is no published evidence that haloperidol reduces the duration of delirium (no evidence)" and that "atypical antipsychotics may reduce the duration of delirium in adult ICU patients" (grade C level of evidence). More data are needed to determine clinical outcomes with the use of antipsychotics for the treatment of delirium. The Modifying the Impact of the ICU-Associated Neurological Dysfunction-USA (MIND USA) Study is a multicenter study that is currently randomizing patients to placebo, ziprasidone, or haloperidol for the treatment of delirium. If an antipsychotic is initiated, low starting doses should be considered, and daily review of drug interactions, adverse effects, dosing titration, and need for the antipsychotic should be completed. Additionally, a strategy for discontinuation or outpatient follow-up should be documented to help avoid inadvertent continuation beyond the hospital environment (Table 7). Serious adverse effects are associated with the use of any antipsychotic; effects such as arrhythmias, serotonin syndrome, neuroleptic malignant syndrome, extrapyramidal symptoms, and oversedation should be closely monitored on a daily basis. Dose ranges for atypical antipsychotics for ICU delirium are not well described. The American Geriatrics Society 2015 Beers Criteria for medication use in older adults includes the following recommendation: "Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options have failed or are not possible AND the older adult is threatening substantial harm to self or others." If the ICU team decides to use antipsychotics in older adults, lower starting doses should be considered, together with daily review of drug interactions and adverse effects.
- G. Inadvertent Continuation of Antipsychotics Beyond ICU Discharge: The PAD guidelines discuss the use of adjunctive medications for ICU patients (e.g., antipsychotics, gabapentin, carbamazepine). Although their use in the ICU may be appropriate, there is a potential for inadvertent continuation of these medications on hospital discharge if a treatment plan is not clear in the medical record. This has been a well-documented problem with other medications initiated in the ICU (e.g., histamine receptor blockers, proton pump inhibitors), and recent studies have been published describing the continuation of newly prescribed antipsychotics from the ICU and hospital, even when an indication for continuation was not documented (J Crit Care 2015;30:814-6; J Crit Care 2016;33:119-24). Continued use of these medications beyond the hospital stay could lead to serious adverse effects, drug interactions, and significant drug cost as well as a presumption of a psychiatric or neuromuscular disorder associated with these drugs. Communication to the next direct patient care provider is crucial to appropriately direct the next steps in medication reconciliation.

Table 7. Antipsychotics^a

Drug	CYP Substrate (major)	Usual Starting Dose	Significant Adverse Effects ^b	Formulations
Haloperidol	3A4, 2D6	1–2 mg older adults; 2–4 mg if history of psychiatric disorders	Anticholinergic: * Sedation: * EPS: ** NMS: *	PO, IM, IV (non-FDA approved)
Olanzapine	1A2	5 mg	Anticholinergic: ** Sedation: ** EPS: * NMS: * Neuromuscular weakness	PO, disintegrating tablet, IM
Quetiapine	3A4	12.5–25 mg	Anticholinergic: ** Sedation: ** NMS: * Orthostatic hypotension: **	PO
Risperidone	2D6	0.5–1 mg	Anticholinergic: * Sedation: * EPS: ** NMS: * Orthostatic hypotension: ** Cardiac conduction abnormalities	PO, disintegrating tablet
Ziprasidone	1A2 (minor) 3A4 (minor)	20 mg PO; 10 mg IM	Anticholinergic: * Sedation: * EPS: * NMS: *	Oral, IM

NOTE: * = lower risk; ** = medium-higher risk

^aNot all medications listed are FDA label approved for use in delirium; not all are recommended by SCCM for the treatment of delirium in the ICU.^bAdverse effects other than QTc prolongation. Documented QTc prolongation incidence: IV haloperidol = ziprasidone > risperidone > olanzapine = quetiapine.

EPS = extrapyramidal symptoms; IM = intramuscular(ly); IV = intravenous(ly); NMS = neuroleptic malignant syndrome; PO = oral(ly)

1. Quetiapine (Seroquel): A randomized, placebo-controlled pilot trial compared the efficacy and safety of scheduled quetiapine with placebo for the treatment of delirium in ICU patients during a 10-day study (Crit Care Med 2010;38:419-27). Significant exclusions were as follows: patients with end-stage liver disease, those with alcohol withdrawal, those with a QTc greater than 500, and those receiving concomitant QTc-prolonging agents. This small pilot study (n=36), in which the placebo group was administered as-needed intravenous haloperidol, found that quetiapine was associated with a shorter time to first resolution of delirium, reduced duration of delirium, and less agitation than placebo. Mortality and ICU length of stay were not different from placebo. Another more recent retrospective study reported outcomes of 113 adult medical-surgical ICU patients with hypoactive delirium. Clinical outcomes were compared in patients who received quetiapine (n=52) with no quetiapine (n=61). Hypoactive delirium was defined as a positive CAM-ICU score and a RASS score of 0 to -3, with no RASS scores of +1 to +4 documented throughout the disease course. SATs and SBTs were performed in all patients. Quetiapine use was associated with a shorter median duration of hypoactive delirium than was no quetiapine use (1.5 vs. 2.0 days; p=0.04) and a reduced probability of delirium persisting in the subsequent 24 hours (p=0.007). There was no difference in time on mechanical ventilation or length of ICU or hospital stay; there was no reported difference in the amount or type of sedatives used 48 hours before the first positive delirium screen. In a predefined

subgroup analysis, patients who had delirium for 2 days or less (n=32) received quetiapine sooner than patients who had greater than 2 days of delirium (n=20). Patients who had delirium for 2 days or less spent less time on mechanical ventilation (4.5 vs. 13.5 days, $p=0.001$), with reduced ICU length of stay (9 vs. 12.5 days, $p=0.03$) compared with patients with delirium for greater than 2 days.

- a. Pharmacokinetics: Hepatically metabolized to one active and two inactive metabolites. Metabolites renally cleared. Many drug interactions, CYP3A4 (major) and CYP2D6 (minor) substrates. Peak plasma concentrations for oral about 1½ hours (immediate release).
 - b. Initial dose range for ICU delirium: 50 mg one to three times daily. Consider lower starting doses for older adult patients because of sedating effects. The Devlin study initiated 50 mg every 12 hours and titrated to a maximum dose of 200 mg every 12 hours.
 - c. Adverse effects (early onset): Sedation, orthostatic hypotension, extrapyramidal symptoms, QTc prolongation
2. Olanzapine (Zyprexa): Available in oral, orally disintegrating, and intramuscular (immediate and extended release) dosage forms. Intramuscular administration may result in plasma concentrations 5 times those of oral administration. The U.S. Food and Drug Administration (FDA) warns that the use of intramuscular olanzapine has resulted in unexplained deaths; use of intramuscular olanzapine with benzodiazepines may result in significant oxygen desaturation.
 - a. Pharmacokinetics: Metabolized by glucuronidation and CYP 1A2, 2D6 oxidation. Clearance is significantly increased (around 40%) in smokers and decreased in females (around 30%). Many drug interactions, CYP1A2 (major) and CYP2D6 (minor) substrates. Weak inhibitor of several CYP isoenzymes. Peak plasma concentrations for oral: About 6 hours.
 - b. Suggested starting dose for ICU delirium: 5 mg orally once daily
 - c. Adverse effects (early onset): Drowsiness, extrapyramidal symptoms, neuromuscular weakness, serotonin syndrome. High doses may cause cardiac arrhythmias, cardiopulmonary arrest, and extreme sedation to coma-like states.
3. Risperidone (Risperdal): Available in oral and oral dispersible tablets (M-tabs) and intramuscular injection dosage forms
 - a. Pharmacokinetics: Hepatically metabolized to active metabolites, renally cleared. Many drug interactions, CYP2D6 (major) and CYP3A4 (minor) substrates and P-glycoprotein. Peak plasma concentrations for oral about 1 hour.
 - b. Suggested starting dose for ICU delirium: 0.25–0.5 mg once or twice daily
 - c. Adverse effects (early onset): Cardiac arrhythmias, anticholinergic effects, extrapyramidal symptoms
4. Ziprasidone (Geodon): Studied in a multicenter, randomized, placebo-controlled pilot trial of mechanically ventilated patients to test the hypothesis that antipsychotics would improve days alive without delirium or coma in the ICU (MIND trial). Medical and surgical adult ICU patients (n=101) from six tertiary-care centers in the United States on mechanical ventilation who had an abnormal level of consciousness or were receiving analgesia/sedative medications were randomly assigned to receive haloperidol, ziprasidone, or placebo every 6 hours for up to 14 days during a 21-day study. During the study, no difference was found in median days alive without delirium or coma between the haloperidol (14 days), ziprasidone (15 days), and placebo (12.5 days) groups, $p=0.66$. The study also found no difference in ventilator-free days, hospital length of stay, or mortality among the three groups (Crit Care Med 2010;38:428-37). Ziprasidone is available in oral and intramuscular dosage forms.
 - a. Pharmacokinetics: Hepatic by glutathione and aldehyde oxidase. Minor substrates of CYP 1A2, 3A4. Peak plasma concentrations for oral about 6 hours; intramuscular about 1 hour.
 - b. Suggested starting dose for ICU delirium: 20 mg twice daily (oral)
 - c. Adverse effects (early onset): Somnolence, extrapyramidal symptoms, dizziness, orthostatic hypotension

V. ABCDEF BUNDLE

- A. Incorporating multiple concomitant patient care interventions into one consolidated bundle may be an effective strategy to improve clinical outcomes in critically ill patients. SCCM recommends implementing the “ABCDEF” bundle to align and coordinate care utilizing an interprofessional approach (e.g., physician, nursing, pharmacy, respiratory therapy, physical and occupational therapy). The following practice principles are applied to the bundle:
1. A: Assess, prevent, and manage pain
 2. B: Both SATs and SBTs
 3. C: Choice of analgesia and sedation
 4. D: Delirium: Assess, prevent, and manage
 5. E: Early mobility and exercise
 6. F: Family engagement and empowerment
- B. Assess, prevent, and manage pain (“A” of the bundle): Asking the patient to self-report pain or to use the CPOT or BPS if the patient is nonverbal. Preventing pain by recognizing patients with known sources of pain (i.e., rib fractures) and scheduling analgesics when indicated. Managing pain by ordering the most appropriate pharmacologic agent based on the source of pain, renal, and liver function.
- C. Daily coordination of the SAT with the SBT (“B” of the bundle) versus usual care with the SBT has been shown to significantly decrease the time on mechanical ventilation and ICU length of stay in randomized studies. This was reviewed earlier in the chapter in the Agitation section.
- D. Choice of Sedation (“C” of the bundle): Use a multidisciplinary approach, including focused pharmacy input, to choose a sedative according to individual patient needs, hemodynamic stability, and organ function (e.g., hepatic, renal, cardiac, pulmonary, pancreatic).
- E. Delirium Assessment, Prevention, and Management (“D” of the bundle): Regularly assess for delirium using the CAM-ICU or the ICDSC every 8–12 hours. Use delirium preventive measures in all patients when safe to do so.
- F. Early Mobility (“E” of the bundle): Perform a mobility safety screen, and implement a daily mobility protocol.
- G. Family Engagement and Empowerment (“F” of the bundle): Good communication with the family is critical at every step of the patient’s clinical course, and empowering the family to be part of the team to ensure best care is adhered to diligently will improve many aspects of the patient’s experience.

VI. POST-INTENSIVE CARE SYNDROME

- A. Advancements in critical care have decreased mortality and resulted in an increased likelihood of surviving critical illness. Post-intensive care syndrome (PICS) describes new or worsening impairments in physical, cognitive, or mental health status after critical illness and persisting beyond acute care hospitalization. Physical impairments include both pulmonary dysfunction and neuromuscular weakness. Impairments in memory and executive functioning are examples of cognitive dysfunction. Mental health impairments include depression, posttraumatic stress disorder, and anxiety. Medication management including glucose control,

utilization of the ABCDEF Bundle, and review of medication lists at every transition of care are important roles of the pharmacist to prevent PICS. Family members can also suffer from PICS, termed PICS-F, in which these individuals suffer from depression, posttraumatic stress disorder, anxiety, and prolonged grief. SCCM has taken progressive steps to help clinicians and families recognize the prolonged PICS and PICS-F through THRIVE. The establishment of an ICU follow-up clinic is one proposed method to manage long-term complications of patients with PICS and family members of PICS-F through optimization of physical, cognitive, and mental health; improved coordination of care; and reduction in health care utilization. The pharmacist should be considered a key member of the PICS clinic team who performs complete medication management on all patients seen in the clinic.

1. **Physical Impairment:** A prospective, longitudinal study of 109 survivors with ARDS was conducted. Median (Interquartile Range) Total Lung Capacity (TVC) was 92% (77-97%), 92% (82-101%), and 95% (81-103%) of predicted value, respectively at 1, 6, and 12 months after ICU discharge. Forced expiratory volume in one second (FEV₁) was 75% (58-92%), 85% (69-98%), and 86% (74-100%) of predicted value, respectively at 1, 6, and 12 months after ICU discharge. Six-minute walk test was 49%, 64%, and 66% of predicted value, respectively at 1, 6, and 12 months after ICU discharge. These 109 survivors of ARDS were further analyzed annually up to 5 years after ICU discharge. TVC was 94% (84-108%), 93% (78-107%), 92% (79-104%), and 94% (78-105%) of predicted value, respectively at 2, 3, 4, and 5 years after ICU discharge. FEV₁ was 87% (75-99%), 79% (66-97%), 85% (68-98%), and 83% (69-98%) of predicted value, respectively at 2, 3, 4, and 5 years after ICU discharge. Six-minute walk test was 68%, 67%, 71%, and 76% of predicted value, respectively at 2, 3, 4, and 5 years after ICU discharge.
2. **Cognitive Impairment:** A large, multicenter, prospective observational cohort study of 821 adult medical ICU and surgical ICU patients (called the BRAIN-ICU study) was conducted to estimate the prevalence of long-term cognitive impairment after critical illness secondary to respiratory failure, cardiogenic shock, or septic shock. Delirium was the strongest independent predictor of cognitive impairment in the 50% of patients after critical illness. A Repeatable Battery for Neuropsychological Status (RBANS) score similar to Alzheimer's disease (2 standard deviations below the population mean) was found in 26% of patients and score similar to moderate traumatic brain injury (1.5 standard deviations below the population mean) was found in 40% of patients 3 months after discharge. Both young and older adults, with and without comorbidities, experienced these deficits, which persisted at 12 months in 24% and 34% of these individuals having RBANS scores similar to Alzheimer's disease and moderate traumatic brain injury, respectively.
3. **Mental Health Impairments:** A multicenter, prospective observational cohort study of 821 adult medical ICU and surgical ICU patients conducted to estimate the prevalence of depression, posttraumatic stress disorder (PTSD), and functional disability after critical illness secondary to respiratory failure, cardiogenic shock, or septic shock. Depression was found in 149 (37%) and 116 (33%) of patients at 3 and 6 months after ICU discharge, respectively. Disabilities in basic activities of daily living were found in 139 (32%) and 102 (23%) of patients at 3 and 6 months after ICU discharge, respectively. Disabilities in instrumental activities of daily living were found in 108 (26%) and 87 (23%) of patients at 3 and 6 months after ICU discharge, respectively. PTSD was found in 27 (7%) of patients at 3 and 6 months after ICU discharge.

B. Medication Management

1. **Glucose Dysregulation:** A retrospective study of 74 patients with ARDS found that a blood glucose value of 153.5 mg/dL resulted in a 2.9 greater chance of developing cognitive impairment. A second retrospective, case-control study of 37 surgical ICU patients with at least 1 episode of hypoglycemia found that cognitive impairment was higher in the hypoglycemic group ($p < 0.01$). Intensive insulin therapy (maintaining blood glucose levels between 80 and 100 mg/dL) in surgical ICU patients decreased neuropathy from 51.9% to 28.7% and the prevalence of critical illness polyneuropathy (CIP) and critical

illness myopathy (CIM) from 49% to 25% in surgical ICU patients ($p<0.0001$). Intensive insulin therapy also decreased CIP and CIM from 51% to 39% in the medical ICU ($p=0.02$) in patients who had an ICU stay of at least one week. The percentage of patients needing mechanical ventilation for at least 2 weeks was reduced from 42% to 32% in the surgical ICU ($p=0.04$) and from 47% to 35% in the medical ICU ($p=0.01$). Subsequently, NICE-SUGAR showed increased mortality in the intensive insulin group (81 to 108 mg/dl) (27.5%) versus conventional glucose control (<180 mg/dl) (24.5%) ($p=0.02$). The SCCM Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients suggests that a blood glucose ≥ 150 mg/dL initiates interventions to maintain blood glucose <180 mg/dL and to avoid hypoglycemia based off the results of NICE-SUGAR.

