Shock Syndromes

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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 the management of a patient with shock.

Abbreviations in This Chapter

- CO Cardiac output
- CVP Central venous pressure
- ED Emergency department
- HES Hydroxyethyl starch
- ICU Intensive care unit
- IVC Inferior vena cava
- LR Lactated Ringer (solution)
- LV Left ventricular
- MAP Mean arterial pressure
- NS Normal saline
- PRBC Packed red blood cell
- PCC Prothrombin complex concentrate
- PCWP Pulmonary capillary wedge pressure
- PE Pulmonary embolism
- PH Pulmonary hypertension
- PLR Passive leg raising (test)
- PPV Pulse pressure variation
- PVR Pulmonary vascular resistance
- rFVIIa Recombinant activated factor IIa
- RV Right ventricular
- SBP Systolic blood pressure
- SPV Systolic pressure variance
- SV Stroke volume
- SVR Systemic vascular resistance
- SVV Stroke volume variation

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 Escherichia coli urinary tract infection. Pertinent vital signs on admission are as follows: blood pressure (BP) 80/40 mm Hg, heart rate (HR) 155 beats/minute with a rhythm of atrial fibrillation, respiratory rate (RR) 26 breaths/minute, and temperature 41°C. The HR is sinus tachycardia on rhythm strip. On physical examination, the patient is weak, lethargic, and confused. Pertinent laboratory values are as follows: sodium 155 mEq/L, potassium 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 best reflects the physiologic or laboratory value that compromises oxygen delivery (Do2) in this patient?
   A. Serum lactate.
   B. Atrial fibrillation.
   C. Acute kidney injury.
   D. Fever.

3. G.G. is a 62-year-old woman who developed ventilator-associated pneumonia in the setting of prolonged intubation after aortic valve replacement surgery. Her pneumonia was complicated by septic shock, and she was given 2 L of 0.9% sodium chloride and 2 L of 5% albumin for resuscitation and initiated on norepinephrine. Her laboratory values revealed the following: sodium 144 mEq/L, potassium 3.6 mEq/L, serum creatinine (SCr) 1.8 mg/dL, 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?
4. C.A. is a 48-year-old man who 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 LR, and he is initiated on norepinephrine. 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?
   A. Continue current therapy.
   B. Increase the norepinephrine dose.
   C. Give 1 L 0.9% sodium chloride.
   D. 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 LR, 500 mL of 5% albumin, and 500 mL of 6% HES 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: HR 131 beats/minute in atrial fibrillation, MAP 62 mm Hg (by arterial BP catheter), RR 22 breaths/minute, and temperature 38.2°C. An arterial blood gas reveals a lactate concentration of 4.4 mmol/L, and hemoglobin 9.6 g/dL. Together with further fluid resuscitation, which agent would be best to initiate or administer?
   A. Packed red blood cells (PRBCs).
   B. Dobutamine.
   C. Milrinone.
   D. Norepinephrine.

6. H.B. is a 19-year-old man 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 BP 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 management. On arrival in the medical ICU, he has a MAP of 62 mm Hg. A right internal jugular central venous catheter is placed, which reveals the following: CVP 3 mm Hg, ScvO2 61%, venous lactate concentration 4.4 mmol/L, and hemoglobin 9.6 g/dL. Together with further fluid resuscitation, which agent would be best to initiate or administer?
   A. Give 1 L of 0.9% sodium chloride.
   B. Do a passive leg raising (PLR) test.
   C. Measure CVP.
   D. Send a blood gas for venous oxygen saturation (SvO2).

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. His vital signs are as follows: BP 82/48 mm Hg, HR 125 beats/minute, RR 34 breaths/minute, and temperature 35°C. Which most accurately reflects this patient’s class of hypovolemic shock?
   A. Class I.
   B. Class II.
   C. Class III.
   D. Class 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.
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 laboratory values.

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 BP 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 in relation to the patient’s preexisting status. This may be challenging in the context of a patient with a poor history or a diminished baseline status.

   b. Evidence of an existing shock syndrome can manifest with cool skin, 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 will often lag behind the immediate observation of urine volume and quality.

6. Laboratory assessment is typified by hyperlactatemia (greater than 2 mmol/L) or reduced Svo₂.

B. Physiology

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

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.

Table 1. Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Value</th>
<th>Equation (as applicable)</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (SBP)</td>
<td></td>
<td>90–140 mm Hg</td>
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<tr>
<td>Diastolic blood pressure (DBP)</td>
<td></td>
<td>60–90 mm Hg</td>
</tr>
<tr>
<td>Mean arterial blood pressure (MAP)</td>
<td>[SBP + (2•DBP)]/3</td>
<td>70–100 mm Hg</td>
</tr>
<tr>
<td>Heart rate (HR)</td>
<td></td>
<td>60–80 beats/minute</td>
</tr>
<tr>
<td>Cardiac output (CO)</td>
<td>HR•SV</td>
<td>4–7 L/minute</td>
</tr>
<tr>
<td>Cardiac index (CI)</td>
<td>CO/BSA</td>
<td>2.5–4.2 L/minute/m²</td>
</tr>
<tr>
<td>Stroke volume (SV)</td>
<td>CO/HR</td>
<td>60–130 mL/beat</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure (PASP)</td>
<td>CO/HR</td>
<td>20–30 mm Hg</td>
</tr>
<tr>
<td>Pulmonary artery diastolic pressure (PADP)</td>
<td></td>
<td>8–12 mm Hg</td>
</tr>
</tbody>
</table>
Table 1. Hemodynamic Parameters (continued)