2. **Continuation of Inappropriate Medications:** The frequency of prescribed potentially inappropriate medications (PIMS) and actually inappropriate medications (AIMs) was evaluated in a single-center study of 120 elderly adult ICU survivors. PIMS were defined as those potentially harmful based on prior studies and pharmacologic effects. PIMS could further be classified as AIMs if the benefit of the drug was considered to be less than the harm. The 2003 Beers Criteria and medication safety data published since 2003 were used to identify medications. Medications were identified at five points during the hospital stay: admission, ward admission, ICU admission, ICU discharge, and hospital discharge. The most common categories of PIMS identified at hospital discharge were opioids, anticholinergic medications, antidepressants, and drugs causing orthostasis. Thirty-six percent of these PIMS were considered to be AIMs. The PIM categories at hospital discharge with the highest positive predictive values for being AIMs were anticholinergics (55%), nonbenzodiazepine hypnotics (67%), benzodiazepines (67%), atypical antipsychotics (71%), and muscle relaxants (100%). In multivariate analysis, the number of discharge PIMS was independently predicted by the number of preadmission PIMS ($p<0.001$), discharge to somewhere other than home ($p=0.03$), and discharge from a surgical service ($p<0.001$). Almost two-thirds of AIMs were initiated in the ICU.
3. **Not Restarting Home Medications:** A large population-based Canadian cohort study of 396,380 patients evaluated records of hospital and outpatient medications prescribed from at least one of five of the following groups: (1) statins, (2) antiplatelet/anticoagulant agents, (3) levothyroxine, (4) respiratory inhalers, and (5) gastric acid-suppressing drugs. Patients were divided into three groups: hospitalization with an ICU admission, hospitalization without ICU admission, and nonhospitalized patients that served as the control group. Compared with control patients, those admitted to a hospital without an ICU stay were more likely to have medications discontinued among all five of the medication groups. Patients admitted to a hospital with an ICU stay were also more likely to have medications discontinued among all five of the medication groups compared with control patients. With the exception of respiratory inhalers, there was a higher risk of medication discontinuation in all medication groups in patients hospitalized with an ICU admission as compared with patients hospitalized without an ICU admission. The composite outcome of death, hospitalization, and emergency department visit up to 1 year after hospital discharge in all study patients was found to be higher in patients in which a statin or antiplatelet or anticoagulant was discontinued.

Patient Cases

5. T.L. (from question 4) was extubated 24 hours ago, is currently receiving dexmedetomidine 0.2 mcg/kg/hour, and has received two doses of fentanyl 25 mcg over 24 hours for pain. She is alert and calm with intermittent periods of agitation. Her pain score is now negative, and she is newly positive for delirium by CAM-ICU. Her laboratory values and vital signs are normal. Which would best be recommended for the management of delirium?
- A. Continue dexmedetomidine, and start quetiapine for delirium.
 - B. Discontinue dexmedetomidine, and increase maintenance fluids for dehydration.
 - C. Discontinue dexmedetomidine, and order patient mobility as tolerated.
 - D. Continue dexmedetomidine, and schedule oxycodone sustained release every 12 hours.
6. P.V. is a 70-year-old woman intubated for severe respiratory failure (Fio₂ 80%) and refractory shock from methicillin-resistant *Staphylococcus aureus* pneumonia, for which she was administered antibiotics, vasopressors, and steroids. She is on day 5 of mechanical ventilation (Fio₂ 50%) and has been off vasopressors for 48 hours. The nurse describes PAD, but the patient denies pain. Medications include vancomycin 1000 mg daily, heparin 5000 units subcutaneously every 12 hours, hydrocortisone 50 mg every 6 hours, and fentanyl 75 mcg/hour. Which is the most appropriate recommendation at this time?
- A. Increase fentanyl, and add midazolam for agitation.
 - B. Decrease fentanyl, and discontinue hydrocortisone.
 - C. Decrease fentanyl, and add haloperidol for delirium.
 - D. Increase fentanyl, and change vancomycin to linezolid.

VII. NEUROMUSCULAR BLOCKADE IN THE INTENSIVE CARE UNIT

- A. The most recent SCCM guidelines for the sustained use of neuromuscular blockade in the ICU were published in 2002. Surveys have reported a dramatic decrease in the use of NMBA during the past 20 years, from around 80% to 15% in patients on mechanical ventilation. This change in practice may be secondary to a better understanding of the serious adverse effects of prolonged paralysis, together with accepted standards of care for modes of mechanical ventilation in patients with ARDS.
- B. Clinical Scenarios for the Use of NMBA in the ICU May Include:
- 1. Rapid sequence intubation
 - 2. ARDS
 - 3. Status asthmaticus
 - 4. Elevated ICP
 - 5. Elevated intra-abdominal pressure
 - 6. Therapeutic hypothermia after cardiac arrest
- C. Acute Respiratory Distress Syndrome
- 1. Cisatracurium has been the most-studied NMBA for ARDS since 2000, primarily as short-term treatment and in severe cases of ARDS. In 2010, a randomized placebo-controlled trial (n=340) found that short-term fixed-dose cisatracurium (48 hours) significantly improved 90-day survival, increased ventilator-free days, increased organ dysfunction-free days, and decreased barotrauma in patients with

severe ARDS ($\text{PaO}_2/\text{FiO}_2$ less than 120 mm Hg). The investigators found no difference in neuromuscular weakness compared with placebo. Other cisatracurium studies have shown improvements in oxygenation and a reduction in inflammatory mediators.

2. In retrospective studies, the use of NMBAs in ARDS was associated with a prolonged duration of mechanical ventilation, prolonged ICU length of stay, and increased mortality.
3. Protective mechanisms of NMBAs in severe ARDS: Researchers have proposed mechanisms by which an NMBA may protect the lung against further injury in severe ARDS. These mechanisms are not completely understood, but they may help explain the beneficial effects of NMBAs in early, severe ARDS:
 - a. Provide improved adaptation to the ventilator through increased thoracopulmonary compliance.
 - b. Increase functional residual capacity, and decrease intrapulmonary shunt.
 - c. Provide uniform distribution of pulmonary perfusion and pressures, favoring the perfusion of ventilated areas.
 - d. Limit over-distention of high-compliance lung regions and recruits areas of smaller compliance.
 - e. Decrease muscular oxygen consumption by decreasing ventilator asynchrony.
 - f. Decrease production of proinflammatory cytokines in lungs and blood.
 - g. Provide protective role against ventilator-induced trauma, including decreased incidence of pneumothoraces.
4. Use of NMBAs in ARDS remains controversial. Short-term use of cisatracurium (48 hours or less) when used early may be beneficial for severe ARDS ($\text{PaO}_2/\text{FiO}_2$ less than 120 mm Hg). It is imperative to understand that the use of NMBAs in ARDS is still considered a last resort and that they are used only after aggressive sedation and appropriate ventilatory adjustments have been tried.

D. Therapeutic Hypothermia After Cardiac Arrest

1. The American Heart Association guidelines for “post-cardiac arrest care” (Circulation 2010;122:S768) provide the following summary statements regarding therapeutic hypothermia: “We recommend that comatose (e.g., lack of meaningful response to verbal commands) adult patients with return of spontaneous circulation (ROSC) after out-of-hospital ventricular fibrillation cardiac arrest should be cooled to 32°C – 34°C for 12–24 hours (class I, level of evidence B). Induced hypothermia also may be considered for comatose adult patients with ROSC after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electrical activity or asystole (class IIb, level of evidence B).”
2. NMBAs have been used to prevent or treat shivering during therapeutic hypothermia.
3. The optimal combination and dosing of sedatives and paralytics have not been well established because the metabolism of these drugs is significantly slowed during hypothermia, and potency may be decreased. NMBAs have been used in both a bolus and a continuous infusion fashion during therapeutic hypothermia.

- E. Sedation During NMBA: It is critical that patients be in a sedated, non-agitated, and pain-free state before initiating an NMBA. Once the patient becomes paralyzed from the NMBA, the ability to accurately assess mental status or pain is ostensibly challenging and often unattainable. The deeper the degree of paralysis, the higher the risk of drug accumulation because nurses cannot routinely complete sedation interruption or taper to a lighter level of sedation. Common scenarios that slow the clearance of sedatives (e.g., hepatic and renal failure or a hypothermic state) can add to the likelihood of increased drug exposure and delayed awakening times once the paralytic and sedatives are discontinued. This risk of drug accumulation underscores the importance of a daily assessment for need of paralysis and frequent tapering of NMBA dosing once it is safe for the patient.

F. Two Classes of NMBAs According to Mechanism of Action: Depolarizing and Nondepolarizing:

1. Depolarizing NMBAs: Bind and activate acetylcholine receptors, causing persistent depolarization, which then renders muscle fibers resistant to further cholinergic stimulation. Succinylcholine is the only available depolarizing NMBA. Because of its quick onset and short duration, it is commonly the drug of choice for urgent or emergency intubation.
 - a. Pharmacokinetics: Hydrolyzed by plasma pseudocholinesterase
 - b. Usual dose: 0.05–1.5 mg/kg intravenously or intramuscularly
 - c. Onset intravenously: 30–60 seconds; intramuscularly: 2–3 minutes
 - d. Duration intravenously: 4–6 minutes; intramuscularly: 10–30 minutes
 - e. Should not be used in patients with a history of malignant hyperthermia, hyperkalemia, stroke, paralysis, glaucoma, penetrating eye injuries, or spinal, crush, or burn injuries after 24 hours
 - f. Adverse effects: Arrhythmias, bradycardia or tachycardia, hyperkalemia, rhabdomyolysis
2. Nondepolarizing NMBAs: Nicotinic receptor antagonists (competitive), blocking the action of acetylcholine at the neuromuscular junction. Divided into aminosteroid group (pancuronium, vecuronium, and rocuronium) and benzyl isoquinolinium group (atracurium, cisatracurium, doxacurium, and mivacurium).
 - a. Pancuronium: Long-acting aminosteroid; intermittent or scheduled bolus may be preferred to continuous infusion because of accumulation and variable clearance. Older NMBA, not used much in the United States.
 - i. Pharmacokinetics: Hepatically metabolized (30%–50%) and renally cleared as unchanged drug (50%–70%). Accumulation and prolonged duration of paralysis will occur with varying degrees of hepatic and/or renal dysfunction. Duration about 60–120 minutes.
 - ii. Adverse effects: Vagolytic activity, sympathetic stimulation, bradycardia, prolonged effect
 - b. Vecuronium (Norcuron): Intermediate-acting aminosteroid; often used as a continuous infusion
 - i. Pharmacokinetics: Hepatically metabolized (30%–50%); cleared renally (20%–30%), with fecal excretion. Has an active metabolite, around half the activity of parent compound. Duration 30 minutes after bolus intubation dose.
 - ii. Adverse effects: Vagolytic activity at higher doses, prolonged weakness
 - c. Rocuronium (Zemuron): An intermediate-acting aminosteroid; considered a suitable alternative to succinylcholine for rapid sequence intubation (dose: 0.6–1.0 mg/kg) because of its rapid onset of action (60–90 seconds). Duration 30–40 minutes.
 - i. Pharmacokinetics: Primarily hepatically metabolized, minimal renal excretion. No active metabolite. Prolonged effects have been observed in patients with hepatic or renal failure.
 - ii. Adverse effects: Vagolytic activity at higher doses, bradycardia
 - d. Atracurium: Intermediate-acting benzyl isoquinolinium; a mixture of 10 stereoisomers (contains 15% cisatracurium)
 - i. Pharmacokinetics: Undergoes Hofmann elimination to form the toxic metabolite laudanosine at high levels. Laudanosine is a cerebral stimulant that may precipitate seizure activity, clearance dependent on liver and kidney function. Duration of atracurium 20–40 minutes.
 - ii. Adverse effects: Histamine release may cause cardiovascular adverse effects and bronchospasm; laudanosine accumulation may cause seizure activity.
 - e. Cisatracurium (Nimbex): An intermediate-acting benzyl isoquinolinium. Differences compared with atracurium: It is only one isomer, has a slower onset at normal bolus doses, no histamine release.
 - i. Pharmacokinetics: Undergoes Hofmann elimination, forms laudanosine but at much lower levels than atracurium. Renal and hepatic dysfunction do not alter cisatracurium clearance. Duration 30–60 minutes.
 - ii. Adverse effects: Prolonged weakness with continued use

- G. Drug Interactions with NMBAs: Certain medications may decrease the activity of NMBAs, whereas others can enhance or prolong the paralytic action.
1. Drugs decreasing the activity of NMBAs:
 - a. Calcium: Antagonizes the effect of magnesium on neuromuscular blockade
 - b. Carbamazepine: Competitor of acetylcholine receptor
 - c. Phenytoin: Depressed postsynaptic response to acetylcholine
 - d. Ranitidine: Unknown mechanism
 - e. Theophylline: Unknown mechanism
 2. Drugs prolonging the activity of NMBAs:
 - a. Antibiotics: Aminoglycosides, clindamycin, tetracyclines, vancomycin. Decreases prejunctional acetylcholine release with decreased postjunctional acetylcholine receptor sensitivity; blocks acetylcholine receptor.
 - b. Cardiac medications: β -Blockers, calcium channel blockers, procainamide, quinidine, and furosemide. Decreases prejunctional acetylcholine release.
 - c. Immunosuppressants: Steroids (decrease end plate sensitivity to acetylcholine), cyclosporine (inhibits metabolism of certain NMBAs)
- H. Choice of NMBA: Intermediate- to longer-acting agents such as vecuronium may be tried in bolus fashion initially before continuous infusion, particularly if organ dysfunction is present. The duration of paralysis for NMBAs cleared by Hofmann degradation may be more reliable when used as a continuous infusion because their clearance is not dependent on renal or hepatic function.
- I. Train-of-Four (TOF) Monitoring and Dose Titration
1. Typically, the goal of using an NMBA is to improve patient-ventilator synchrony and increase oxygenation. This may be achieved with varying degrees of paralysis and may not necessitate 100% block.
 2. Monitoring the depth of neuromuscular blockade by peripheral nerve stimulators (e.g., TOF), together with measured oxygenation parameters, helps find the “lowest effective paralytic dose” and allows quicker recovery of spontaneous neuromuscular transmission once the NMBA is discontinued. Some clinicians do not believe that TOF monitoring is necessary and believe that using the clinical values alone is sufficient to determine NMBA dosing.
 3. TOF delivers four supramaximal electrical impulses every 0.5 seconds to the ulnar, facial, or posterior tibial nerve. Response to the impulse is then measured by muscle twitches visualized from the associated innervated muscles (thumb or eye). Goals of paralysis can usually be reached with 2 or 3 of 4 twitches; 0 of 4 twitches indicates complete neuromuscular blockade, usually necessitating a decrease in NMBA dose. Oxygenation goals may be reached even with 4 of 4 twitches, indicating that the NMBA dose is effective and an increase is not warranted.
 4. A baseline electrical current should be established before initiating an NMBA to determine how much electrical current is needed to produce a twitch. Usually 10–20 mA (amperage) is sufficient. The conduction of the electrical impulse may be dampened because of peripheral edema, loss of electrode adhesion, incorrect electrode placement, and hypothermia, which can lead to inaccurate readings. These factors should be reassessed with each use of the TOF.
- J. Complications of NMBAs
1. Prolonged weakness: Several case reports associate the use of NMBAs and prolonged weakness, which could include myopathy, polyneuropathy, or neuromyopathy. Other risk factors may include concomitant use of corticosteroids, persistent hyperglycemia, and type of NMBA used. However, data are inconsistent and not controlled, and further studies are needed to clarify specific risk factors for prolonged weakness associated with NMBAs. Following a trend in creatine kinase concentration every 48–72 hours may help

assess the presence of myopathy secondary to paralysis and prolonged immobilization. A creatine kinase concentration should not be solely relied on for the presence of myopathy, and daily determination of the need for the NMBA should still be considered, even with a normal creatine kinase.

2. Corneal abrasions: Paralysis eliminates the ability of the eyes to close and blink, increasing the risk of corneal ulcerations and infection. Prophylactic eye protection must be used in all patients on NMBAs (e.g., lubricating eye ointments or eye covers).
3. Thrombosis: Caused partly by immobility, patients receiving an NMBA may be up to 8 times more likely to have a DVT than those not on an NMBA. Prophylaxis for a DVT must be provided for all patients on an NMBA.
4. Awareness: Recent case reports document patient awareness during paralysis in the ICU. These patients report weird dreams, fear, resistance of restraints, thoughts of life and death, and pain. It is critical that patients be deeply sedated before initiating an NMBA.
5. Resistance to paralysis and/or potentiation: Certain disease states may produce an up-regulation in acetylcholine skeletal muscle receptors, leading to higher-than-normal doses of the NMBA (e.g., muscle trauma, muscle atrophy, burns). Acid-base disorders, electrolyte imbalances, and adrenal insufficiency may also cause unpredictable alterations in dosing requirements.
6. Anaphylaxis: Allergic reactions can occur after the first dose of an NMBA because the ammonium ions in NMBAs are commonly found in the household environment and in household products. If an allergic reaction is suspected, skin prick testing for the NMBA against a control can be done within 6 weeks of the reaction.

Patient Cases

7. A 55-year-old man intubated for severe ARDS (P_{aO_2}/F_{iO_2} ratio less than 100) is receiving fentanyl 200 mcg/hour, midazolam 8 mg/hour, and propofol 40 mcg/kg/minute. He is deeply sedated but remains hypoxic and dyssynchronous with the ventilator after several changes in mechanical ventilation settings. Which is the most appropriate consideration at this time?
 - A. Start scheduled lorazepam every 6 hours.
 - B. Add quetiapine 50 mg every 8 hours.
 - C. Change propofol to dexmedetomidine.
 - D. Start a cisatracurium infusion.
8. A 70-year-old female who is day 2 in the ICU is receiving a neuromuscular blocking agent (NMBA) and is sedated for severe ARDS. The TOF over 24 hours is 2 of 4 twitches at an amplitude of 10 mA. Arterial blood gas is pH 7.38, P_{CO_2} 40, P_{O_2} 91, and bicarbonate 24 mEq/L on 50% inspired oxygen and 10 cm PEEP; the patient is synchronous with the ventilator, and other clinical markers are stable. Which changes in management would be best to recommend?
 - A. Decrease stimulator amplitude to decrease pain from excessive electrical current.
 - B. Increase stimulator amplitude to test for more frequent twitches.
 - C. Decrease the NMBA dose because the patient is clinically stable.
 - D. Increase the NMBA dose until the TOF induces fewer twitches.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES**1. Answer: D**

This patient has a clear indication for intravenous pain medication from his recent trauma and multiple fractures. An “as-needed” opiate would likely not keep up with his pain control needs (Answers B and C are incorrect). His age and history of hypertension place him at risk of delirium; therefore, a benzodiazepine is not the best initial choice for this patient. A propofol infusion would be the most appropriate sedative (Answer A is incorrect; Answer D is correct).

2. Answer: D

Chest tube removal is specifically cited in the PAD guidelines as an indication for both preemptive analgesia and nonpharmacologic relaxation techniques. This is given a “strong” recommendation, determining that the benefits outweigh the risks of preemptive therapy (Answer D is correct). Acetaminophen given just before the procedure will most likely not adequately treat pain associated with chest tube removal (Answer A is incorrect). Increasing an opiate infusion several hours before a bedside procedure can expose the patient to substantially higher amounts of drug than needed and cause delayed awakening times or other significant adverse effects from opiates (Answer C is incorrect). Extensive studies of appropriate preemptive analgesia for chest tube removal have not been completed; however, administering an opiate appropriately timed before manipulation of a chest tube is an accepted standard of therapy (Answer B is incorrect).

3. Answer: A

This patient has end-stage liver failure and acute renal failure; he will therefore not predictably clear midazolam or fentanyl infusions. With a RASS of -4 to -5, indicating no meaningful responsiveness to stimuli, all sedatives should be held if the patient is otherwise clinically stable to allow time for clearance of medications (Answer A is correct). A decrease in sedative dose or changing to a different sedative is not needed at this time based on the deeply sedated RASS score and would only further delay awakening time.

4. Answer: B

Withdrawal from certain home medications may occur if these medications are not reinitiated within a few days of admission. The onset of withdrawal symptoms

will vary depending on the half-life of each medication. Symptoms may include agitation, anxiety, psychosis, insomnia, hypertension, and tachycardia and can occur with medications such as opiates, GABA receptor agonists, antiepileptics, antidepressants, and antipsychotics. A pharmacist can assist the medical team by obtaining a thorough medication history and assessment of home medication adherence to help identify drug withdrawal symptoms. Reinitiating these medications can be considered, unless contraindicated because of the clinical scenario (e.g., drug-drug interactions, drug-disease state interactions). The Agitation and Sedation section of the PAD guidelines discusses identifying and treating the etiology of agitation before adding other medications; reinitiating the benzodiazepine and antidepressant to treat withdrawal symptoms is the most appropriate answer (Answer B is correct). Neither fentanyl nor dexmedetomidine would treat withdrawal from a benzodiazepine or antidepressant (Answers A, C, and D are incorrect).

5. Answer: C

The PAD guidelines stress using nonpharmacologic means to manage delirium when it is safe for the patient. Strong evidence for using medications such as antipsychotics and dexmedetomidine to treat delirium is still not available. This patient’s presentation of “alert and calm with intermittent periods of agitation” is a common scenario, and initial therapy should focus on reorienting and getting the patient interactive and mobile (Answers A and D are incorrect; Answer C is correct). Dehydration is a common cause of agitation, and it should be addressed; however, with normal laboratory values and vital signs, this patient is unlikely dehydrated at this time (Answer B is incorrect).

6. Answer: B

In the general population, systemic corticosteroids are known to cause many neuropsychiatric events, including hyperactivity and agitation; in a recent study of adult ICU patients with acute lung injury, only age and use of systemic corticosteroids in the preceding 24 hours were independently associated with the transition to delirium from a non-delirious state (Answer B is correct). Benzodiazepines have a sedating effect and may calm an acutely agitated patient; however, they would not be recommended in this patient because they could worsen her

confusion or delirium (Answer A is incorrect). The PAD guidelines state that no evidence supports the use of haloperidol to reduce the duration of delirium (Answer C is incorrect). Vancomycin is not currently recognized as a cause of delirium; therefore, changing to linezolid is not indicated (Answer D is incorrect).

7. Answer: D

The midazolam dose is high, and the patient is “deeply sedated”; therefore, adding another benzodiazepine will likely not improve this patient’s clinical status. Quetiapine has no indication for general sedation in a critically ill patient, and it should not be a consideration for sedation in this patient with severe ARDS. Dexmedetomidine is considered a weak sedative with no effect on respiratory drive; therefore, it would likely not improve this patient’s ventilator dyssynchrony and hypoxia (Answers A–C are incorrect). At this stage in the patient’s clinical course, it is reasonable to consider an NMBA. In a 2010 study of cisatracurium versus placebo for 48 hours in early ARDS, the cisatracurium group had more days free of mechanical ventilation and decreased mortality (30% vs. 44%) at 90 days for the subgroup of patients with severe ARDS ($\text{PaO}_2/\text{FiO}_2$ ratio less than 120). The incidence of pneumothorax was lower in the cisatracurium group than in the placebo group (4% vs. 11%). There were more days free of organ failure (non-lung) in the cisatracurium group than in the placebo group (15.8 vs. 12.2 days) in the first 28 days. A recent meta-analysis concluded that using short-term cisatracurium in patients with severe ARDS decreases mortality and time on mechanical ventilation compared with placebo. The risk of prolonged neuromuscular weakness was not found in these studies; however, use beyond 48 hours may increase this risk (Answer D is correct).

8. Answer: C

The TOF method of assessment is primarily used to help determine the degree of neuromuscular blockade and should not be used to titrate the dose of the NMBA. The patient’s clinical status and laboratory values are the true determinants for dose adjustment of the NMBA. Patients may be at their clinical goal with a TOF of 2 or 3 twitches of 4. This is the ideal scenario, and it will predict a faster reversal of neuromuscular blockade (Answer C is correct). A TOF of 0 or 1 of 4 twitches predicts a significantly slower neuromuscular recovery time, and clinicians should try to decrease the NMBA as

soon as the patient is clinically stable by laboratory values and ventilator management (Answer D is incorrect). A baseline electrical current intensity (amperage) should be established before the onset of neuromuscular blockade and should not be changed during paralysis unless a new baseline is indicated (Answer A is incorrect). As the electrical intensity (amperage) is established, an increase in the amperage is not indicated during infusion of the NMBA in order to increase the number of twitches. A decrease in the dose of NMBA would be indicated if an increase in the number of twitches were the clinical goal (Answer B is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: D**

Propofol infusion syndrome is a well-documented and complex set of adverse events, potentially resulting in multiorgan failure. An elevation in lactate, creatine kinase, transaminases, SCr, and triglycerides and the presence of a metabolic acidosis are some of the abnormalities that should concern the critical care provider for the presence of PRIS (Answer D is correct). Both DVT and critical illness polyneuropathy are serious concerns in the ICU patient; however, the abnormalities in the case are not representative of these complications (Answers A and B are incorrect). There are currently no known abnormal laboratory values to help determine whether delirium is present in an ICU patient (Answer C is incorrect).

2. Answer: B

This patient is at risk of propylene glycol toxicity after receiving a lorazepam drip for more than 48 hours. Lorazepam is dissolved in propylene glycol, an alcohol that can induce an osmolar gap and metabolic lactic acidosis, particularly in patients with significant hepatic or renal failure. Quantitative propylene glycol levels may be unavailable; therefore, surrogate markers such as an abnormal osmolar gap (greater than 10 mmol) and metabolic acidosis may indicate propylene glycol toxicity and a need to discontinue lorazepam. Although lorazepam drips are not routinely used for general sedation in adult ICUs, they may be used for other indications (e.g., severe EtOH [ethyl alcohol] or benzodiazepine withdrawal), and clinicians should remain aware of this serious complication (Answer B is correct). With an oxygen saturation of 98% on 2 L of oxygen, this patient does not meet the predefined criteria of ARDS (Answer A is incorrect). Encephalopathy will not cause a metabolic acidosis; therefore, an ammonia concentration would not be helpful at this stage (Answer C is incorrect). With a low fractional excretion of sodium and a high BUN/SCr ratio, the patient's laboratory values are indicative of a pre-renal concern versus acute tubular necrosis (Answer D is incorrect).

3. Answer: D

It is inappropriate to initiate an NMBA in a patient who has a sedation score indicating "agitation." This implies that the patient may potentially detect pain or discomfort

while paralyzed (Answers B and C are incorrect). The goal should be to achieve a deeply sedated and/or non-agitated state before initiating an NMBA in an effort to avoid any patient discomfort that may be undetected during paralysis (Answer D is correct). The SAT would be inappropriate in someone who is rated "agitated" on the sedation scale or in a patient requiring escalating doses of sedation (Answer A is incorrect).

4. Answer: B

The pharmacokinetics/dynamics of prolonged fentanyl infusions have not been well described in the adult ICU population. Most data for fentanyl are derived from short-term infusions or boluses in healthy volunteers and in animal models. Fentanyl is hepatically metabolized primarily by the CYP3A4 enzyme, and decreased clearance of fentanyl has been described in patients with significant liver disease. Other properties of fentanyl (e.g., high volume of distribution, high protein binding, and high lipophilicity) may contribute to unpredictable clearance and a prolonged context-sensitive half-time for patients in acute renal failure or in patients who have inadequate nutritional status (Answer B is correct). Propofol is a CYP3A4 inhibitor; therefore, it should not induce the metabolism of fentanyl (Answer C is incorrect). Propofol is known to chelate trace elements and increase urinary loss of zinc when used for more than 5 days; propofol has not been shown to cause hypocalcemia (Answer D is incorrect). Disease states identified as risk factors for PRIS may include sepsis, acute liver failure, and history of pancreatitis; ARDS is not currently a documented risk factor (Answer A is incorrect).

5. Answer: B

Withdrawal from certain home medications may occur if these medications are not reinitiated within a few days of admission. The onset of withdrawal symptoms will vary depending on the half-life of each medication. Symptoms may include agitation, anxiety, psychosis, insomnia, hypertension, and tachycardia and can occur with medications such as opiates, GABA receptor agonists, antiepileptics, antidepressants, and antipsychotics. A pharmacist can assist the medical team by obtaining a thorough medication history and assessment of home medication compliance to help identify drug withdrawal symptoms. Reinitiating these medications can be

considered unless contraindicated because of the clinical scenario (e.g., drug-drug interactions, drug-disease state interactions). The Agitation and Sedation section of the PAD guidelines discusses identifying and treating the etiology of agitation before adding other medications; fentanyl should treat this patient's chronic pain and treat opiate/tramadol withdrawal (Answer B is correct). Adding quetiapine or lorazepam for agitation would not address or treat the underlying etiology of potential opiate/tramadol withdrawal (Answers A and C are incorrect). Patient-controlled analgesia with an opiate would help treat opiate withdrawal; however, this patient is not alert enough to use it (Answer D is incorrect).

6. Answer: D

Up to 30%–60% of ICU patients may go through alcohol withdrawal on cessation of alcohol use. The presence of alcohol withdrawal in ICU patients may prolong their ICU stay, increase hospital costs significantly, and lead to other complications during the hospital stay. Early and aggressive symptom-triggered management with a benzodiazepine, particularly in a patient with a history of alcohol withdrawal, is a key element in management. There is no otherwise published protocol for alcohol withdrawal in ICU patients. In this case, although dexmedetomidine is useful as an adjunctive agent to help decrease sympathetic storm and agitation secondary to alcohol withdrawal, it is not currently recommended for use as a single agent for alcohol withdrawal (Answer A is incorrect). Opiates do not treat alcohol withdrawal (Answer C is incorrect). Phenytoin is a known antiepileptic for use in epilepsy; however, it has not been shown to be effective in preventing or treating alcohol withdrawal (Answer B is incorrect). Benzodiazepines are the drugs of choice for alcohol withdrawal seizures; therefore, midazolam is the most appropriate drug for this patient, whose medical history is significant for recurrent alcohol withdrawal seizures (Answer D is correct).

7. Answer: B

Giving several medications that carry a risk of QTc prolongation is a common scenario in the ICU. Clinicians should seek to find alternatives to decrease this risk, if possible, particularly if the QTc is already high (e.g., QTc of 500 or greater is considered high risk of cardiac arrhythmias, including torsades de pointes). Switching levofloxacin to piperacillin-tazobactam is an acceptable alternative to treat an aspiration pneumonia and would

decrease the risk of increasing the QTc interval further (Answer B is correct). This patient is at risk of delirium given the patient's age and being critically ill in the ICU. Avoiding medications that may cause or worsen delirium, such as benzodiazepines, is a strong recommendation in the PAD guidelines (Answer D is incorrect). With a QTc of 500 milliseconds, increasing the quetiapine dose for agitation could further increase the QTc and put this patient at high risk of cardiac arrhythmias (Answer A is incorrect). Amiodarone and quetiapine are home medications for this patient, and they should be continued, if safe. Alternative methods for decreasing the risk of QTc prolongation should be considered before discontinuing chronic medications (Answer C is incorrect).

8. Answer: D

Dementia is a progressive and chronic state of cognitive impairment that worsens over weeks to months; this differs from the acute onset characteristic of ICU delirium (Answer A is incorrect). Alcohol withdrawal should always be a consideration for patients who become altered or agitated in the ICU. This patient's vital signs are normal, and she is presenting in a hypoactive state; these findings are not typical for acute alcohol withdrawal, and alternative causes for her decline in mental status need to be considered (Answer B is incorrect). Adrenal insufficiency in the ICU usually presents with abnormal laboratory values and/or hemodynamic instability. This patient's laboratory values and hemodynamics are reported as normal; therefore, adrenal insufficiency is unlikely (Answer C is incorrect). Both iatrogenic and non-iatrogenic causes for delirium are well documented in the literature. Dehydration and infection are common causes of delirium, particularly in the older adult population. This patient has several reasons for being dehydrated in the hospital: NPO status, persistent fevers, and taking hydrochlorothiazide. Untreated infection or lack of source control is also a concern with the presence of persistent fever, even while the patient is taking antibiotics (Answer D is correct).

PRACTICE ADMINISTRATION AND DEVELOPMENT: PHARMACOECONOMICS AND SAFE MEDICATION USE

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Learning Objectives

1. Review pharmacoeconomic principles and their application to patient care.
2. Compare a medication error, an adverse drug event (ADE), an adverse drug reaction, and a preventable ADE.
3. Design an ADE reporting program, including committee structure, committee reporting mechanisms, and methods of detecting, reporting, and managing ADEs.
4. Describe the safety measures for drug interaction detection and prevention.
5. Develop and implement a drug formulary proposal.

Abbreviations in This Chapter

ADE	Adverse drug event
ADR	Adverse drug reaction
ASHP	American Society of Health-System Pharmacists
CPOE	Computerized prescriber order entry
DIPS	Drug Interaction Probability Scale
FDA	U.S. Food and Drug Administration
ICU	Intensive care unit
ISMP	Institute for Safe Medication Practices
P&T	Pharmacy and therapeutics (committee)
QALYs	Quality-adjusted life-years
TJC	The Joint Commission
WHO	World Health Organization

Self-Assessment Questions

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

1. Which best represents a direct medical cost?
 - A. Delirium.
 - B. Employment time lost.
 - C. Medical professional time.
 - D. Transportation to doctor's appointments.
2. When quantifying the value of a critical care pharmacist's services, which economic evaluation method is best to use?
 - A. Cost-of-illness analysis.
 - B. Cost-benefit analysis.
 - C. Cost minimization analysis.
 - D. Cost-effectiveness analysis.
3. A 60-year-old woman is admitted to the surgical intensive care unit (ICU) with a history of penicillin allergy. She is administered cefazolin before a surgical procedure and develops a life-threatening anaphylaxis reaction. Which best describes this patient's reaction to cefazolin?
 - A. An adverse drug reaction (ADR).
 - B. A side effect.
 - C. An adverse drug event (ADE).
 - D. A preventable ADE.
4. Which is most accurately considered an effective tracer medication to aid in the detection of ADEs?
 - A. Naloxone.
 - B. Clopidogrel.
 - C. Propofol.
 - D. Enoxaparin.
5. Which is most likely to be considered an effective tracer medication to aid in ADE detection?
 - A. Sumatriptan.
 - B. Lorazepam.
 - C. Kayexalate.
 - D. Amitriptyline.
6. Institutions have been met with an unfortunate and drastic propofol shortage. Therefore, ICUs are temporarily revising sedation protocols to replace propofol with midazolam when necessary. What concerns arise with the sudden increase in midazolam use when compared with sedatives such as lorazepam and propofol?
 - A. Oversedation due to a long half-life.
 - B. Challenges in mixing midazolam drips.
 - C. Monitoring for propylene glycol toxicity.
 - D. Drug interactions.
7. Which drug selection criterion is most important in making decisions for drug formulary approval?
 - A. Unlabeled indications.
 - B. U.S. Food and Drug Administration (FDA) approval.
 - C. Efficacy.
 - D. Storage.

8. The pharmacy and therapeutics committee designs drug formularies to:
 - A. Guide rational and consistent prescribing.
 - B. Control institutional costs and manage drug budgets.
 - C. Scrutinize the use of newly FDA-approved drugs.
 - D. Direct necessary medication use evaluations.