<table>
<thead>
<tr>
<th>Value</th>
<th>Equation (as applicable)</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pulmonary artery pressure (mPAP)</td>
<td>([\text{PASP} + (2 \times \text{PADP})]/3)</td>
<td>12–15 mm Hg</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (PCWP) or pulmonary arterial occlusion pressure (PAOP)</td>
<td></td>
<td>5–12 mm Hg</td>
</tr>
<tr>
<td>Central venous pressure (CVP) or right atrial pressure (RAP)</td>
<td></td>
<td>2–6 mm Hg</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (PVR)(^c)</td>
<td>(80 \times [(\text{mPAP} – \text{PCWP})/\text{CO}]) (divide by 80 for Wood units)</td>
<td>20–120 dynes (\times) cm(^{-5}) (&lt; 2 Wood units)</td>
</tr>
<tr>
<td>Systemic vascular resistance (SVR)(^c)</td>
<td>(80 \times [(\text{MAP} – \text{CVP})/\text{CO}])</td>
<td>800–1200 dynes (\times) cm(^{-5})</td>
</tr>
</tbody>
</table>

\(^a\)May be directly measured or calculated.

\(^b\)May 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).

\(^c\)May also be expressed as an indexed value calculated by multiplying the value by body surface area.

BSA = body surface area in square meters.


3. BP is the product of CO and systemic vascular resistance (SVR).
4. CO is the product of HR 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 this mechanism has limitations).
   b. Intrinsic contractility is the ability of the myocardium to contract and may be reduced by several factors, including myocardial ischemia.
   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. Systemic vasoconstriction increases SVR, whereas vasodilation decreases SVR.
   b. 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 (\(D_{O_2}\)) and Consumption (\(V_{O_2}\))
1. The circulatory systems serves the vital need to deliver oxygen and vital nutrients to tissue beds for homeostasis and end-organ function.
2. Metabolic function of tissue beds requires consistent \(D_{O_2}\).
3. Oxygen is inspired and delivered to the alveoli, where it binds reversibly to hemoglobin. Oxygen is then transported by CO to the tissues. On reaching the tissues, oxygen is taken up by the mitochondria for aerobic metabolism.

4. The Fick equation states that 
   \[ CO = \frac{V_{O_2}}{(C_{aO_2} - C_{VO_2})} \]
   where \( V_{O_2} \) is resting oxygen consumption and \( C_{aO_2} \) and \( C_{VO_2} \) are the oxygen contents of arterial and venous blood, respectively.

5. The amount of oxygen delivered to the tissues can also be calculated using the Fick equation.
   \[ D_{O_2} (\text{mL/minute}) = 10 \times CO (\text{L/minute}) \times C_{aO_2} \]
   \[ C_{aO_2} = (1.34 \times Hb \times S_{aO_2}) + (0.003 \times P_{aO_2}) \]

6. \( V_{O_2} \) can be estimated to be 250 mL/minute with a CO of 5 L/minute.
   \[ V_{O_2} (\text{mL/minute}) = 10 \times CO (\text{L/minute}) \times (C_{aO_2} - C_{VO_2}) \]
   \[ C_{VO_2} = (1.34 \times Hb \times S_{VO_2}) + (0.003 \times P_{VO_2}) \]

7. The ratio of \( V_{O_2}/D_{O_2} \) is known as the oxygen extraction ratio. In a resting state, the oxygen extraction ratio is around 25%. The oxygen extraction ratio is relatively stable and can accommodate temporary fluctuations in \( D_{O_2} \) or \( V_{O_2} \). Sustained \( D_{O_2}/V_{O_2} \) mismatch will contribute to tissue hypoxia and deranged metabolic function.

8. Treatment of shock syndromes should be rapid to minimize permanent tissue organ damage.

9. In the setting of a shock state, BP 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 \( D_{O_2} \) to vital organs.

10. Blood flow is prioritized to maximize \( D_{O_2} \) to the heart and brain. Consequently, blood flow to extravital organs (e.g., skin, gut, kidneys) is redirected.

II. MONITORING TECHNIQUES

A. Hemodynamic Monitoring Devices

1. Hemodynamic variables may be obtained through non-invasive 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).

<table>
<thead>
<tr>
<th>Device or Category</th>
<th>Obtainable Parameters</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Non-invasive BP monitoring\(^a\) | SBP, DBP, MAP | • Non-invasive  
• Bedside practitioner familiarity | • Limited accuracy in shock  
• Does not provide continuous monitoring  
• Less sensitive in predicting end-organ dysfunction |
| Arterial BP catheter | SBP, DBP, MAP | • More accurate BP measurement in shock than non-invasive 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) |
### Table 2. Hemodynamic Monitoring Devices (continued)