I. PHARMACOECONOMICS

A. Overview

1. Outcome research: Economic, clinical, and humanistic (ECHO model)
2. Pharmacoeconomics is defined as the description and analysis of the costs of drugs and pharmaceutical services and their effects on individuals, health care systems, and society.
3. Economic evaluations: Studies that identify, measure, and compare the costs and consequences of a pharmaceutical product or service. Outcome-based economic analysis allows one to retain a patient advocacy role while remaining financially responsible.
 - a. Full economic evaluations
 - i. Cost minimization analysis
 - ii. Cost-benefit analysis
 - iii. Cost-effectiveness analysis
 - iv. Cost-utility analysis
 - b. Other cost evaluations
 - i. Cost of illness
 - ii. Budget impact analysis
4. Economic studies can convey different results, depending on the following:
 - a. Disease and therapy under evaluation
 - b. Other therapies available to treat the condition
 - c. Perspective: Providers, payers, patients, and society
 - d. Primary economic message: The therapy is good value for the cost. Always requires a clinical judgment.
5. Humanistic outcomes or patient-reported outcome measures
 - a. Quality of life
 - b. Health-related quality of life
 - c. Health status
 - d. Well-being
 - e. Symptoms and functional status
 - f. Patient satisfaction

B. Types of Costs

1. Costs vs. charges
 - a. Charges are often reported in the literature and are referred to as costs.
 - b. Charges are costs plus profit.
 - c. Ratio of cost to charge used to estimate costs from charges.
2. Total cost of care – Extends beyond the acquisition cost of a drug and also includes waste cost, preparation cost, distribution cost, administration cost, toxicity cost, monitoring cost.
3. Direct costs – The resources consumed in the prevention, detection, or treatment of a disease or illness. These costs can be medical or nonmedical.
 - a. Medical – Costs associated with medical care
 - i. Fixed costs – Overhead costs; costs remain constant and do not change. Not typically included in a pharmacoeconomic analysis. Examples: Cost of electricity, rent, lighting, building maintenance
 - ii. Variable costs – Medications, hospitalization, laboratory testing, procedures – All depend on the volume of use; the more services used, the greater the expense.
 - b. Nonmedical – Costs as a result of the illness or disease that do not involve the purchase of medical services. Examples: Transportation to health care, child care, specialty diets, clothing

4. Indirect costs – Costs as a result from morbidity or mortality. Relate to the change in productivity ability as a result of the disease or illness. Examples: Income lost resulting from premature death, inability to work. Sometimes a challenge to assign dollar values.
5. Intangible costs – Costs that represent nonfinancial outcomes of the disease and medical care. Examples: Costs from pain and suffering, grief, other nonfinancial outcomes of disease
6. Incremental costs – Extra costs needed to purchase an additional benefit or effect of the medical care. Example: Additional medications to control hypertension above standard therapy. Often used in cost-effectiveness analysis.

C. Economic Evaluations

1. Cost minimization analysis – Outcomes are compared and determined to be equal and so not included in the evaluation, therefore expressed in monetary form. Results are provided as cost savings.
 - a. Compares the cost of two or more treatment alternatives, treatments, or services and determined to be equal in efficacy
 - b. Costs are compared to determine the least expensive alternative.
 - c. Should not be used if no evidence exists to support the efficacy of the treatment alternative
Example: Comparing therapeutic agents in the same therapeutic class; comparing different dosage forms or dosing strategies of the same drug
Challenge: Proving identical efficacy
2. Cost-benefit analysis – Compares the outcomes of the intervention in monetary terms with the cost of the resources consumed for two or more programs or interventions
 - a. Resources consumed in the program are measured in dollars.
 - b. Benefits of the intervention or program are translated to dollar values, including direct benefits, indirect benefits, intangible benefits.
 - c. Assigning monetary value to health outcomes: Human capital approach or willingness to pay
 - d. Results expressed as either cost-benefit ratio or net cost or benefit
 - e. Provides the yield of an investment
Example: May be an appropriate method to use when justifying and documenting the value of an existing pharmacy service or the potential worth of an existing service, specifically, determining the value of pharmacokinetic service compared to a vaccination program.
Challenge: Putting a dollar value to an outcome, consequence, or benefit
Limitation: Does not evaluate the internal efficacy of the programs
3. Cost-effectiveness analysis – Compares two or more treatment alternatives or programs where resources used are measured in monetary terms and consequences in units of effectiveness
 - a. Goals of cost-effectiveness analysis – To determine which alternative can produce the desired effect or maximization of effect
 - b. Tries to reveal the optimal alternative, which may not always be the least expensive but provides the desired outcome
 - c. Results expressed as the incremental cost-effectiveness ratio = the additional cost to the next most effective intervention of producing another unit of output.
Example: Comparing treatment options for smoking cessation. Unit of effectiveness is successful quit attempted for all treatment options. Cost per successful quit attempted on average for each treatment and then incremental cost per quit attempted between treatment options are reported.
4. Cost-utility analysis – Method to compare two or more treatment alternatives or programs where costs are measured in monetary terms and outcome is expressed in terms of patient preferences or quality of life or quality-adjusted life-years (QALYs)
 - a. Form of cost-effectiveness analysis where values (utilities) are assigned to the outcome
 - b. Life and death are reference states for the utilities, with perfect health = 1.0 and death = 0.0.

- c. Determine the life-years gained and then multiply by the utility of that life-year. For example, if a person has a life expectancy of 20 years but is disabled and functioning at only 70% of his or her capacity, then the QALY is $20 \text{ years} \times 0.7 = 14 \text{ QALYs}$.
 - d. Measuring utilities or a patient's preference for a disease state can be done by obtaining information from the literature, approaching a convenience sample of experts, decision theory using a direct approach, or psychometric methods using indirect approaches. Direct approaches include rating scales, time trade-off, and standard gamble. Indirect approaches include multiattribute health state scores (e.g., quality-of-life assessment tools).
 - e. Measures the function and overall well-being of patients using quality-of-life assessment tools, such as those used in the ICU, which are general and disease specific.
 - i. General health-related quality-of-life instruments
 - (a) Nottingham Health Profile
 - (b) Sickness Impact Profile
 - (c) Posttraumatic Stress Disorder Questionnaire
 - (d) EuroQol Questionnaire
 - (e) Medical Outcome Study Short Form 36 (SF-36)
 - ii. Disease-specific quality-of-life instruments
 - (a) Hospital Anxiety and Depression Scale
 - (b) Asthma Quality of Life Questionnaire
 - f. Example: Pharmacist-managed sedation in the critically ill population; the effect of sedation medications on the critically ill population. The evaluation could measure quality of sedation provided according to the patient's perception.
- 5. Cost of illness
 - a. Estimate of the overall cost of a particular disease in a defined population
 - b. Considers direct and indirect costs of the disease or illness
 - c. Examples: Cost of diabetes, cost of kidney disease
 - 6. Budget impact analysis or budget impact model
 - a. Estimates the financial impact of a new health care intervention within the health care setting, therefore limited in its perspective
 - b. Useful in budget planning
 - c. Aids in determining the projected impact of a formulary addition
- D. Application of Pharmacoeconomics
- 1. Formulary management
 - a. Inclusion of newly marketed or other target drugs
 - b. Exclusion of newly marketed drugs
 - c. Inclusion of drugs with criteria or restriction
 - d. Deletion of medications from the formulary
 - e. Limiting the use of nonformulary items
 - f. Affecting physician or provider prescribing patterns
 - 2. Clinical guidelines, policies, or protocols – Assists in influencing prescribing and promoting the most cost-effective and desirable use of drugs
 - 3. Drug use policy – Policies implemented to promote the most efficient use of health care products and services. Drug use policies can influence providers' prescribing practices to provide high-quality care given the resources available.
 - 4. Services or program evaluations – Use of pharmacoeconomics can aid in determining the value of an existing medical or pharmacy service or the potential worth of starting a new service.
 - 5. Individual patient treatment decisions – The most important principles and methods of economic outcome

Patient Case

1. From the patient's perspective, which best describes indirect costs?
 - A. Cost of visit to the health care provider's clinic.
 - B. Cost of treatment for hypertension based on hypertension management goals.
 - C. Loss of income based on admission days in the hospital.
 - D. Drug effects on activities of daily living.

II. ADVERSE DRUG EVENTS

- A. In the United States, 770,000 injuries or deaths are caused by ADRs annually; the cost burden of ADEs is greater than \$5.6 million per hospital.
- B. A severe ADE increases the hospital length of stay by 8–12 days at a cost of \$16,000–\$24,000.
- C. The cost burden of preventable ADEs in the United States is \$2 billion annually.
- D. Medical malpractice lawsuits are often related to or occur because of ADEs.
- E. The risk of ADEs increases when patients are critically ill and taking many high-risk medications—specifically intravenous medications—with several illnesses and multiorgan failure.
- F. The Joint Commission (TJC) Medication Management Standard requires hospitals to respond to actual or potential ADEs, significant ADRs, and medication errors.
- G. At the very least, hospitals need to respond, document and report, and manage ADEs. The pharmacist, who is the drug expert, should play an integral role in the ADE process.
- H. Definitions: Medication Errors, ADEs, and ADRs
 1. A medication error is a mishap that occurs during prescribing, transcribing, dispensing, administering, or monitoring a drug. Medication errors that are intercepted and stopped before they occur are called “near misses.” Some medication errors cause injury (result in an ADE), and some do not. Medication errors that cause significant harm may be reported through the health system's patient incident reporting system.
 - a. Harm is physical or psychological injury or damage to the health of a person, including both temporary and permanent injury.
 - b. Medication errors are categorized into the following: no error (category A), error and no harm (categories B–D), error and harm (categories E–H), and error and death (category I). Specifically,
 - i. Category A: No error – Scenarios that have the capacity to cause error
 - ii. Category B: An error occurred but did not reach the patient.
 - iii. Category C: An error occurred and reached the patient but did not cause harm.
 - iv. Category D: An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient or required intervention to prevent harm.

- v. Category E: An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.
 - vi. Category F: An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.
 - vii. Category G: An error occurred that may have contributed to or resulted in permanent patient harm.
 - viii. Category H: An error occurred that required intervention necessary to sustain life.
 - ix. Category I: An error occurred that may have contributed to or resulted in the patient's death.
2. Medication errors may be reported through the Institute for Safe Medication Practices (ISMP).
 - a. A confidential and voluntary system
 - b. Reports are investigated by ISMP staff and then reported to the FDA's MedWatch Program and product vendors.
 - c. A separate reporting method is used for vaccines.
 - d. Vaccine medication error reports provide an option to submit the vaccine's manufacturer name, dosage, lot number, expiration date, and National Drug Code.
 - e. Consumers may also report medication errors through ISMP.
 - f. In addition to describing the error, images may be submitted and uploaded.
 - g. Medication errors may be reported directly to the FDA by the MedWatch System. The FDA's MedWatch allows ADE and medication error reporting.
 3. An ADE is an injury resulting from the use of a drug, which includes harm caused by the drug (ADRs and overdoses) and harm from the use of the drug, including dose reductions and discontinuations of drug therapy.
 4. An ADR is defined by the World Health Organization (WHO) as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."
 5. Karch and Lasagna (JAMA 1975;234:1236-41) define an ADR as "any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose."
 6. The primary difference between the WHO and the Karch and Lasagna ADR definitions is that, according to the WHO definition, therapeutic failures are an unintended effect and an ADR, whereas according to the definition by Karch and Lasagna, they are not. ADRs caused by therapeutic failures with easily retrievable, detailed data that document the drug and the therapeutic failure can have a significant impact on improving patient care. Also of note, both definitions refer to doses normally used in humans, which excludes overdoses and medication errors that exceed normal doses.
 7. Overall, *ADE* is the broader term that is used to describe any harmful event associated with a medication, including inappropriate use such as an overdose, whereas *ADR* is used when an adverse response, including harm, occurs with normal use of the medication.
 8. Examples of therapeutic failures that may be documented as ADRs according to the WHO criteria include the following:
 - a. Clopidogrel failure to prevent an ischemic stroke
 - b. Enoxaparin failure to prevent deep vein thrombosis
 - c. Famotidine failure to prevent intravenous ketorolac-induced gastropathy
 - d. Pantoprazole failure to prevent gastrointestinal bleeding from a stress ulcer in a critically ill patient
 - e. Haloperidol failure for sedation in a delirious critically ill patient
 9. Examples of ADRs
 - a. Lorazepam when being used to treat anxiety may cause sedation – This is an unintended adverse reaction; conversely, lorazepam for sedation in a critically ill patient is an intended effect, not an ADR.
 - b. Diphenhydramine causing sedation when it is being used to treat allergic rhinitis is unintended – This is an ADR; conversely, diphenhydramine as a sedative hypnotic is an intended effect, not an ADR.

I. ADR or Side Effect

1. There is often controversy regarding whether all ADRs should be reported and documented and whether ADRs are the same as or different from side effects.
2. The American Society of Health-System Pharmacists (ASHP) defines a side effect as an expected well-known reaction resulting in little or no change in patient treatment, such as antihistamine-induced drowsiness. The term *side effect* may minimize or downplay the risk of injury from medications. It has been suggested that the term *side effect* be avoided in favor of the term *ADR*. In general, *side effects* and *ADRs* are terms used synonymously.
3. Although the ASHP definition of a side effect differs from the WHO definition of an ADR, any reaction to a medication, including a side effect, must be documented in the patient's medical record. It is also prudent and good practice to document side effects in the patient's ADE profile. Medication side effects are not without consequences and can lead to harmful effects. For example, antihistamine-induced drowsiness may lead to a traumatic fall and hip fracture, resulting in hip replacement surgery. Documenting the ADR and managing the event with a lower dose of the antihistamine or switching to a less sedating agent could prevent a side effect from leading to harm, an ADE.
4. ASHP further defines a side effect as an effect with a predictable frequency and an effect whose intensity and occurrence are related to the size of the dose. Predictable "side effects" should also be reported as ADRs, such as:
 - a. Insulin-induced hypoglycemia
 - b. Chemotherapy-induced nausea
 - c. Opioid-induced pruritus

J. Preventable ADEs

1. A preventable ADE occurs when a breach of standard professional behavior, practice, or technique was identified or when necessary precautions were not taken, or when the event was preventable by modification of behavior, practice, technique, or care.
2. Results from any medication error that reaches the patient and causes harm
3. About 30%–50% of all ADEs are preventable.
4. Drug interactions account for 3%–5% of all preventable in-hospital ADRs (drug interactions discussed further in section IV).
5. Nonpreventable ADEs are ADEs not associated with a medication error. Unintended reactions (ADRs) without known mitigation strategies resulting in patient harm (a patient with a bleed despite appropriate dosing, administration, and monitoring of the anticoagulant)
6. Examples of preventable ADEs (note that all examples have definitive harm)
 - a. Heparin administration without the use of weight-based dosing, causing an elevated partial thromboplastin time and an intracranial hemorrhage
 - b. Phenytoin mixed accidentally with dextrose rather than normal saline, causing precipitation and lack of drug potency and leading to a patient developing withdrawal seizures and status epilepticus
 - c. Levofloxacin intravenous and azithromycin intravenous prescribed to a patient receiving haloperidol with a known prolonged corrected QT interval on the electrocardiogram, causing torsades de pointes
 - d. Bactrim intravenous prescribed to a patient receiving warfarin, causing inhibition of warfarin metabolism, displacement from warfarin's plasma protein-binding sites, and hypoprothrombinemia, causing the patient to develop a gastrointestinal bleed
 - e. Rivaroxaban prescribed to a patient for nonvalvular atrial fibrillation stroke prevention who is receiving rifampin; rifampin increases rivaroxaban hepatic metabolism through cytochrome P450 3A4 and induction of P-glycoprotein, which may cause subtherapeutic rivaroxaban serum concentrations and lead to decreased efficacy, in turn causing the patient to develop a stroke
 - f. Carbamazepine prescribed for an Asian patient with bipolar disorder without testing for the *HLA-B*1502* allele; in turn, the patient develops carbamazepine-induced toxic epidermal necrolysis

K. FDA-Reportable ADEs

1. For reporting an ADE to the FDA, the FDA defines ADEs as serious adverse events related to drugs or devices in which “the patient outcome is death, life threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage.” Reportable serious ADEs to the FDA may include the following:
 - a. Phenytoin-induced toxic epidermal necrolysis
 - b. Linezolid-induced thrombocytopenia with genitourinary hemorrhage
 - c. Clopidogrel-induced thrombotic thrombocytic purpura with seizures and hepatic failure and the use of plasmapheresis
 - d. Rivaroxaban-induced intracranial hemorrhage
 - e. Olanzapine-induced torsades de pointes
 - f. Gentamicin-induced irreversible auditory ototoxicity
 - g. Acetaminophen-induced hepatotoxicity
2. An example of a reportable adverse event caused by a device may be the mechanical failure of a pneumatic compression device, leading to a pulmonary embolism and death.
3. The FDA is also interested in serious ADE reports for newly marketed drugs or novel adverse events that have not been previously reported for new or old drugs.
4. The FDA Adverse Event Reporting System is a database that contains information on adverse events and medication error reports that have been submitted to the FDA. The database is used as a postmarketing surveillance system for medications and therapeutic biological products.
5. The reporting of ADEs by health care professionals and consumers to the FDA is voluntary and may be done through the FDA’s MedWatch program (initiated in 1993). All of the following may be reported with respect to an FDA-regulated medication, biologic, tobacco product, dietary supplement, cosmetic, or medical device:
 - a. Serious ADE
 - b. Serious ADR
 - c. Product quality problem
 - d. Product use error
 - e. Therapeutic inequivalence
 - f. Therapeutic failure
6. Clinicians may report an ADE directly to the drug’s manufacturer. The pharmaceutical manufacturer has a legal responsibility to follow up with the reporter on all ADEs reported and to report the ADE to the FDA.
7. ADE reports and medication error reports submitted directly by health care professionals or manufacturers are entered in the FDA Adverse Event Reporting System database.
8. If the FDA detects a safety concern, it may take regulatory action to protect the public, such as updating the product labeling, restricting the drug, communicating the safety concerns to health care professionals and consumers, or removing the drug from the market.

L. Designing an ADE Reporting Program

1. A comprehensive ADE program should have a policy and procedure, with guidelines for ADE detection, reporting, management, surveillance, and education (see Appendix 1 for an ADE reporting form).
2. Because of the pharmacist’s expertise in drug-induced diseases and the pharmacist’s role in preventing and managing ADEs, pharmacists often serve as chair or co-chair of the ADE committee.
3. The ADE committee should be multidisciplinary and should be composed of the following:
 - a. Physicians
 - b. Pharmacists

- c. Nurses
- d. Risk management personnel
- e. Quality assurance and performance improvement personnel
- f. Other health care providers
4. In general, the ADE committee is a subcommittee of the pharmacy and therapeutics (P&T) committee that reports to the P&T committee.
5. The ADE committee should meet periodically and can meet monthly, bimonthly, or quarterly, depending on the number of reports and actionable items that need review.
6. ADE data can be reported by specialty unit or service, such as:
 - a. Intensive care
 - b. Internal medicine
 - c. Telemetry
 - d. Rehabilitation
 - e. Psychiatry
 - f. Emergency medicine
 - g. Operating room
 - h. Oncology
 - i. Pediatric
 - j. Geriatric

This will ensure appropriate preventative measures are developed for that specialty unit.
7. ADR and ADE data should be reported as mild, moderate, and severe ADRs. There are multiple scales available in the literature. Definitions for each should be established. An example is provided in Box 1.

Box 1. Definitions for the Degree of ADR Severity (in ascending order of severity)^a

1.	Mild ADR: Results in heightened need for patient monitoring with or without a change in vital signs, but no ultimate patient harm, or any adverse event that results in the need for increased laboratory monitoring
2.	Moderate ADR: Results in the need for aggressive intervention with antidotes or increased length of hospital stay (e.g., severe hypotension [e.g., BP < 90/50 mm Hg], bleeding necessitating transfusions)
3.	Severe ADR or ADE: Results in harm to the patient, prolonged hospitalization, transfer to a higher level of care, permanent organ damage (e.g., irreversible hepatotoxicity or renal failure), or death with probable ADE causality nomogram score

^aOther ADE severity scales are available.

ADE = adverse drug event; ADR = adverse drug reaction; BP = blood pressure.

8. The ADE subcommittee should designate which ADEs are preventable and should provide explanations regarding why they were preventable. Examples of preventable ADEs include the following:
 - a. A patient receiving vancomycin who develops nephrotoxicity as a result of an incorrect high-dosing regimen and lack of serum concentration monitoring
 - b. A patient with epilepsy maintained on intravenous valproic acid who develops breakthrough seizures as a result of subtherapeutic valproate serum concentrations caused by a drug-drug interaction with the concomitant use of doripenem
9. The ADE committee will determine which ADEs will be reported to the FDA or the manufacturer.
10. The committee should report the data regarding who is detecting ADEs and who reports, documents, and manages the ADEs.
11. The committee should provide trending data based on either drug or drug class and by specialty units.

12. The committee should benchmark the hospital's ADEs against itself in previous years and compare them with the data from other hospitals published in the biomedical literature. Total ADE data can be reported according to the following:
 - a. Total number of ADEs
 - b. ADEs per admission
 - c. ADEs per patient
 - d. ADEs per patient days
 - e. ADEs per doses dispensed
 - f. ADEs per doses administered
13. A popular method of reporting ADEs is by the total number of admissions, with an acceptable benchmark of 2.5%–10%. For example, a hospital with 10,000 admissions reporting 1000 ADEs would have a 10% ADE reporting rate.
14. ADE benchmarks are daunting to determine because of the many variables that affect the reporting methods, such as the ADE definition used by the facility or the definition used by the reporter, the number of clinical pharmacists or pharmacy residents available to report, the vigilance and emphasis of the reporting systems, and the use of technology or reports to increase reporting.

M. Documenting ADRs and ADEs in the Patient's Medical Record

1. Allergy data are always documented in the patient's medical record and are a required element of the patient profile, which also includes demographics, diagnosis, and pregnancy category. Preferably, the medication that caused the allergy, the type of reaction, and when the allergy occurred should be documented.
2. A drug-induced allergy is an ADR or ADE. It is of paramount importance to report and document ADE data in the patient's medical record for the same purpose as documenting allergy data: to prevent recurrence with the same drug or a drug from the same or similar drug class and to mitigate risk when the same drug may need to be used again or to mitigate risk when other medications that can cause the same adverse event are used.
3. ADR and ADE data should be recorded in the electronic medical record and should be maintained in the record infinitely.
4. For severe ADRs and ADEs: When the same drug is prescribed, the computerized prescriber order entry (CPOE) system could be programmed to cause a hard stop and prevent the drug from being prescribed or a hard stop requiring a text message with an explanation for use. For example, a case of isoniazid-induced hepatotoxicity may be classified as a severe ADE, and if it is prescribed to the same patient again, the prescriber would receive a hard stop and would need to provide an explanation for its use to have the order validated by the pharmacist.
5. For moderate ADRs: When the same drug is prescribed, the CPOE system could be programmed to highlight or warn the prescriber or require a text response with an explanation for its continued use.
6. For mild ADRs: When the same medication is prescribed, the CPOE system could be set to highlight the prescriber, or the data could be retrievable for review but without prompting the clinician. A case of enalapril-induced hypotension may be recorded as a mild ADR and be maintained for informational purposes but will not prevent the medication from being prescribed to the patient again, nor will it require the prescriber to provide an explanation.

N. Methods of Medication Error and ADR or ADE Surveillance

1. ADEs can be detected prospectively and retrospectively. Pharmacists may detect ADEs prospectively while on patient care daily rounds, or from communication with patients while administering medication histories or discharge counseling. Clinical decision support with automated triggers can be used for prospective surveillance of events. Pharmacists may also detect ADEs retrospectively through medical record reviews or during medication histories.

2. Retrospective incident voluntary reporting is an ethical obligation of all health care professionals. Voluntary reporting is the primary source of event identification for most institutions; however, events are grossly underreported. Typically, safety pharmacists are responsible for aggregating these data. The aggregate reports are reviewed by the ADE committee for the institution. Possible prevention methods are determined by the committee. This is a retrospective evaluation because typically events are evaluated when there is allotted time, and this is often when the patient is discharged from the hospital. This could be a prospective method if real-time evaluation was an option.
 - a. A way to detect ADRs is by using clinical decision support within a CPOE system for trigger or tracer drugs – These terms are used synonymously. Trigger or tracer drugs are drugs that are routinely prescribed to treat ADEs, such as antidotes or physiologic antagonists or agents for gastric decontamination. These triggers prompt a targeted medical record review. Examples of tracer drugs:
 - i. Dextrose for hypoglycemia
 - ii. Naloxone for opioid-induced respiratory depression
 - iii. Protamine for heparin toxicity
 - iv. Activated charcoal for drug toxicity, such as with phenytoin or acetaminophen
 - b. The CPOE system can be programmed with a list of tracer drugs so that when prescribers order a tracer drug, they are asked whether the order is for an ADE and, if so, what type of ADE occurred. The potential ADE can then be reported and managed by the clinical pharmacist. One of the benefits of this system is that it captures ADEs that might not have been reported, especially when a clinical pharmacist may not be present on the unit or on daily patient care rounds, and it allows a greater number of physician-reported ADEs. Some trigger or tracer drugs are listed in Box 2.
 - c. Therapeutic drug concentration and abnormal laboratory value monitoring can be another source for ADR detection. The pharmacy may design daily reports that contain all the abnormal drug serum concentrations such as the phenytoin, digoxin, lithium, amiodarone, vancomycin, and aminoglycoside concentrations. The clinical pharmacist can then review all cases of supratherapeutic concentrations by performing a targeted medical record review for ADEs such as:
 - i. Phenytoin-induced confusion, ataxia, or nystagmus
 - ii. Amiodarone-induced pulmonary or thyroid toxicity
 - d. A daily report can also provide abnormal electrolytes and abnormal serum creatinine and hepatic function (bilirubin, aspartate aminotransferase, and alanine aminotransferase) to detect:
 - i. Rifampin-elevated liver enzymes
 - ii. Lisinopril-induced hyperkalemia
 - iii. Esomeprazole-induced hypomagnesemia
 - e. The trigger drug list can be monitored by clinical pharmacists, allowing the pharmacist to ensure that ADR documentation occurred and appropriate management is taking place.
 - f. Identified events must be confirmed for causality. Many instruments are available to aid in the link between drug and event. Structured instruments create a more reliable and valid assessment. A sample ADE form with the Naranjo Criteria for causality determination is described in Appendix 1. This is the most frequently used ADR causality instrument, although its reliability and validity in the critically ill population need improvement.
 - g. Causality assessment includes temporal sequence, dechallenge (removal of the suspect drug), rechallenge (reintroducing the suspect drug), evaluation of other causes, objective evidence that is available or obtained, and previous history of a reaction to a similar drug.
3. Prospective
 - a. Direct observation – One method of medication error detection is through direct observation; this can be accomplished using the medication pass method, in which the pharmacist observes nurses in the medication administration process and notes any errors that occur. Direct observation provides the unique advantage of capturing medication administration errors that are not typically identified

with other detection methods. Other examples of direct observation include nurses observing nurses or physicians observing physicians during medication administration. This is considered prospective because observation occurs in real time, but errors are evaluated later.

- b. Clinical decision support with alert generation can be used for prospective or real-time surveillance.
 - i. Prescribing – Physicians can be notified of high-risk scenarios during the ordering process to prevent medication errors, such as prescribing enoxaparin in a patient with a glomerular filtration rate of <30 mL/minute. Alerts during medication ordering should be used judiciously to avoid alert fatigue.
 - ii. Order verification – Pharmacists receive preventive alerts during order verification to avoid medication errors and the potential for ADEs. Common alerts that pharmacists receive are to prevent drug-drug interactions. These alerts still need to be improved for specificity to prevent overalerting.
 - iii. High-risk scenarios in real time – Pharmacist may receive advanced alerts outside order verification, indicating when a patient is started on a drug but the patient's clinical scenario presents a risk. An alert for a patient on an epidural and initiated on an anticoagulant presents an opportunity for intervention to prevent an ADE.

Box 2. Medications Used as Triggers or Tracers to Aid in Reporting ADEs

1. Atropine sulfate 1-mg injection	12. Kaopectate suspension
2. Activated charcoal suspension	13. Kayexalate
3. Benztropine PO, IM, or IV	14. Loperamide
4. Diphenhydramine PO, IM, or IV	15. Diphenoxylate/atropine
5. D ₅₀ IV push	16. Metronidazole IV or PO
6. Digibind	17. Naloxone
7. Epinephrine 0.15-mg injection	18. Prednisone solution or tablet
8. Epinephrine 1-mg injection	19. Protamine
9. Fidaxomicin	20. Sodium phosphate injection or solution
10. Flumazenil	21. Vancomycin capsule
11. Hydrocortisone cream, ointment, or injection	22. Vitamin K

ADE = adverse drug event; CPOE = computerized prescriber order entry; D₅₀ = dextrose 50%; IM = intramuscularly; IV = intravenously; PO = per os.

Patient Cases

2. Which best classifies the degree of severity of an ADE in a patient who develops enalapril-induced asymptomatic hyperkalemia (potassium 5.7 mEq/L) managed with one dose of Kayexalate?
 - A. Mild.
 - B. Moderate.
 - C. Severe.
 - D. Life threatening.

Patient Cases (*continued*)

3. Which best classifies the degree of severity of an ADE in a patient who is in the geriatric psychiatry unit and develops intravenous haloperidol-induced torsades de pointes that is successfully treated with intravenous magnesium and managed with additional monitoring in the cardiac care unit and telemetry?
- A. Mild.
 - B. Moderate.
 - C. Severe.
 - D. No classification.

Questions 4 and 5 pertain to the following case.

M.S., a 77-year-old man residing in a nursing home, has taken lisinopril 10 mg daily for the past 3 months. He is admitted to the ICU with lisinopril-induced angioedema and presents with severe tongue swelling, stridor, and shortness of breath that necessitated a tracheotomy. He had no history of allergies and did not miss any doses of lisinopril.

4. Which best describes this patient's reaction to lisinopril?
- A. An ADE.
 - B. A preventable ADE.
 - C. A medication error.
 - D. A preventable ADR.
5. Which best classifies the degree of severity of this patient's ADE to lisinopril?
- A. Mild.
 - B. Moderate.
 - C. Severe.
 - D. No classification

III. DRUG INTERACTION SURVEILLANCE AND PREVENTION

- A. Definition of Drug Interactions
 - 1. When the effects of one drug can be changed by the presence of another
 - a. Can be benign and insignificant
 - b. Can be harmful and life threatening
 - 2. Related toxicity (ADR) is preventable.
 - a. Avoid the combination and switch to an alternative therapy.
 - b. Adjust doses to compensate for the interaction.
 - c. If the combination cannot be avoided, monitor for efficacy and toxicity of the object drug.
- B. A documented drug interaction with known outcomes can be considered an ADR, medication error, or preventable ADR.

- C. Drug interaction databases include Lexicomp, Micromedex, Epocrates, Clinical Pharmacology, Hansten and Horn's Drug Interaction Analysis and Management, Stockley's Drug Interactions, and PDR Drug Interactions.
1. Most compilation databases have drug interaction software in which the pharmacist can provide a list of drugs, and the database will provide the type of interaction and severity.
 2. Lexicomp scale for drug interactions
 - A = No known interaction
 - B = No action needed
 - C = Monitor therapy
 - D = Consider therapy modification
 - X = Avoid combination
 3. Micromedex scale for drug interactions
 - Severity scale: Unknown, minor, moderate, major, contraindicated
 - Documentation scale: Excellent, good, fair, unknown
 4. Hansten and Horn's Drug Interaction Analysis and Management
 - a. Provides summary, risk factors, mechanism, clinical evaluation, related drugs, and references
 - b. Class of interaction with brief explanation
 - 1 = Avoid combination. Risk always outweighs benefit.
 - 2 = In general, avoid combination. Use combination only under special circumstances.
 - 3 = Minimize risk. Take action as necessary to reduce risk.
 - 4 = No action needed. Risk of adverse outcomes appears small.
 - 5 = No interaction. Evidence suggests no interaction.
 5. Stockley's Drug Interactions: Provides outcome, clinical evidence, mechanism, importance, and management
- D. Safety Measures to Avoid Drug Interactions
1. Pharmacist review and validation
 - a. Pharmacists are highly trained in pharmacology and drug interactions and are expected to be highly knowledgeable in drug interactions.
 - b. Pharmacists' scope of practice includes a comprehensive review of patients' medications for drug interactions.
 - c. All prescription records are maintained in one profiling system.
 - d. Fill all medications in the same pharmacy, if possible, to maintain a comprehensive and accurate medication record.
 2. Using CPOE and clinical decision support that detects drug interactions
 - a. Pop-up warnings (alerts)
 - b. Soft stops with explanation required
 - c. Hard stops
 - d. In general, does not detect pharmacodynamic antagonistic interactions such as a β -blocker and a β -agonist or a cholinergic drug with an anticholinergic drug
 - e. CPOE system must have clinical decision support activated. May prompt prescriber or pharmacist during order verification with a high frequency of alerts and desensitize the clinicians, known as alert fatigue or burden
 - f. Drug-drug interaction alert fatigue can be managed by reducing the alert number, using severity of the interaction as a criterion for alert selection.
 3. Education as a method to prevent drug interactions
 - a. Lectures, grand rounds, daily patient care rounds
 - b. Pocket drug cards
 - c. Drug alerts
 - d. Electronic drug information databases

E. How to Evaluate Drug Interaction Cases

1. Assessment of causation of a drug interaction includes a temporal relationship, consideration of the pharmacologic properties of the object and precipitant drug, patient factors and disease states, the possible contribution of other drugs, and, when possible, a positive dechallenge. The temporal sequence is the key element in these considerations to aid in a causation determination.
2. ADE nomograms such as the Naranjo nomogram are designed to evaluate ADEs, not drug-drug interactions; therefore, they should not be used to evaluate drug-drug interaction cases.
3. The Drug Interaction Probability Scale (DIPS) may be used to determine drug-drug interaction causation, including the adverse outcomes in a specific patient (see Appendix 2).
4. The DIPS is patterned after the Naranjo ADR Probability Scale. A series of 10 questions related to the drug interaction are assessed with “yes,” “no,” “unknown,” or “not available” answers and then scored and tabulated. The total score determines the probability of the drug-drug interaction occurring in the patient; it is scaled as follows:
 - a. Highly probable: More than 8
 - b. Probable: 5–8
 - c. Possible: 2–4
 - d. Doubtful: 2 or fewer
5. When using the DIPS, the evaluator must have comprehensive knowledge of the pharmacologic properties of both the object and the precipitant drug, especially their pharmacokinetic and pharmacodynamic properties and their mechanisms of drug action and mechanisms of drug interactions.

IV. FORMULARY PROPOSAL

- A. The drug formulary should be comprehensive and include all the medications needed for patient care.
- B. TJC Medication Management Standard requires hospitals to develop and approve the criteria for selecting medications into the drug formulary.
- C. At a minimum, the drug selection criteria should include the following:
 1. Indications for use (FDA label approved and off-label)
 2. Efficacy and effectiveness
 3. Drug interactions
 4. Adverse effects
 5. Sentinel event advisories
 6. Cost acquisition and total cost of care – This is a good application of the budget impact analysis. Ideally, if cost-effectiveness analysis and cost-utility analysis were also available, then they would be considered; however, they are typically not available this early in the drug approval process.
- D. The P&T committee is responsible for maintaining the drug formulary and ensuring that new medications that can improve patient care are reviewed for formulary inclusion.
- E. Critical care pharmacists should be cognizant of new medications and new medication dosage forms that may be used to improve the treatment of critically ill patients. Critical care pharmacists should collaborate with intensivists to request the addition or deletion of a drug from the formulary.

- F. Box 3 lists the elements of a drug evaluation monograph that should be reviewed before a drug is approved to the hospital formulary.