<table>
<thead>
<tr>
<th>Device or Category</th>
<th>Obtainable Parameters</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial catheter</td>
<td>Measured left atrial pressures</td>
<td>• More accurate measurement of LV function</td>
<td>• Risk of air embolus</td>
</tr>
<tr>
<td>Central venous catheter (CVC)</td>
<td>CVP/RAP, Scvo₂</td>
<td>• Easier and more safe to insert than a PAC</td>
<td>• CVP/RAP not a true estimate of LV end diastolic pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Scvo₂ may be available as a continuous measurement</td>
<td>• CVP/RAP does not accurately predict fluid responsiveness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Access for administration of highly osmotic and caustic agents</td>
<td>• Scvo₂ not equivalent to SvO₂ (see later in the chapter)</td>
</tr>
<tr>
<td>Pulmonary artery catheter (PAC)</td>
<td>• Measured: PASP, PADP, mPAP, CVP/RAP, PCWP/PAOP, CO and CI by thermodilution, SvO₂</td>
<td>• Only method available to directly measure pulmonary artery pressures</td>
<td>• Outcomes data supporting superiority to CVC lacking</td>
</tr>
<tr>
<td></td>
<td>• Calculated: PVR, SVR, CO and CI by Fick equation, SV</td>
<td>• Direct measurement of CO and SvO₂ (may be available as continuous variables)</td>
<td>• May cause arrhythmias</td>
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<tr>
<td></td>
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<td>• Assumes right heart function approximates left heart function (usually, but not always, true)</td>
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<td></td>
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<td></td>
<td>• Fick CO calculation typically uses an estimated value for oxygen consumption, which may be falsely low in a patient with septic shock (and under-estimate of CO)</td>
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<td></td>
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<td></td>
<td>• Valvular abnormalities may make values inaccurate (particularly mitral stenosis, mitral regurgitation, tricuspid regurgitation, or aortic regurgitation)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Correct catheter tip location (lung zone 3) needed for accurate readings</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>• Cardiac chamber size and function, pericardial appearance (and presence of fluid), inferior vena cava (IVC) collapsibility, ejection fraction</td>
<td>• Non-invasive (transthoracic)</td>
<td>• Subjectivity of user assessment</td>
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<tr>
<td></td>
<td></td>
<td>• Visualization of ventricular function instead of presumed function based on CO</td>
<td>• Not done continuously; therefore, cannot detect acute changes or must be repeated when the patient’s status changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IVC collapsibility can predict fluid responsiveness</td>
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Table 2. Hemodynamic Monitoring Devices (continued)

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<tr>
<th>Device or Category</th>
<th>Obtainable Parameters</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal Doppler (ODM II™, CardioQ™, HemoSonic100™)</td>
<td>• CO and CI</td>
<td>• Ease of use</td>
<td>• Assumes 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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bedside practitioner familiarity</td>
<td>• Accuracy depends on position (need for frequent repositioning)</td>
</tr>
<tr>
<td>Arterial pulse pressure waveform analysis (FloTrac™/Vigileo™, PICCOplus™, PulsioFlex™, LiDCO™plus, PRAM-MostCare®, Nexfin™)</td>
<td>• CO and CI, SV, SVR (calculated), stroke volume variation (SVV), pulse pressure variation (PPV)</td>
<td>• Continuous measurement of values</td>
<td>• Accuracy relies on optimal arterial waveform from arterial catheter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Allows for assessment of SVV and PPV, which are dynamic markers of fluid responsiveness in mechanically ventilated patients (see later in the chapter)</td>
<td>• Inaccurate in patients with mitral or aortic valve disease or when used concomitantly with an intra-aortic balloon pump</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Continuous ScvO₂ measurement may also be available with a separate module attached to a CVC</td>
<td>• Arrhythmias reduce the accuracy of reported CO and CI (though this may be accounted for by internal software with some devices)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Minimally invasive (Nexfin™ is non-invasive)</td>
<td>• Accuracy may be limited during rapid changes in vascular resistance</td>
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<td></td>
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<td></td>
<td>• Some devices require a CVC in addition to an arterial pressure catheter</td>
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<td></td>
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<td></td>
<td>• Interpretation of SVV and PPV limited by need for positive pressure ventilation and relatively large tidal volumes</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• SVV and PPV are not accurate predictors of fluid responsiveness in the setting of arrhythmias</td>
</tr>
<tr>
<td>Bioimpedance/bioreactance (NICOM®, BioZ®, ECOM™)</td>
<td>• Continuous CO and CI, SV, SVR</td>
<td>• Non-invasive</td>
<td>• Conflicting validation results with BioZ® and ECOM™, particularly in patients with septic shock</td>
</tr>
<tr>
<td></td>
<td>• SVV (NICOM®)</td>
<td>• NICOM® CO correlates well with CO values from thermodilution and pulse pressure waveform analysis</td>
<td>• ECOM™ requires endotracheal intubation</td>
</tr>
</tbody>
</table>

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

CI = cardiac index; CO = cardiac output; DBP = diastolic blood pressure; SBP = systolic blood pressure; PAOP = pulmonary arterial occlusion pressure; RAP = right atrial pressure.

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 levels may be the result of increased production, decreased clearance, or both.
            (a) Type A lactic acidosis occurs in the setting of $D\text{O}_2/V\text{O}_2$ 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 ($S\text{cVO}_2$ and $S\text{vO}_2$)
         i. $S\text{cVO}_2$ and $S\text{vO}_2$ are the oxyhemoglobin saturation of venous blood drawn from a central vein and the pulmonary artery, respectively, and are expressed as a percentage.
         ii. Rearrangement of the Fick equation shows that a decrease in $S\text{vO}_2$ indicates a decrease in CO, whereas an increase in $S\text{V}\text{O}_2$ indicates an increase in CO.
         iii. $S\text{cVO}_2$ is drawn from a subclavian or internal jugular central venous catheter where the catheter tip terminates in the superior vena cava. As such, $S\text{cVO}_2$ is a reflection of oxygen extraction in the brain and upper body more than is systemic oxygen extraction. Of importance, an $S\text{cVO}_2$ drawn from a femoral central venous catheter cannot be used interchangeably with an $S\text{cVO}_2$ drawn from a thoracic central venous catheter and should not be used as a marker of perfusion.
         iv. $S\text{vO}_2$ is a better representation of systemic oxygen extraction because it represents mixing of venous blood from the superior vena cava, the inferior vena cava (IVC), and the coronary sinus.
         v. In normal physiology, $S\text{cVO}_2$ is about 2%–3% lower than $S\text{vO}_2$ because the upper body extracts more oxygen than the lower body.
         vi. In the setting of shock, $S\text{cVO}_2$ exceeds $S\text{vO}_2$ by about 5%–8% because of increased mesenteric and renal oxygen extraction (with a similar cerebral extraction ratio).
         vii. The difference between $S\text{cVO}_2$ and $S\text{vO}_2$ decreases in low CO states.
         viii. Although $S\text{cVO}_2$ and $S\text{vO}_2$ are not equivalent, they have a good (albeit not perfect) correlation, and $S\text{cVO}_2$ may be a reasonable approximation of $S\text{vO}_2$.
         ix. An $S\text{cVO}_2$ drawn from a central venous catheter with the tip terminating at the entrance or in the right atrium gives a better approximation of $S\text{vO}_2$ than an $S\text{cVO}_2$ drawn from a central venous catheter with the tip terminating in the superior vena cava far from the right atrium.
         x. A decreased $S\text{cVO}_2$ or $S\text{vO}_2$ is a sign that tissue oxygen demands are not completely met by $D\text{O}_2$ (more discussion on this topic later in this chapter).
         xi. In general, $S\text{vO}_2$ above 70% is considered adequate, whereas $S\text{vO}_2$ less than 40% is considered critically low and approaches the critical oxygen extraction ratio (where anaerobic metabolism will occur and lactate concentrations will increase). $S\text{vO}_2$ values between 50% and 70% by themselves do not lead to firm conclusions about the oxygen extraction ratio; they must be interpreted in the context of other markers of tissue perfusion (e.g., lactate concentrations).
xii. S\textsubscript{v}O\textsubscript{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 (Sc\textsubscript{v}O\textsubscript{2} greater than 89%) within the first 6 hours of their treatment course had a higher mortality than those with normoxia (Sc\textsubscript{v}O\textsubscript{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 resuscitative strategies have focused on hemodynamic and DO\textsubscript{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\textsubscript{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 frequently because of its accessibility.
      vi. Studies have shown that the microcirculation is frequently 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 severe 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 more commonly used 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.
         (a) Gastric luminal P\textsubscript{CO}\textsubscript{2} is measured by the tonometer.
         (b) Increases in gastric P\textsubscript{CO}\textsubscript{2} and in the difference (gap) between gastric and arterial P\textsubscript{CO}\textsubscript{2} suggest splanchic hypoperfusion.
      iii. 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.
iv. 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 non-invasive 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).

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**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: BP 88/54 mm Hg, HR 124 beats/minute, RR 18 breaths/minute, and temperature 39°C. While interviewing the patient, you note that he appears lethargic and confused. His serum chemistry panel results are as follows: sodium 138 mEq/L, potassium 3.8 mEq/L, chloride 105 mEq/L, carbon dioxide 22 mEq/L, blood urea nitrogen 25 mg/dL, creatinine 1.1 mg/dL, and glucose 78 mg/dL. Results of the complete blood cell count are as follows: white blood cell count 10.2 x 10$^3$ cells/mm$^3$, hemoglobin 6.6 g/dL, hematocrit 19.2%, and platelet count 180,000/mm$^3$. Which value is most likely contributing to compromised Do$_2$ 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 (SeVO₂ or SVO₂ may serve as a surrogate), and afterload (SVR) (see Table 3). Left ventricular size and function on echocardiography may serve as surrogates for preload and CO, respectively.

Table 3. Hemodynamic Profiles of Shock States

<table>
<thead>
<tr>
<th>Shock state</th>
<th>CVP</th>
<th>PCWP</th>
<th>CO</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>↓²</td>
<td>↓²</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>↑</td>
<td>↑</td>
<td>↓²</td>
<td>↑</td>
</tr>
<tr>
<td>Obstructive</td>
<td>↑</td>
<td>↑</td>
<td>↓²</td>
<td>↑</td>
</tr>
<tr>
<td>Impaired diastolic filling (e.g., cardiac tamponade)</td>
<td>↑</td>
<td>↑</td>
<td>↓²</td>
<td>↑</td>
</tr>
<tr>
<td>Impaired systolic contraction (e.g., massive PE)</td>
<td>↑</td>
<td>↓</td>
<td>↓²</td>
<td>↑</td>
</tr>
<tr>
<td>Vasodilatory/distributive</td>
<td>↓²</td>
<td>↓²</td>
<td>↓²</td>
<td>↓²</td>
</tr>
<tr>
<td>Pre-resuscitation</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓²</td>
</tr>
<tr>
<td>Post-resuscitation</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓²</td>
</tr>
</tbody>
</table>

*Pathophysiologic hallmark of shock state.

B. Of note, the hemodynamic profiles in Table 3 are those 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. Blood Pressure

1. As noted earlier, BP is the driving pressure for peripheral blood flow. As such, an adequate BP 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 over 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 BP for a patient in shock is generally 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., BP may be at goal when CO is inadequate).

B. Adequate End-Organ Perfusion

1. Each organ has a critical perfusion pressure that must be exceeded in order 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 those with chronic organ dysfunction (e.g., end-stage renal disease).