Box 3. Elements of a Drug Evaluation Monograph

Brand name
Generic name
Manufacturer
Therapeutic classification
FDA status: Prescription, nonprescription, or controlled substance
Look-alike sound-alike names with any other FDA label-approved medications
Look-alike sound-alike names with any other FDA label-approved medications on the formulary
Date of FDA label approval
FDA rank (priority or standard)
FDA label-approved indication
Unlabeled indications
Potential unlabeled uses
Similar agents not on the formulary
Similar agents on the formulary
How the drug can be used when applied to available national guidelines
How the drug can be used when applied to hospital guidelines, protocols, or pathways
Dosage form
Dosage strength
Mechanism of action
Absorption
Distribution
Metabolism
Excretion
Common ADRs
Significant or life-threatening ADRs or ADEs
Boxed warnings
Precautions
Contraindications
Drug-drug interactions
Drug-food interactions
Drug-laboratory tests interactions
IV incompatibilities
IV compatibilities
Pregnancy category
Use during breastfeeding
Dosage regimen recommendations
Dosage regimen recommendations for special populations such as pediatrics, geriatrics, renal and hepatic impairment, and dialysis
Any special administration techniques (prescriber certification)
Preparations available
Storage
Any availability concerns (specialty pharmacy restrictions)

Box 3. Elements of a Drug Evaluation Monograph (*continued*)

Critical review of pertinent clinical trials with salient critique and conclusions

Critical review of comparison trials with similar or alternative agents

Cost analysis including annual projected costs

Economic evaluations

Pharmacoeconomic analyses available

Budget impact analysis specific to the institution

Reimbursement from third-party payers

Are there any severe medication errors or sentinel events with this agent?

Does this medication need to be stored under specific circumstances to avoid medication errors or mix-ups?

Does this medication require tall man lettering labeling or precautionary or high-risk labeling to avoid potential medication errors or mix-ups?

Is the manufacturer-provided labeling considered clear and safe for dispensing?

Is an abuse potential associated with the use of this medication?

Patient education requirements

Will this agent replace an existing agent, and should a formulary deletion take place?

Reason why this medication should be included in the formulary

Recommendation for addition to the formulary

References

ADE = adverse drug event; ADR = adverse drug reaction; FDA = U.S. Food and Drug Administration; IV = intravenous(ly).

- G. Evidence-based decisions should be made when adding drugs to the formulary.
- H. A comprehensive literature review should be used to determine a drug's efficacy and toxicity profile, with stronger levels of evidence guiding decisions.
 - 1. Prospective double-blind randomized controlled trials should have greater weight than retrospective trials and meta-analyses.
 - 2. Case reports should be used only when no other evidence is available.
- I. It is important that the pharmacists developing the drug evaluation monograph be adept in drug literature evaluation and pharmacoeconomics.
- J. The drug evaluation should contain references to evidence, and opinion statements should be so noted.
- K. Internal prescribing data may also be used in formulary decisions, such as
 - 1. Quantity of drug used over a specified time
 - 2. Medication use evaluation data
 - 3. Adverse drug reaction data
 - 4. Medication error data
- L. Most new drugs are studied in 1500–3000 patients, which may make it difficult to detect less common severe or life-threatening adverse effects. Some drugs may cause life-threatening toxicity such as hepatic failure at a rate of 1:20,000 patients, thus requiring more than 100,000 postmarketing patient exposures before generating a signal of toxicity. It may be prudent to observe safety profiles of all new drugs for 1–2 years before admitting them into the formulary, if possible.
- M. Drugs may be added to the formulary without any use restrictions, or they may be added with restrictions.

- N. Drugs can be restricted for many reasons, such as the following:
1. Efficacy
 2. Safety
 3. Patient-specific populations (because of limited efficacy or safety evidence)
 4. Cost
- O. It is common to restrict drugs to a prescriber who is a specialist or a clinical pharmacist specialist, a specialty unit such as the ICU, or a population such as pediatric patients or postoperative surgical patients.
1. For example, propofol may be restricted to use in intensive care and surgical units or to use by intensivists or anesthesiologists.
 2. Parenteral fosphenytoin may be restricted to use in the intensive care and surgical units and the emergency department or units, where appropriate continuous cardiac monitoring will take place, such as in telemetry.
 3. Antimicrobials are often restricted to approval from infectious disease physicians or infectious disease pharmacist specialists.
 4. Fidaxomicin indicated for *Clostridium difficile*-associated diarrhea may be restricted to infectious disease physicians or pharmacist specialists, but to better curtail costs, there may also be select criteria that the specialists must document before use.
 5. Dexmedetomidine indicated for sedation in intubated and mechanically ventilated patients during treatment in an ICU setting may be restricted to use by intensivists; however, to curtail costs, there may be additional criteria that must be met by the intensivist before use.
- P. Once a drug is admitted for formulary approval, periodic assessments in the form of a medication use evaluation or reviews of use, cost, safety, and efficacy should be made, preferably within 3–6 months and again in 1 year. The goal is to determine the effectiveness of the drug (different from efficacy). Effectiveness is the use of a drug in the real-world setting outside a randomized controlled trial.
- Q. An assessment of all drugs that are on formulary within a class should be made annually or more often when there is an important change in prescribing information, when a landmark trial or publication affects the drug's use, or when new FDA label-approved agents are available within the drug class. Medication assessments typically prompt updates and modifications to the drug's current use.

Patient Case

6. Which criterion for drug selection is most important in making decisions for drug formulary approval?
- A. Adverse events.
 - B. FDA status.
 - C. FDA rank.
 - D. Absorption.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES**1. Answer: C**

Indirect costs occur because of work loss, and decreased productivity occurs because of illness. From the patient's perspective, Answer C is correct because loss of income is an indirect cost, a cost not directly associated with the health care or illness. Drug effects on patient functioning are an indirect cost from the employer's perspective (Answer D). Costs of clinic visits (Answer A) and hypertension treatment (Answer B) are direct costs.

2. Answer: A

A mild ADE is defined as an ADE that resulted in a heightened need for patient monitoring with or without a change in vital signs but no ultimate patient harm, or as any adverse event that resulted in the need for increased laboratory monitoring. Enalapril-induced hyperkalemia managed by one dose of Kayexalate did not require aggressive interventions, nor did it lead to any patient harm; however, it did require increased laboratory monitoring, making Answer A correct and Answers B–D incorrect.

3. Answer: C

A severe ADE results in patient harm, prolonged hospitalization, transfer to a higher level of care, permanent organ damage, or death, which did occur in this case (Answer D is incorrect). Haloperidol-induced torsades de pointes is a life-threatening dysrhythmia (end-organ damage) that required aggressive and successful management with intravenous magnesium and patient transfer to higher level of care (Answer C is correct). A moderate ADE is defined as an ADE that resulted in the need for aggressive intervention with antidotes or an increased length of hospital stay (Answer B is incorrect). A mild ADE is defined as an ADE that resulted in a heightened need for patient monitoring with or without a change in vital signs but no ultimate patient harm, or as any adverse event that resulted in the need for increased laboratory monitoring, which did not occur in this case, making Answer A incorrect.

4. Answer: A

Because this patient developed lisinopril-induced angioedema, had no history of allergy to angiotensin-converting enzyme inhibitors, and missed no doses of lisinopril, this ADE was not a preventable error and was not caused by a medication error, making Answer A correct and Answers B–D incorrect.

5. Answer: C

A severe ADE is defined as an ADE that results in harm to the patient, prolonged hospitalization, transfer to a higher level of care, permanent organ damage, or death, with the probable ADE causality nomogram score. Because this patient developed life-threatening lisinopril-induced angioedema and needed a tracheotomy, resulting in patient harm, hospitalization, and transfer to a higher level of care, this case meets the criteria for a "severe" ADE, making Answer C correct and Answers A, B, and D incorrect.

6. Answer: A

Answer A is correct; TJC requires that the minimum drug selection criteria for adding a drug to the formulary include indications for use, effectiveness, drug interactions, adverse effects, sentinel event advisories, and cost. Answers B–D are incorrect; although it is important to include the FDA status and rank of a drug and the drug's absorption when reviewing a drug for the formulary or preparing a drug monograph, these are not required elements, nor are they more important than ADEs in making formulary decisions.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: C**

Answer C, medical professional's time, is correct. Direct medical costs are associated with the medical products and services used in the identification, prevention, detection, and treatment of a disease. Of note, it is a fixed direct medical cost. Examples of direct medical costs include medications, supplies, and hospitalizations. Delirium is an example of intangible costs (Answer A). Time lost from employment is significant and considered an indirect cost (Answer B). Transportation, food, and lodging are considered direct nonmedical costs (Answer D).

2. Answer: B

A cost-benefit analysis (Answer B) is the best economic tool to evaluate the value of a critical care pharmacist's service. For example, the financial value can be determined in dollars by comparing the cost of implementing a critical care pharmacist's service (pharmacist salary and benefits) with the benefits gained through the critical care pharmacist's activities such as reduced length of stay and decreased drug cost. A cost-of-illness analysis (Answer A) is not a cost analysis. A cost minimization analysis compares the cost of two or more treatment alternatives that are equal in efficacy (Answer C is incorrect). A cost-effectiveness analysis estimates costs and outcomes of treatment (intervention), but the two are measured in different units (Answer D is incorrect).

3. Answer: D

A preventable ADE, by definition, is a medication error that occurs and reaches the patient to cause harm because of a breach of standard professional behavior or practice. The patient had a documented history of penicillin allergy but still received cefazolin and developed a life-threatening anaphylaxis reaction; this is a medication error, and the anaphylactic reaction is the harm. Allergy cross-reactivity between penicillin and cefazolin is well documented; therefore, this is a preventable ADE (Answer D is correct). Although this case of cefazolin-induced life-threatening anaphylaxis is an ADE, a preventable ADE best describes this case (Answer C is not the best selection). In general, *ADRs* and *side effects* are synonymous terms, and a cefazolin-induced allergy is an ADR; however, a preventable ADE best describes this case (Answers A and B are incorrect).

4. Answer: A

Naloxone is an opioid antagonist and is an antidote indicated for opioid overdose, for the complete or partial reversal of opioid depression, including respiratory depression induced by natural or synthetic opioids. Because of naloxone's indication, it is an excellent tracer drug to detect opioid ADEs (Answer A is correct). Clopidogrel, propofol, and enoxaparin are not antidotes and are not indicated or routinely used to treat or manage drug-induced disorders (Answers B–D are incorrect).

5. Answer: C

Kayexalate is sodium polystyrene sulfonate and is an antidote for the treatment of hyperkalemia. Kayexalate is an excellent tracer drug to detect drug-induced causes of hyperkalemia such as angiotensin-converting enzyme inhibitors, potassium-sparing diuretics, spironolactone, β -blockers, heparin, and sulfamethoxazole/trime-thoprim (Answer C is correct). Sumatriptan, lorazepam, and amitriptyline are not antidotes, and these agents are not indicated or routinely used to treat or manage drug-induced disorders (Answers A, B, and D are incorrect).

6. Answer: D

The half-life of midazolam is shorter than that of lorazepam and longer than that of propofol (Answer A is incorrect). There are challenges in compounding lorazepam drips (Answer B is incorrect). Propylene glycol toxicity is associated with lorazepam administration (Answer D is incorrect). Midazolam is metabolized by cytochrome (a substrate of) P4503A4 and has the potential for drug interactions, whereas midazolam and propofol are not, so the correct answer is D.

7. Answer: C

The Joint Commission requires that the minimum criteria for selection of a drug to the formulary include indications for use, effectiveness, drug interactions, adverse effects, sentinel event advisories, and cost (Answer C is correct). Although it is important to include unlabeled indications, date of FDA approval, and storage when reviewing a drug for the formulary or preparing a drug monograph, these are not required elements, nor are they more important than the drug's effectiveness in making formulary decisions (Answers A, B, and D are incorrect).

8. Answer: A

Drug formularies are intended to guide rational prescribing by identifying and designating drug choices. The World Health Organization encourages all institutions to have a committee to oversee formularies, in addition to TJC providing criteria for formulary decisions (Answer A is correct). The primary goal of a formulary is not cost containment, because the criteria set forth by TJC incorporate many elements with emphasis on safety and efficacy (Answer B is incorrect). Although the pharmacy and therapeutics committee does evaluate newly approved drugs, it also considers new indications for old drugs (Answer C is incorrect). Making recommendations for medication use evaluations is a function of the pharmacy and therapeutics committee in response to maintaining an effective drug formulary; however, this is not the primary goal (Answer D is incorrect).

Appendix 1. Adverse Drug Event Reporting Form

ADVERSE EVENT INFORMATION						ADE#: 	
1. NAME	2. PATIENT ID #	3. LOCATION	4. AGE	5. SEX	6. REACTION ONSET DATE		
					7. DATE OF REPORT		
8. DESCRIBE REACTION AND ITS MANAGEMENT. (Continue on the back if necessary. Use Arial Narrow Font Size 10)					9. Check all appropriate		
					☐ Patient Expired		
					☐ Reaction Treated with Drug		
					☐ Resulted in, or prolonged inpatient hospitalization		
					☐ None of the Above		
					10. Did event abate after stopping the drug?		
					☐ YES		
					☐ NO		
					☐ MAYBE		
					11. Was patient's electronic allergy/ADE profile updated		
					☐ YES		
					☐ NO		
(If no, please explain on second page)							
12. RELEVANT TESTS/LABORATORY DATA							
SUSPECTED DRUG(S) INFORMATION							
13. SUSPECTED DRUG(S) Give manufacturer & lot number for vaccine/ biologics/ biotechnological					17. DATES OF ADMINISTRATION		
14. DOSE AND FREQUENCY			15. ROUTE OF ADMINISTRATION		18. DURATION OF ADMINISTRATION		
16. INDICATION(S) FOR USE							
CONCOMITANT DRUG HISTORY							
19. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat the reaction)							
20. OTHER RELEVANT HISTORY (e.g., diagnoses, past medical history, allergies, pregnancy, etc.)							
INITIAL REPORTER (In confidence)							
JCAHO Standard PI. 2.20 states that all serious adverse drug reactions are intensely analyzed. Standard MM. 6.20 maintains that the responsible individual complies with internal and external reporting requirements for adverse drug reactions. (2006 Comprehensive Accreditation Manual for Hospitals) Please take the time to complete this form for each suspected adverse drug reaction, and forward it to the Department of Pharmacy for reporting at the next Adverse Drug Reaction Subcommittee meeting.					NAME AND ADDRESS OF REPORTER (Including zip code)		
					TELEPHONE NO. (Include area code)		
					HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?		
							☐ YES ☐ NO
Date		Time		MD notified about possible ADR		Pharmacist's Signature	
Submission of a report does not necessarily constitute an admission that the drug caused the reaction							

Appendix 1. Adverse Drug Event Reporting Form (*continued*)

KJMC ADVERSE DRUG EVENT REPORTING FORM
Naranjo Criteria for Causality (also called ADR Probability Scale)

ASSESSMENT	YES	NO	DON'T KNOW	SCORING SYSTEM
1. Are there previous reports of this reaction? (If no, please provide documentation of search strategy)	+1	0	0	Based on the total score, circle the term that best defines this ADR: ≥9 Definite 5 – 8 Probable 1 – 4 Possible ≤0 Doubtful
2. Did the ADR appear after the suspected drug was administered? (If no, please explain).	+2	-1	0	
3. Did the ADR improve when the drug was discontinued or a specific antagonist was administered? (If no, please explain).	+1	0	0	
4. Did the ADR reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could, on their own, have caused the ADR? (If yes, please explain).	-1	+2	0	
6. Did the ADR reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood or other fluids in concentrations known to be toxic?	+1	0	0	
8. Was the ADR more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patients have a similar reaction to the same or similar drugs in any other previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
TOTAL SCORE				

Source: Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.

Appendix 2. Drug Interaction Probability Scale

The Drug Interaction Probability Scale (DIPS) is designed to assess the probability of a causal relationship between a potential drug interaction and an event. It is patterned after the Naranjo ADR Probability Scale (Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45).

Directions

- o Circle the appropriate answer for each question, and add up the total score.
- o Object drug = Drug affected by the interaction.
- o Precipitant drug = Drug that causes the interaction.
- o Use the Unknown (Unk) or Not Applicable (NA) category if (a) you do not have the information or (b) the question is not applicable (e.g., no dechallenge; dose not changed).

Questions	Yes	No	NA/Unk
1. Are there previous credible reports of this interaction in humans?	+1	-1	0
2. Is the observed interaction consistent with the known interactive properties of the precipitant drug?	+1	-1	0
3. Is the observed interaction consistent with the known interactive properties of object drug?	+1	-1	0
4. Is the event consistent with the known or reasonable time course of the interaction (onset or offset)?	+1	-1	0
5. Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug? (if no dechallenge, use Unknown or NA and skip Question 6)	+1	-2	0
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	+2	-1	0
7. Are there reasonable alternative causes for the event? ^a	-1	+1	0
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	+1	0	0
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	+1	-1	0

^aConsider clinical conditions, other interacting drugs, lack of adherence, risk factors (e.g., age, inappropriate doses of object drug). A NO answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation.

Total Score _____

Highly Probable: > 8
 Probable: 5–8
 Possible: 2–4
 Doubtful: < 2

RESEARCH DESIGN, BIOSTATISTICS, AND LITERATURE EVALUATION

ISHAQ LAT, PHARM.D., FCCP, FCCM, BCPS, BCCCP

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Learning Objectives

1. Identify factors influencing the conduct of essential critical care research.
2. Judge the appropriateness of various statistical tests for a set of data.
3. Distinguish between various types of knowledge for application to patient care.