C. Lack of Fluid Responsiveness
1. Intravenous fluids are given to increase preload and subsequently increase SV, increase CO, and increase $D_O_2$.
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 BP is not a reliable indicator of CO response to a fluid challenge.
   d. In one systematic review, only 56% 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), but 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 (SPV), PPV, and IVC collapsibility.
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.
   a. 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), SPV 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).
   b. Because of their ability to be obtained from monitoring devices, PPV and SVV are more commonly used in practice than is SPV.
7. 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. 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%.
d. Values for PPV and SVV above the noted thresholds do not reliably predict fluid responsiveness in the setting of arrhythmias (e.g., atrial fibrillation).

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. 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%.

8. The passive leg raising (PLR) test measures the hemodynamic effects of a positional change of the patient’s legs. Lifting the legs passively from the horizontal position to a 45-degree angle 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, non-intubated 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 BP 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 or bioreactance device (non-invasive approach).

9. 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. 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.

10. Despite the superiority of dynamic markers to static markers in predicting fluid responsiveness, the incorporation of dynamic markers into a resuscitative strategy that improves patient outcomes in the ICU is still lacking.

### Patient Cases

2. 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 BP of 82/36 mm Hg, and new-onset confusion. After 2 L of LR and 2 units of PRBC, the patient’s hemoglobin increased to 9.1 g/dL, but he remained hypotensive. The medical team placed a pulmonary artery catheter and an arterial BP catheter, which revealed the following: central venous pressure 8 mm Hg, PCWP 14 mm Hg, CO 7.4 L/minute, and MAP 58 mm Hg. With which shock state are the patient’s hemodynamic parameters most consistent?

   A. Hypovolemic.
   B. Obstructive.
   C. Vasodilatory.
   D. Cardiogenic.
Patient Cases (continued)

3. After further resuscitation, the patient developed hypoxemia requiring intubation and mechanical ventilation. A postintubation radiograph revealed diffuse bilateral alveolar opacities. The patient remained hypoxemic with an $\text{FiO}_2$ 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.

D. Adequate $\text{Do}_2$

1. CO, $\text{ScVO}_2$, and $\text{Svo}_2$
   a. A strategy of systematically increasing CO to predefined “supranormal” levels was not associated with a mortality benefit; hence, it is not recommended. The decision to augment CO must be individualized according to organ perfusion.
   b. $\text{ScVO}_2$ may be used as a component of an early resuscitative strategy.
      i. A decreased $\text{ScVO}_2$ or $\text{Svo}_2$ is a sign that tissue oxygen demands are not completely met by $\text{Do}_2$.
      ii. Strategies to increase $\text{Do}_2$ (and subsequently increase $\text{ScVO}_2$ or $\text{Svo}_2$) include fluids to optimize preload, red blood cell transfusion to increase $\text{CaO}_2$, and inotropes to increase CO. Because $\text{PaO}_2$ does not contribute significantly to $\text{CaO}_2$, it should not be used as a therapeutic target.
   c. Use of predefined $\text{ScVO}_2$ or $\text{Svo}_2$ targets may be more important in the early resuscitation period (first 6 hours after presentation) than in the later resuscitation periods.
   d. Caution must be taken with using $\text{ScVO}_2$ or $\text{Svo}_2$ in isolation as a resuscitation goal.
      i. The assumption that decreased $\text{ScVO}_2$ or $\text{Svo}_2$ is synonymous with $\text{Do}_2$ and oxygen demand mismatch is not true because, by definition, tissue oxygen demand exceeds $\text{Vo}_2$ in shock.
      ii. During resuscitation, $\text{Vo}_2$ depends on $\text{Do}_2$, and increasing $\text{Do}_2$ will result in an increase in $\text{Vo}_2$ without substantial changes in $\text{ScVO}_2$ or $\text{Svo}_2$ until the critical $\text{Do}_2$ threshold is reached.
      iii. $\text{Svo}_2$ 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 $\text{Svo}_2$ will not increase substantially with increases in CO.
      iv. Venous hyperoxia may indicate mitochondrial dysfunction and impaired tissue oxygen use (achieving a high $\text{ScVO}_2$ or $\text{Svo}_2$ is not always best).
   e. It is likely best to interpret CO, $\text{ScVO}_2$, or $\text{Svo}_2$ 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, $\text{ScVO}_2$, or $\text{Svo}_2$ are inadequate, interventions to raise $\text{Do}_2$ should be done.

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. In one study of patients with severe 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 $\text{ScVO}_2$ above 70%.
   c. Significant discordance between lactate clearance and $\text{ScVO}_2$ may occur. In one study, 79% of patients with a lactate clearance of less than 10% had a concomitant $\text{ScVO}_2$ of 70% or greater.
   d. A protocol-based approach to the resuscitation of patients with severe sepsis or septic shock targeting a lactate clearance of at least 10% was noninferior to an approach targeting an $\text{ScVO}_2$ above 70%.
e. 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.

f. Targeting lactate clearance or normalization is an attractive end point because it does not require invasive hemodynamic monitoring.

g. Use of both lactate clearance and ScvO₂ above 70% as resuscitation goals may be best.

E. Microcirculatory Perfusion: See the Sepsis section of the Infectious Diseases II chapter for a further discussion of this topic.

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

A. See the Fluids, Electrolytes, and Nutrition section 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. Of note, vasoactive agents may have several of these properties.

2. Vasopressor agents are indicated if hypotension is refractory to fluid administration or in the setting of severe hypotension while fluids are being administered. It is important to acknowledge that both criteria are arbitrary and lack any definitive definition. This means that the treating clinician will often need to make a patient-specific assessment to define severe hypotension or hypotension refractory to fluid administration.

3. Vasopressor agents primarily exert pharmacologic benefit by augmenting SVR. Some vasopressors may have an augmented benefit of increasing CO. Table 4 highlights the receptor pharmacology of the various agents.

a. Selection of a specific vasopressor agent is largely guided by expert opinion and clinician preference. For the treatment of select shock syndromes, limited literature exists to guide therapy.

b. Vasopressor agents should be administered through central venous access to minimize the risk of extravasation and tissue necrosis. Continuous BP monitoring is preferred by arterial catheterization. Phentolamine (α-receptor antagonist) can be administered directly to prevent tissue damage should extravasation occur in the peripheral tissue. If phentolamine is unavailable, topical nitroglycerin ointment can be administered to the injury site with periodic assessment to determine the need for readministration.

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 β₁ activity, dobutamine may induce tachyarrhythmias as well as hypotension, given its β₂ activity.

b. Milrinone is a phosphodiesterase type 3 (PDE-3) inhibitor. PDE-3 inhibition potentiates cyclic adenosine monophosphate, leading to increased ventricular contractility and vasodilation.

i. Milrinone may be desirable for patients receiving β-antagonists prior to critical illness or for patients experiencing tachyarrhythmias while receiving dobutamine.

ii. Milrinone may cause an increase or a decrease in BP, depending on the individual patient’s SVR and CO when it is administered.
Table 4. Vasoactive Pharmacology

<table>
<thead>
<tr>
<th></th>
<th>$\alpha_1$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>DA</th>
<th>Vasopressin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dopamine</td>
<td>++</td>
<td>+++</td>
<td>+</td>
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<td>-</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>

DA = dopamine.

C. Outcomes Studies

1. Fluids
   a. A study enrolling almost 7000 patients with varied shock types requiring fluid resuscitation, with 90% power, did not detect a difference in 28-day mortality between treatment with 0.9% sodium chloride and 4% albumin (20.9% vs. 21.1%, p=0.87). Of note, however, is that 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 generally preferred to albumin for the initial resuscitation of patients with shock because of their lower cost.

   b. A pragmatic open-label randomized study of crystalloid compared with colloids for resuscitation did not detect a 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 resuscitative fluids within each study group make this study challenging to implement into practice.

   c. The type of crystalloid fluid, whether chloride rich (i.e., 0.9% sodium chloride) or chloride poor (i.e., LR), that should be used for resuscitation 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” or “balanced salt” solutions) have been evaluated.

Table 5. Chloride and Lactate Content of Commonly Used Resuscitative Fluids

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Chloride (mmol/L)</th>
<th>Lactate (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Chloride-rich”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9% sodium chloride</td>
<td>154</td>
<td>0</td>
</tr>
<tr>
<td>Hydroxyethyl starch 6% (130/0.4)</td>
<td>154</td>
<td>0</td>
</tr>
</tbody>
</table>
Shock Syndromes

Table 5. Chloride and Lactate Content of Commonly Used Resuscitative Fluids (continued)

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Chloride (mmol/L)</th>
<th>Lactate (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Chloride-poor&quot;*a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% albumin</td>
<td>128</td>
<td>0</td>
</tr>
<tr>
<td>Hydroxyethyl starch 6% (670/0.75)</td>
<td>124</td>
<td>28</td>
</tr>
<tr>
<td>Lactated Ringer solution</td>
<td>111</td>
<td>29</td>
</tr>
<tr>
<td>Plasma-Lyte®</td>
<td>98</td>
<td>0</td>
</tr>
<tr>
<td>Normosol®-R</td>
<td>98</td>
<td>0</td>
</tr>
</tbody>
</table>

*Distinction of “chloride rich” and “chloride poor” based on chloride content above or below 128 mmol/L.


ii. An open-label sequential period study evaluated outcomes between a control period in which chloride-rich fluids were routinely administered and an intervention period in which chloride-rich fluids were restricted to attending physician approval and chloride-poor fluids were routinely used. 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).

iii. A retrospective cohort study of patients undergoing open major abdominal surgery compared 0.9% sodium chloride with a balanced crystalloid solution (Plasma-Lyte®) 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 multivariate analysis.

iv. Balanced salt solutions may lead to hyponatremia (with LR) or cardiotoxicity (with acetate-containing solutions) when administered in large volumes.

v. Although intriguing, these data do not definitively support the benefit of balanced salt solutions, and a large randomized trial comparing these crystalloid solutions is anxiously awaited.

d. HES 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) HES solution with 0.9% sodium chloride. There was no difference in 90-day mortality between the HES and 0.9% sodium chloride groups (18.0% vs. 17.0%, p=0.26), but patients allocated to HES 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 trials without documented investigator misconduct found an association between HES use and increased patient mortality (relative ratio 1.09; 95% CI, 1.02–1.17; p=0.02) and need for renal replacement therapy (relative ratio 1.32; 95% CI, 1.15–1.50; p<0.001).

e. Studies of fluid therapy in patients with severe sepsis and septic shock will be discussed in the Infectious Diseases II chapter. These studies are listed for reference:

   i. Albumin for resuscitation

   ii. Crystalloid comparisons
      (a) Crit Care Med 2014;42:1585-91
      (b) Ann Intern Med 2014;161:347-55
Shock Syndromes

iii. HES solutions
   (b) N Engl J Med 2012;367:124-34

2. Vasopressors
   a. A multicenter randomized trial included patients requiring vasopressors because of shock of any type and excluded patients requiring vasopressors for more than 4 hours. 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 frequently 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 may not improve mortality compared with dopamine, it is a safer and more effective agent. As such, norepinephrine is preferred to dopamine for shock of any type.
   