Abbreviations in This Chapter

ARDS	Acute respiratory distress syndrome
CDI	<i>Clostridium difficile</i> infection
IRB	Institutional review board
NMBA	Neuromuscular blocking agent
QI	Quality improvement

Self-Assessment Questions

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

1. A clinical trial is being planned to determine the optimal resuscitation fluid for trauma patients. This study will seek to determine whether administering crystalloid fluid, lactated Ringer solution, or a transfusion strategy—packed red blood cells—in the trauma field improves survival to hospital discharge. The investigator team has consulted with various ethics scholars to identify relevant issues to be addressed in the trial design. Which issue is most relevant to the ethical conduct of this study?
 - A. Treatment blinding
 - B. Uninformative study population
 - C. Consent obtained from injured subjects
 - D. Design as a noninferiority trial
2. In recent studies of septic shock, 28-day mortality was around 20% in the standard treatment arm. Earlier estimates of septic shock mortality were 35%–40%, according to the results of previous trials and epidemiologic studies from the past 10 years. The investigators of a new study are seeking to identify the optimal end point or study population to test the effectiveness of a novel drug compound for the treatment of septic shock. The novel drug compound is a recombinant protein that mediates the inflammatory cascade of sepsis and has shown impressive results for all etiologies of septic shock in preclinical animal studies. Which best describes the rationale for selecting a study population or primary end point?
 - A. The study should limit study inclusion to patients without a high level of comorbid conditions at baseline to limit confounders.
 - B. The study should expand the target population to include patients with severe sepsis, not just septic shock, to show a 28-day mortality benefit.
 - C. The study should select 90-day mortality instead of 28-day mortality as a primary end point to show the durability of the treatment effect.
 - D. The study should limit study inclusion to patients with septic shock caused by pneumonia to test a relevant study population.
3. A quality improvement (QI) initiative is implemented to improve the dosing of antimicrobials for patients with septic shock presenting to the emergency department. As the pharmacy representative, you have worked with the pharmacy operations team to ensure that an appropriate selection of antibacterial agents and doses are available in the automated drug-dispensing machines. Which factor will be most important in showing the effectiveness of this QI initiative?
 - A. Obtaining informed consent for participation in the QI initiative
 - B. Identifying patients with septic shock in triage
 - C. Creating a community advertising campaign to bring awareness to the initiative
 - D. Determining the social value of the QI initiative
4. An epidemiologic study seeks to determine the impact of adverse drug events in the intensive care unit (ICU) on patient outcomes. Which would be the best approach to conducting this study?
 - A. A randomized controlled trial with a test for continuous variables to determine the difference in outcomes
 - B. A retrospective case-control study with a test for proportions to determine the difference in outcomes
 - C. A prospective observational study with survival analysis to determine the difference between cohorts

- D. A retrospective case-cohort study with a test for proportions to determine the difference in outcomes
5. A case-control study is performed to determine whether proton pump inhibitor (PPI) use is associated with an increased risk of developing *Clostridium difficile* infection (CDI). The final analysis shows the odds ratio (OR) for the CDI with PPI exposure to be 1.3 (95% confidence interval [CI], 0.8–1.5). Which best describes the results?
- A. PPI exposure increases the risk of CDI by 130%.
 - B. PPI exposure reduces the risk of CDI by 20%.
 - C. PPI exposure increases the risk of CDI by 30%.
 - D. PPI exposure is not associated with an increased risk of CDI.
6. A systematic review evaluated the effect of albumin for fluid resuscitation. A meta-analysis that evaluated the effect of albumin use compared with normal saline (NS) on 28-day mortality reported a combined OR of 0.45 (95% CI, 0.3–0.75) for the treatment of hypovolemic shock caused by trauma. For the treatment of septic shock, albumin compared with NS resulted in a combined OR of 1.1 (95% CI, 0.98–1.21) when evaluating 28-day mortality. Which best represents the findings of the review?
- A. Albumin increased mortality in trauma but did not affect survival in the treatment of septic shock.
 - B. Albumin increased survival in trauma but did not affect survival in the treatment of septic shock.
 - C. Albumin did not affect survival in the treatment of hypovolemic shock caused by trauma but improved survival in the treatment of septic shock.
 - D. Albumin did not affect survival in the treatment of hypovolemic shock caused by trauma or septic shock.
7. A critical care pharmacist is faced with an acute drug shortage in which no furosemide is available for immediate use in patient care. During patient care rounds in the ICU, the decision is made to implement a fluid-conservative strategy for the treatment of a patient with acute respiratory distress syndrome (ARDS) (central venous pressure [CVP] goal less than 4 mm Hg). The critical care pharmacist is able to procure an allotment of bumetanide. Which statement best describes the course of action for this patient?
- A. The pharmacist uses her understanding of the medical literature and experiential knowledge to develop a titration scheme using bumetanide to achieve a CVP of less than 4 mm Hg.
 - B. The pharmacist uses her understanding of research trial design and experiential knowledge to develop a titration scheme using bumetanide to achieve a CVP of less than 4 mm Hg.
 - C. The pharmacist uses her friendly rapport to convince the nephrologist to treat this patient with hemodialysis to achieve a goal CVP of less than 4 mm Hg.
 - D. The pharmacist uses her understanding of research ethics to obtain informed consent from the patient's surrogate for treatment with bumetanide.
8. In a study of ARDS, patients are treated with a neuromuscular blocking agent (NMBA) or placebo to determine whether administering an NMBA within the first 48 hours of presentation improves 28- and 90-day survival. The study has an unequal distribution of patients, with a greater proportion of patients with severe ARDS compared with moderate and mild ARDS. The post hoc analysis of the results finds a survival benefit to administering NMBA to the patients with severe ARDS. Which rationale best describes why NMBAs should not be administered to patients with mild to moderate ARDS?
- A. Patients with mild ARDS have a lower mortality rate and are therefore less likely to benefit from the test treatment.
 - B. Patients with mild and moderate ARDS are inherently different from patients with severe ARDS because of their etiology and presentation.
 - C. NMBAs are periodically on shortage from the manufacturer and need to be prioritized for necessary medical indications.
 - D. The end points selected do not carry sufficient social value to warrant treatment.

I. INTRODUCTION

- A. Epidemiology of Critical Care in the United States – And why continued research is essential to improving the delivery of care to patients
 - 1. 10.1%–28.5% of all hospital inpatients receive care in an intensive care unit (ICU), approximating 5.7 million adults admitted to an ICU. Estimated mortality for ICU care ranges from 20%–40% for common critical care syndromes (Crit Care Med 2012;40:1072-9).
 - 2. 16.9%–38.4% of total hospital costs are spent on critical care services, approximating \$121–\$263 billion.
 - a. 5.2%–11.2% of national health care expenditures
 - b. 1% of GDP
- B. Why Pharmacists Need to Understand the Fundamentals of Research Practice, Trial Design, and Literature Evaluation – High rates of morbidity and mortality necessitate efficient decision-making on the part of caregivers.
- C. The Necessity of Clinical Research in Critical Care – To optimize patient outcomes while providing the efficient stewardship of finite resources
- D. Synthesizing Medical Knowledge with Experiential Knowledge and Pathophysiologic Reasoning – Essential to creating patient-specific therapy care plans

II. BIOETHICS

- A. The Belmont Report – Outlines the fundamental ethical principles for the conduct of clinical research
 - 1. Respect for individuals dictates that each research participant be treated with respect for his or her dignity and autonomy. As such, informed consent shall be obtained from research participants or their surrogates.
 - 2. The principle of justice requires that investigators recruit research subjects in a manner that allows equal access to participation for all populations that may potentially benefit from the research endeavor.
 - 3. Beneficence requires research investigators to ensure that risks are minimized and benefits maximized for research participants.
- B. A framework for the ethical conduct of clinical research includes seven requirements: (1) social value, (2) scientific validity, (3) fair selection of research participants, (4) a favorable risk-benefit ratio, (5) independent review, (6) informed consent, and (7) respect for enrolled participants (JAMA 2000;283:2701-11).
- C. Equipoise – Must be present for the conduct of a clinical trial. Equipoise is defined as the state of uncertainty between treatments A and B for a given population of subjects with a predefined disease and/or syndrome. Once the balance of uncertainty between treatments A and B is disturbed such that one treatment is believed to be superior, the risk-benefit ratio is altered such that treatment may not be beneficial to the individual research subject. Example: Call for restraint for implementing vasopressin into routine clinical practice in lieu of randomized controlled trials (Crit Care Med 2003;31:2707-9).

III. PRACTICAL CHALLENGES TO CRITICAL CARE RESEARCH

- A. Research Subject Recruitment – To maximize external validity, research subjects recruited for participation in a clinical trial should be representative of the general population of patients afflicted with the disease or syndrome.
 - 1. Critical care is exemplified by the provision of supportive care for the treatment of diseases and syndromes.
 - a. Diseases are characterized by the specific test to identify the pathophysiologic process.
 - b. Syndromes are often identified by the presence of a constellation of signs and symptoms that suggest the presence of a disease.
 - 2. Recognizing the attendant syndrome is critical for the timely provision of therapy and, in research, subject recruitment.
 - a. Heterogeneity in syndromes challenges the ability to identify subjects for participation in clinical research.
 - b. In addition, heterogeneity challenges the ability to interpret the results from dissimilar populations, even though they may have a single syndrome in common.
 - c. Discrepancies between results from basic and early clinical studies versus adequately powered controlled trials show that surrogate outcome measures (e.g., organ function) cannot reliably predict clinical benefit (Am J Respir Crit Care Med 2015;191:1367-73).
 - 3. Specific to critical care clinical research is the need to enroll subjects similar in acuity or at a similar stage in the process of their syndrome to allow meaningful comparisons (e.g., N Engl J Med 2010;363:1107-16).
 - 4. Lack of standard definitions and lack of power complicate synthesis and meta-analysis (Am J Respir Crit Care Med 2014;189:1469-78).
 - 5. Selection of end points should be based in part on the ethical values outlined previously. End points should provide social value and possess scientific validity. A growing area of emphasis in research is on the need to design studies that are patient centered (JAMA 2012;307:1583-4).
- B. Informed Consent
 - 1. Because of the acute nature of critical illness, it may be singularly difficult to obtain informed consent within a short period.
 - 2. Obtaining informed consent is particularly challenging for critically ill patients, primarily because many critically ill patients lack decisional capacity because of the acute nature of their illnesses and the effect of medications.
 - 3. Informed consent is usually not required in studies that are deemed quality initiatives because the intent of these studies is to improve the delivery of care. However, the application of this principle is variable and may vary between institutional review boards (IRBs).
 - a. Keystone ICU project was a joint collaboration between investigators at Johns Hopkins University and the state of Michigan to reduce central line–associated bloodstream infections (CLABSIs) in ICU patients using a checklist (N Engl J Med 2006;355:2725-32).
 - b. Study was classified as exempt from IRB review and informed consent because of the QI nature of the study.
 - c. After a complaint, the Department of Health and Human Service’s Office for Human Research Protections (OHRP) originally faulted the investigators for not obtaining informed consent. Subsequently, the OHRP reversed course and classified the project as a “non-research” activity.
 - d. Inconsistent interpretation by local IRBs, in the absence of clear guidance from the OHRP, contributes to confusion regarding the role of QI in research activities (Jt Comm J Qual Patient Saf 2008;34:349-53).

4. Surrogates and family members are recognized as having authority to provide consent on the behalf of patients, despite the ambiguous legal standing on this issue in several states. It is important to realize that underlying motives for proxy consent may include the belief that participating in the research protocol will lead to improved care.
 - a. Important to acknowledge that patients and surrogates entrust clinical researchers to act in their best interests
 - b. Research supports the notion that surrogate consent and patient preferences agree most of the time (Chest 2001;119:603-12).
- C. Waiver of Informed Consent
1. In select circumstances, informed consent may be waived by the IRB.
 2. Of note, differences exist in the guidance between the Department of Health and Human Services and the U.S. Food and Drug Administration (FDA) for waiver of informed consent. In many circumstances, local IRBs will follow the Common Rule as the minimum standard.
 3. Waiver of informed consent is typically granted for any of the following circumstances:
 - a. Research that is deemed of minimal risk to the participant, does not adversely affect the welfare of the subject, and could not otherwise be practicably carried out
 - b. Research that is carried out to evaluate public benefits or service programs
 - c. Research in emergency settings where consent would be impractical to obtain. An example is a study testing the hypothesis of whether drug A is non-inferior to drug B for the treatment of status epilepticus (N Engl J Med 2012;366:591-600).
 4. A recent trial conducted in France investigating the timing of initiation of renal replacement therapy did not require written informed consent because the standard of care was included in both treatment arms (N Engl J Med 2016, published online May 15).
 5. Controversy exists regarding how QI projects should be evaluated. Currently, QI research is subject to the interpretation of local IRBs, as mentioned previously (N Engl J Med 2015;372:855-62).
- D. Community Consent
1. Occasionally, critical care research will need to be conducted in the general community. Obtaining consent in this scenario would be impossible given the medical condition of the research subject. Example: N Engl J Med 2012;366:591-600.
 2. Guidance exists for investigators to inform the community and community leaders before undertaking the research endeavor.
 3. Approval for this type of research is required from local/national IRBs.

IV. STUDY DESIGN

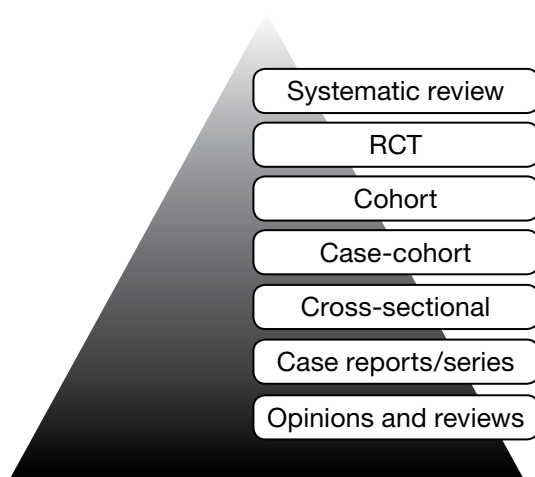


Figure 1. Hierarchy of clinical evidence.

RCT = randomized controlled trial.

A. Figure 1 (Crit Care Med 2010;38:1882-9)

B. Randomized Controlled Trial

1. Hallmark of clinical research. Study design seeks to minimize bias through randomization of subjects, blinding of participants, and analytic approach. This should leave two groups that differ only in study treatments.
2. Experimental design to test the effects of an intervention compared with either placebo or the established standard of care (treatment or process of care); allows for description and causality
3. Preliminary research should exist to suggest that the intervention is based on an existing scientific foundation sufficient to warrant the proposed testing on patients.

Table 1. Examples of Randomized Controlled Trials in Critical Care

Trial	Control	Intervention	Specific Feature
Comparison of dopamine and norepinephrine for the treatment of shock (N Engl J Med 2010;362:779-89)	Dopamine	Norepinephrine	Blinded
Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial (JAMA 2012;308:1985-92)	Protocolized sedation	Protocolized sedation + daily sedation interruption	Testing a process of care
A multifaceted intervention for quality improvement in a network of ICUs: a cluster randomized trial (JAMA 2011;305:363-72)	Usual care	• QI interventions • Semirecumbent positioning • VTE prophylaxis • Daily breathing trials • Prevention of CLABSI • Early enteral feeding • Decubitus ulcer prevention	• Educational outreach, local champions, audit/feedback • Cluster randomization by ICU

CLABSI = central line-associated bloodstream infection.