   b. A multicenter randomized trial comparing norepinephrine with epinephrine for patients with undifferentiated shock did not find a 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 HRs and lactic acid concentrations on the first study day (but not on subsequent days) and were more frequently withdrawn from the study by the treating clinician (12.9% vs. 2.8%, p=0.002). These data suggest that epinephrine does not offer efficacy benefits over norepinephrine and is associated with an increased incidence of adverse effects (at least initially).
   
   c. Given these data, a case could be made for norepinephrine as the first-line vasoactive medication of choice in all shock types.

Patient Cases

4. J.B. is a 28-year-old man 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 LR, 1 L of 5% albumin, and 2 L of 6% HES and was initiated on norepinephrine. The patient remains on norepinephrine 12 mcg/minute with a lactate of 6.8 mmol/L and had a CO increase of 18% with a PLR. Which would best meet J.B.’s fluid needs?
   
   A. 5% albumin.
   B. 6% HES.
   C. 0.9% sodium chloride.
   D. No fluids necessary.
Shock Syndromes

Patient Cases (continued)
5. After 12 hours in the surgical ICU, J.B. remains hypotensive with a lactate of 5.2 mmol/L. He currently requires norepinephrine 14 mcg/minute and has a MAP of 64 mm Hg and an \( \text{ScVO}_2 \) 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.
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 \( \text{DO}_2 \).
2. The estimated blood volume for a 70-kg patient is 5 L.
3. 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. Classification of Trauma Hemorrhage

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss (mL)%</td>
<td>&lt; 750</td>
<td>750–1500</td>
<td>1500–2000</td>
</tr>
<tr>
<td>HR (beats/minute)</td>
<td>&lt; 100</td>
<td>&gt; 100</td>
<td>&gt; 120</td>
</tr>
<tr>
<td>RR (breaths/minute)</td>
<td>14–20</td>
<td>20–30</td>
<td>30–40</td>
</tr>
<tr>
<td>Urine output (mL/hour)</td>
<td>&gt; 30</td>
<td>20–30</td>
<td>5–15</td>
</tr>
<tr>
<td>CNS symptoms</td>
<td>Normal</td>
<td>Anxious</td>
<td>Confused</td>
</tr>
</tbody>
</table>

CNS = central nervous system.

6. Physiologic response includes:
   a. Neural response (immediate response within minutes):
      i. Sympathetic response: Activation of the low-pressure receptors (right and left atria) and high-pressure receptors (aortic arch and carotid sinus) leading to the vasomotor center of the medulla and pons to signal an increase in HR, myocardial contractility, and peripheral arteriolar/venous tone by efferent impulses through sympathetic and vagus nerves
      ii. Parasympathetic response: Reduction in vagal tone leads to increased HR
      iii. Increased secretion of epinephrine and norepinephrine
   b. Intrinsic response (immediate response within hours):
      i. Reduced capillary pressure leads to fluid redistribution from the interstitium to the vascular compartment and subsequent albumin shifts into the plasma from the interstitium
      ii. Fluid shifts to the intravascular compartment to replace the acute loss of blood and plasma.
   c. Humoral response (delayed response over days): Secretion of antidiuretic hormone, aldosterone, and renin secretion to increase volume retention

C. Resuscitation
   1. Identify and treat reversible causes of blood loss.
   2. Fluids
      a. Indications: Diminished mental status or absent radial pulse (SBP less than 90 mm Hg)
      b. Crystalloids: LR and normal saline (NS) are both recommended as resuscitative fluids.
      c. Colloids do not confer any incremental benefit over crystalloids and are associated with increased mortality (SAFE trial).
   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.
      c. Trying to maintain hemoglobin greater than 10 g/dL in the setting of trauma may be reasonable.
      d. In the setting of acute upper GI bleeding, 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 a higher 6-week survival rate (95% vs. 91%, hazard ratio 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).
   4. Vaspressors
      a. Recommended only after hypovolemia has been corrected or when cardiac arrest is imminent
      b. May be used as a temporizing measure in the setting of profound hypoperfusion despite ongoing volume resuscitation
   5. End points of resuscitation
      a. General recommendations include SBP greater than 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. Oxygen transport variables may be more patient-specific. Lactate, D_o2, and cardiac index may be more sensitive.

D. Burn Resuscitation
   1. Acute burn 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. Concomitant concern 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 LR 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 following 16 hours.
5. The use of colloids for burn resuscitation is controversial. No consensus exists for fluid type, timing, and re-dosing.