C. Observational

1. Observation of clinical practice; no intervention is tested
2. Describes associations between phenomena
3. Hypothesis-generating: Case-control study – Retrospective design
 - a. Retrospective design
 - b. Provides an efficient means to determine the association between the risk factor and the outcome of interest
 - c. Two groups (with and without the outcome) are compared to identify the differences and risk factors for developing the outcome of interest
 - d. Potential for selection bias and confounding
 - e. Cases and controls are representative of the population with the disease and are chosen to minimize selection bias.
 - f. The process for handling missing data should be defined a priori. Significant amounts of missing data may introduce bias.
 - g. Confounding variables must be handled in a manner that can be controlled for in the analytic process.
4. Case-cohort study (aka cohort study) – Prospective or retrospective design
 - a. Observational study of a given population during a given time to determine the association between risk factors and the outcome of interest. Identifies the relationship between exposure and outcome.
 - b. Describes the natural progression of a disease or syndrome
 - c. Example: Delirium is an independent predictor of mortality in mechanically ventilated patients (JAMA 2004;291:1753-62).
 - i. Cohort of mechanically ventilated patients observed during ICU stay for presence of delirium
 - ii. Determination of outcome: ICU mortality, 6-month mortality
 - iii. Regression models to determine whether delirium is predictive of 6-month mortality, controlled for covariates
5. Incidence versus prevalence
 - a. Incidence – Measures the occurrence of a disease (or event) during a period
 - b. Prevalence – Measures the occurrence of a disease (or event) at a fixed point in time
6. Case reports/case series: Describes the experience in the treatment of a single patient or the cumulative experience in the treatment of a series of patients
7. Validity
 - a. Internal
 - i. Does the study design adequately test the hypothesis?
 - ii. Are the study methods sound?
 - b. External
 - i. Is the study population representative of the clinical setting?
 - ii. Are the study findings generalizable outside the study setting?
 - iii. Can the study be replicated in clinical practice?
8. Bias – Systematic error leading to an estimate of association in the study population that varies from the source population (Am J Health Syst Pharm 2008;65:2159-68)
 - a. Selection bias: Systematic selection of subjects that leads to an imbalance, or an advantage, in favor of one cohort over the other
 - b. Observation bias: Observers (research team) are aware of the research purpose and allow this knowledge to influence interpretation of results.
 - c. Recall bias: Methodological error that is introduced in survey research when the participant is asked to provide recall of a past event
 - d. Misclassification bias: Inappropriately categorizing a group of patients with or without the disease/syndrome

- e. Confounding variables – Extraneous variables that influence both the dependent and the independent variable, affecting how the overall result can be interpreted. Controlling for confounding variables.
 - f. Bias can be accounted for with sufficient planning for design, data collection, and analysis and can potentially be minimized.
9. Study design: Randomization, matching. Analysis: Multivariate analysis, propensity score matching to control for confounding variables and bias

V. STATISTICAL ANALYSIS

- A. Hypothesis Testing – To determine whether the observation was caused by chance
- 1. Null hypothesis (H_0): No difference exists between groups. Not rejecting the null hypothesis means that no difference exists between groups (or is unlikely to exist).
 - 2. Alternative hypothesis (H_1): There is a difference between group A and group B.
 - a. Type I error (alpha [α] error): To reject the H_0 when, in fact, it is true. Decisional threshold to reject/not reject the H_0 is conventionally set at $\alpha = 0.05$. The α value represents the likelihood that a type I error will be made (i.e., rejecting the H_0 when the H_0 should not be). An α set at 0.05 means that the H_1 will be erroneously accepted 1 in 20 times.
 - b. Type II error (beta [β] error): Not to reject the H_0 when, in fact, there is a difference between groups (i.e., the H_1 is true). Decisional threshold to set β at 0.20. What does “power” really mean? The ability to detect a difference if one truly exists. Contingent on sample size. However, this is an estimate and may be inaccurate (usually based on previous literature).
- B. Types of Data
- 1. Continuous
 - a. Counting, chronological order (e.g., 7.0, 7.1, 7.2, 7.3)
 - b. Sample tests: t-test, Wilcoxon rank sum/Mann-Whitney U
 - 2. Categorical (e.g., nominal, ordinal)
 - a. Categories or groups for data to be designated to (e.g., race, sex, hypertension, heart failure)
 - b. Sample tests: Chi-square, Fisher exact test
 - 3. Descriptive statistics
 - a. Measures of central tendency
 - i. Mean: Used for continuous and normally distributed data, sensitive to outliers
 - ii. Median: 50th percentile, used for ordinal data or nonparametric continuous data
 - iii. Mode: Value occurring most often in a distribution
 - b. Standard deviation
 - i. Used for continuous, parametric data
 - ii. Describes variability around the mean
 - c. Range: Describes spread of data, minimum to maximum values
 - d. Percentiles
 - i. The value where the percentage of values falls below. Example: The 75th percentile is where 75% of values are smaller.
 - ii. Interquartile range (IQR): Describes the values between the 25th and 75th percentile
- C. Parametric Data
- 1. Student t-test: Comparison of means between two independent groups
 - 2. Analysis of variance: Comparison of means between three or more groups

- D. Nonparametric Data
 - 1. Two groups: Wilcoxon rank sum or Mann-Whitney *U* test
 - 2. Three or more groups: Kruskal-Wallis
- E. Nominal Data
 - 1. Categories (e.g., sex, race, treatment groups, confusion assessment method for the ICU)
 - 2. Chi-square test
 - 3. Fisher exact test: Specific to small data sets (fewer than five observations)
- F. Ordinal Data
 - 1. Groups represented by scale (e.g., Richmond Agitation-Sedation Score, Sequential Organ Failure Assessment score)
 - 2. Central tendency expressed as median and quartiles
 - 3. Statistical tests: Wilcoxon rank sum, Mann-Whitney *U* test, Kruskal-Wallis
- G. Confidence Interval
 - 1. A method to describe a point estimate within the study population
 - 2. CIs offer a more descriptive interpretation of the data.
 - a. Magnitude of difference between groups
 - b. Range of values (possible spread of point estimates)
 - c. A 95% CI has a 0.95 probability of containing the true mean.
- H. Correlation: Describes the association between two variables
 - 1. Correlation value (*r*) contains a range of values from -1 to +1. An *r* value of -1 or +1 indicates a perfect negative or positive relationship. The closer the values are to 1, the stronger the relationship between the two variables.
 - 2. Pearson: Parametric continuous data
 - 3. Spearman rank: Nonparametric continuous data or ordinal data
- I. Regression Analysis: Describes whether an independent variable can predict the dependent outcome. Can be used to describe the strength of the association between a predictor variable and a dependent variable.
- J. Linear Regression
 - 1. Used when the dependent variable is continuous (e.g., length of stay)
 - 2. A single predictor variable (continuous or categorical) can be tested in a simple linear regression model.
 - 3. More than one predictor variable (continuous or categorical) can be tested at a time in a multiple linear regression model.
- K. Logistic Regression
 - 1. Used when the dependent variable is a categorical variable (e.g., mortality)
 - 2. A single predictor variable (continuous or categorical) can be tested in a simple logistic regression model.
 - 3. More than one predictor variable (continuous or categorical) can be tested at a time in a multiple logistic regression model.
- L. Odds Ratio
 - 1. Describes the odds of patients being exposed to a risk factor and the occurrence of the outcome of interest compared with those who are not exposed to the risk factor
 - 2. The OR is interpreted in relation to a reference point (1.0). If the 95% CI includes 1, the odds of the event occurring are equally likely in either group.

M. Survival Analysis (time-to-event analysis)

1. Censoring: Adjusts data so that patients are not included (i.e., “censored”) in the analysis if they did not experience or were not observed for the event
2. Kaplan-Meier method
 - a. Describes the impact of a single predictor variable on the time-to-event between cohorts
 - b. Compares the survival times between two cohorts while controlling for a singular predictor variable
 - c. Survival curves are typically analyzed using the log-rank test.
 - d. Results were OR with 95% CI
3. Cox proportional hazards model
 - a. Describes the impact of several predictor variables on the time-to-event
 - b. Compares the survival times between two cohorts while controlling for several predictor variables
 - c. Results were HR (hazard ratio) with 95% CI

Table 2. Statistical Tests According to Type of Data

Dependent Variables	Independent Variables	Test(s)
Continuous, parametric	Categorical	Two-sample t-test
Continuous, nonparametric	Categorical	Mann-Whitney <i>U</i> test
Categorical	Categorical	Chi-square test
Continuous	Continuous	Linear regression
Continuous	Categorical	Linear regression
Categorical	Continuous	Logistic regression
Categorical	Categorical	Logistic regression

VI. NONINFERIORITY TRIAL DESIGN

- A. Traditional approach to randomized controlled trials seeks to establish novel treatment as superior to established standard. Noninferiority trials seek to answer whether a competing treatment is no worse than the established standard therapy (JAMA 2015;313:2371-2). H_1 = treatment A is no worse than treatment B; H_0 = treatment B is better than treatment A.
- B. Seek to establish utility by showing similar effectiveness while improving safety or reducing treatment burden (costs, inconvenience, labor, etc.) (JAMA 2012;308:2605-11). Clinically important difference, severity of disease, toxicity, costs, regulatory standards, etc.
- C. Analytic Approach to a Noninferiority Trial
 1. What is an acceptable threshold for “noninferiority”?
 - a. First step is to determine the marginal difference.
 - b. What is the maximum allowable negative outcome events acceptable when comparing the treatment with the standard therapy? (The maximum increase in risk that you are willing to accept for a tradeoff in reducing treatment burden.)
 - i. Typically, some fraction of the standard treatment effect to be preserved

- ii. The FDA provides guidance for noninferiority thresholds: (1) Establish the smallest plausible benefit of the existing standard therapy. (2) Insist on some preservation of the treatment effect of the standard therapy. The FDA recommends that 50% of the standard treatment effect be preserved when evaluating mortality for thrombolytic trials.
- c. Some examples of threats to meaningful comparisons to establishing noninferiority:
 - i. Effect of standard treatment was not preserved. Suboptimal standard treatment administered. Example: Heparin infusion does not achieve therapeutic anticoagulation.
 - ii. Intention-to-treat analysis – Suboptimal administration of the standard treatment results in a large proportion of undertreated patients for comparison.
2. Interpreting the results of a noninferiority trial
 - a. Looking for an acceptable difference between groups that can be plausibly described as “noninferior”
 - b. Event rate can be established by existing literature and clinical practice. Example: A trial to compare alternative approaches to sedation therapy for mechanically ventilated patients while reducing the incidence of delirium
 - i. Vasopressor A (novel treatment) achieved a goal mean arterial pressure greater than 65 mm Hg at 6 hours in 50% of patients with septic shock compared with 53% of patients treated with vasopressor B (standard treatment). The a priori noninferiority margin is set at 5% between groups. Simultaneously, the incidence of new-onset atrial fibrillation is 7% for vasopressor A compared with 15% for vasopressor B ($p=0.02$).
 - ii. Vasopressor A is noninferior with respect to the outcome of goal mean arterial pressure at hour 6 while reducing the harm associated with the incidence of new-onset atrial fibrillation.

VII. APPLICATION OF KNOWLEDGE TO PATIENT CARE

Table 3. Assessment of Primary Literature for Clinical Application

	Assessment
Study design	• Were the hypothesis and study purpose clearly stated? • Is the study sample representative of the population with the disease/syndrome? • Are the inclusion/exclusion criteria too restrictive? • Did the study meet power? Was a sample size calculation described? • How were blinding and randomization conducted? • Is the study design translatable to clinical practice? • How were the primary and secondary end points defined? • Have those definitions been validated in the critically ill?
Outcomes	• Is the primary outcome scientifically valid and meaningful? • Are the secondary outcomes clearly described? • How were adverse effects defined and analyzed?
Analysis	• Were the statistical tests appropriate? • How were the data analyzed (intention to treat, per protocol, as treated)? • How large was the treatment effect? • Will the effect size be duplicated in clinical practice? • Did the author(s) provide an interpretation of the study findings and describe them in the context of the available knowledge?

A. Integration of Various Types of Knowledge**1. Medical literature**

- a. Remaining current with evolving literature is a necessary skill for the critical care clinician.
- b. Knowledge gained from the primary literature can be objective, can limit bias, and may be translatable compared with experiential knowledge.
- c. The findings of clinical research can be limited to the conditions of the study and may not easily confer the same benefit in clinical practice.
 - i. Number needed to treat (NNT) – Quantifies the anticipated effect of a treatment in a patient population on the basis of study results. A low number signifies an effective treatment; a high number indicates a less effective therapy. $NNT = 1/\text{absolute risk reduction}$.
 - ii. Number needed to harm (NNH) – Quantifies the associated harm after exposure to a treatment. A low number signifies a harmful treatment; a high number indicates a safer drug. $NNH = 1/\text{attributable risk}$.
- d. The study results limit the findings attributable to chance but may not fully exclude chance.

2. Experiential knowledge

- a. Knowledge accumulated through clinical experience and for a sustained period is valuable.
- b. Valuable when determining how an individual patient differs from a study population in a clinical trial
- c. When possible, this type of knowledge should be reinforced with scientific evidence. Example: N Engl J Med 2009;361:1925-34.

3. Pathophysiologic reasoning

- a. Application of physiologic concepts to drive therapeutic choices
- b. Can aid in determining short-term goals. Example: Selecting an initial dose of loop diuretic according to the home medication dose and current therapeutic goal of urine output greater than 1 L in 24 hours.
- c. Primary literature on which to base treatment decisions for all clinical scenarios may not exist; therefore, use of pathophysiologic reasoning is key to the sound provision of pharmaceutical care for critically ill patients.

B. Negotiating Between Various Types of Medical Knowledge for Direct Application to Patient Care

1. Applying the knowledge gained from the primary literature that is based exclusively on the hierarchy of study design may not be practical for all patient interactions.
2. Integrating the various types of knowledge can lead to systematic problem solving rather than arbitrary judgments. This becomes necessary when making systems-based treatment decisions (i.e., treatment protocols) and understanding when to modify existing protocols to fit the needs of individual patients.

C. Synthesizing the Available Evidence to Develop Treatment Protocols

1. Protocols are intended to synthesize the best available evidence and standardize a series of treatment options to reduce variability and error while maximizing treatment effect. Examples: Sterile technique for central line placement, heparin infusion, and aPTT (activated partial thromboplastin time) monitoring, the mnemonic FASTHUG, sepsis resuscitation protocols.
2. Determining which literature to incorporate and its applicability to the local practice environment is key.
3. Determine the homogeneity of various studies on the same topic (e.g., early goal-directed therapy for septic shock) and confounding variables that influence the interpretation of results. Study design affecting the screening and time to treatment for subjects compared with actual practice, improvements in the processes of usual care over time, etc.

D. Specific Factors That Promote/Impede the Application of Treatment Protocols

1. Resource use
 - a. Personnel (e.g., Lancet 2010;375:475-80)
 - b. Drug shortage
 - c. Fiscal
2. Ease of protocols
 - a. Complexity
 - b. Familiarity
3. Lack of consensus

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ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: C**

This study seeks to compare two viable treatments of hypovolemic shock in trauma patients. Because subject identification would be trauma patients from the community and treatment would be initiated in the field, potential harm is associated with each treatment, and it is expected that many potential patients would lack decisional capacity at the time of informed consent. Although treatment blinding is an essential component to trial design to limit investigator and clinician bias, it is not an ethical consideration (Answer A is incorrect). Given the incidence of trauma in the general population and its burden on society, treatments to improve the outcomes of trauma patients are necessary and informative (Answer B is incorrect). Acknowledging the limited supply of blood products, a superiority trial is essential to help steward the use of a finite resource (Answer D is incorrect). The issue of informed consent in this study is challenging, but the issue has to be addressed for the ethical conduct of this study. There is precedent for this trial to receive an exception for informed consent requirements under the FDA code of regulations (Answer C is correct).

2. Answer: C

The study seeks to establish the effectiveness of a novel drug compound for the treatment of septic shock. This is challenging because of the dramatic improvements made in 28-day mortality during the past decade. To demonstrate the effectiveness of a novel drug compound, the drug should be tested in a representative population of patients with the disease. Excluding patients because of baseline comorbidity would limit external validity (Answer A is incorrect). Including patients with severe sepsis, which has a lower 28-day mortality rate than septic shock, would not address the issue of an appropriate end point (Answer B is incorrect). Limiting study inclusion to patients with a pneumonia etiology would be inappropriate unless the pharmacology of the novel drug specifically targeted pneumonia pathophysiology (Answer D is incorrect). Answer C is correct because the study should maximize external validity and provide survival benefit in a heterogeneous patient population with the syndrome. However, if 28-day survival is increasingly difficult to show, a more appropriate end point might be 90-day survival to show the durability of the treatment beyond intensive care.

3. Answer: B

A QI study would likely show effectiveness using a pre/postintervention cohort design. In this type of study, informed consent is generally not required because the treatment is provided to all patients as a standard of care (Answer A is incorrect). A community advertising campaign might improve the delivery of care and improve patient adherence, but it is unnecessary to measure the effectiveness of the QI initiative (Answer C is incorrect). The QI initiative is believed necessary and has therefore been deemed to possess intrinsic social value (Answer D is incorrect). To show the effectiveness of the intervention, it is critical to recognize the syndrome before initiating treatment (Answer B is correct).

4. Answer: C

To effectively determine the incidence and clinical impact of adverse drug events on clinical outcomes in the ICU, it would be unethical to randomize patients to experience the event (Answer A is incorrect). A retrospective design would not be ideal because of the limitations in data extraction, assignment of events, and interpretation of causality (Answers B and D are incorrect). A prospective observational design would allow the investigator team to identify the incidence of events and sequential events and determine causality (Answer C is correct).

5. Answer: D

A correct interpretation of the results is recognizing that even though the OR suggests an associated increase of 30% in the risk of being exposed to CDI, the 95% CI crosses 1, meaning that the odds of exposure to CDI are as likely to increase the risk as to decrease that risk (Answers A–C are incorrect).

6. Answer: B

Use of albumin reduced the odds of mortality and, conversely, increased the odds of survival with an OR of 0.45, and the 95% CIs were all less than 1 in the treatment of hypovolemic shock in trauma. In addition, the OR was 1.1 for septic shock, whereas the 95% CI crossed 1, showing that the odds were as likely that albumin increased mortality as that it reduced it (Answer B is correct). Because the OR and the 95% CI for the treatment of hypovolemic shock were both less than 1, mortality was decreased with albumin use (Answers A, C, and D are incorrect).

7. Answer: A

This patient case provides a practical example of a critical care pharmacist's integration of various types of knowledge to optimize patient care. The fluid and catheter treatment (FACT) trial showed that a fluid-conservative strategy improves ventilator-free days for patients with acute lung injury and ARDS. The drug used in the study to show the outcome benefit was furosemide. However, the study was testing a treatment strategy, not specifically a drug strategy. Therefore, it can be reasoned that similar treatment outcomes can be shown with similar drugs if the study drug is unavailable—in this case, because of drug shortage. Knowledge of trial design is helpful but not critical to optimizing this patient's therapy with bumetanide (Answer B is incorrect). Hemodialysis is invasive, requires finite resource use, and has an associated morbidity risk (Answer C is incorrect). Because this patient case does not include a broader hypothesis test in a systematic design, this is not a research activity, and informed consent is not required (Answer D is incorrect). A critical care pharmacist, using her knowledge of the FACT trial (medical knowledge) together with her understanding and experience with bumetanide therapy (experiential knowledge), can develop a treatment plan (Answer A is correct).

8. Answer: A

Acute respiratory distress syndrome is a clinical syndrome with an associated mortality with each progressing phase (mild, moderate, and severe). Although the syndrome is also a constellation of findings and pathologic observations, patients with ARDS present with a similar finding of severe, refractory hypoxia from a common etiology (Answer B is incorrect). Given the associated mortality of about 45% for severe ARDS, a finite resource should be prioritized for it (in this case, an NMBA) (Answer C is incorrect). Mortality/survival is readily identified as an end point of social value for research design (Answer D is incorrect). Given the relatively low mortality associated with mild ARDS (around 20%) compared with severe ARDS (around 45%), administering NMBAs would be less likely to improve survival and more likely to increase harm if systematically administered to patients with mild ARDS (Answer A is correct).