E. Management of Coagulopathy
1. Lethal triad: Hypothermia, acidosis, and coagulopathy
   a. Hypothermia, severe academia (pH less than 7.20), and hypocalcemia inhibit the procoagulant enzyme function.
   b. Therefore, management of the acutely bleeding patient should prioritize warming the patient to a temperature greater than 34°C, correcting acidosis to a pH greater than 7.20, and administering calcium to an ionized calcium greater than 4.4 mg/dL.
2. Blood component therapy (e.g., plasma, platelet count, cryoprecipitate) remains the standard treatment for coagulopathy. However, this therapeutic approach is challenged by supply and safety.
   a. Blood component therapy will replete individual components but will not address other parts of hemostasis (e.g., fibrinolysis).
   b. Standard repletion protocols suggest a 1:1:1:1 strategy of PRBCs/plasma/cryoprecipitate/platelets.
3. Recombinant activated factor VIIa (rFVIIa)
   a. 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.
   b. Case series and case reports suggest that the administration of rFVIIa improves clinical outcomes.
   c. A randomized controlled trial, which was terminated because of the futility for the primary end point of mortality, did show a reduction in PRBC transfusion.
   d. 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 readministration of rFVIIa.
   e. Database reviews document an increased incidence of venous and arterial thromboembolic events associated with off-label rFVIIa use.
4. Prothrombin complex concentrates (PCCs)
   a. A combination of complex clotting factors II, VII, IX, and X and proteins C and S.
      i. 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)
      ii. Of note, FEIBA (factor eight inhibitor bypassing activity) is the only PCC composed of activated clotting factors. Although theoretically more efficacious, this may also lead to increased thrombotic events.
   b. Kcentra has FDA-approved labeling for use for the reversal of warfarin-related acute bleeding disorders (discussed further in section F, Reversal of Oral Anticoagulant Agents). The other PCC products are approved for the treatment of hemophilia-related bleeding. The package insert warns of increased thromboembolic risk with Kcentra administration.
5. Tranexamic acid
   a. 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.
b. 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 (relative risk 0.91; 95% CI, 0.85–0.97; p=0.0035).
   i. Number needed to treat is 67.
   ii. Mortality caused by bleeding: Tranexamic acid, 489 (4.9%) vs. placebo, 574 (5.7%) (relative risk 0.85; 95% CI, 0.76–0.96; p=0.0077)
   iii. Greatest benefit for tranexamic acid observed with administration within 3 hours of injury (relative risk 0.79; 95% CI, 0.64–0.97; p=0.03)

6. Aminocaproic acid
   a. Aminocaproic acid is a lysine analog that is 10-fold weaker than tranexamic acid.
   b. The recommended dose of aminocaproic acid is a 150 mg/kg bolus, followed by a 15 mg/kg/hour infusion.
   c. Less high-level evidence exists for aminocaproic acid in the management of the acutely bleeding patient.

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

<table>
<thead>
<tr>
<th></th>
<th>Factor II (units/vial)</th>
<th>Factor VII (units/vial)</th>
<th>Factor IX (units/vial)</th>
<th>Factor X (units/vial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bebulin VH</td>
<td>120</td>
<td>13</td>
<td>100</td>
<td>139</td>
</tr>
<tr>
<td>FEIBAa</td>
<td>650</td>
<td>1200</td>
<td>700</td>
<td>550</td>
</tr>
<tr>
<td>Kcentrab</td>
<td>380–800</td>
<td>200–500</td>
<td>400–620</td>
<td>500–1020</td>
</tr>
<tr>
<td>Profilnine SD</td>
<td>148</td>
<td>11</td>
<td>100</td>
<td>64</td>
</tr>
</tbody>
</table>

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

aFEIBA contains mainly non-activated factors II, IX, and X; factor VII is mainly in the activated form. Values expressed are for the FEIBA 500 units vial, which also contains 550 units of Protein C. FEIBA is also available as 1000 units and 2500 units vials; the individual factor contents for these vials are two and five times, respectively, the values expressed.

bValues expressed are for the Kcentra 500 units vial, which also contains Protein C 420–820 units and Protein S 240–680 units. Kcentra is also available as a 1000 units vial; the individual factor contents for this vial are two times the values expressed.

F. Reversal of Oral Anticoagulant Agents

1. Indications for reversal: Acute major bleeding involving a critical anatomic site (e.g., central nervous system [CNS], retroperitoneal, pericardial, GI, and intramuscular with compartment syndrome)

2. Warfarin: Kcentra has been approved by the FDA (U.S. Food and Drug Administration) for the urgent reversal of warfarin therapy in adult patients with acute major bleeding or requiring reversal for an invasive procedure. Dose is determined by patient weight and pretreatment international normalized ratio (INR) (see Table 9). Black box warning for an increased risk of arterial and venous thromboembolic events

3. Target-specific oral anticoagulants – Dabigatran/apixaban/rivaroxaban: Proposed reversal with PCCs is theoretical.
   a. Activated charcoal may be considered if the last dose was administered less than 2 hours previously.
   b. Existing literature does not provide conclusive evidence for the efficacy, safety, dosing, and monitoring of PCCs or rFVIIa for NOACs. PCCs may not reverse the ongoing inhibition of factors IIa and Xa.
   c. In the setting of reduced kidney function, dabigatran clearance may be aided by instituting hemodialysis.
Table 8. Summary of Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action</td>
<td>Vitamin K antagonist</td>
<td>Direct factor IIa inhibitor</td>
<td>Direct factor Xa inhibitor</td>
<td>Direct factor Xa inhibitor</td>
</tr>
<tr>
<td>Peak action</td>
<td>4–5 days</td>
<td>~2 hours</td>
<td>~2 hours</td>
<td>~2 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>~2 days</td>
<td>24 hours</td>
<td>12 hours</td>
<td>12 hours</td>
</tr>
<tr>
<td>Renal elimination</td>
<td>-</td>
<td>+++ (Cl with CrCl &lt; 30 mL/minute)</td>
<td>+ (Cl with CrCl &lt; 15 mL/minute)</td>
<td>++ (Cl with CrCl &lt; 30 mL/minute)</td>
</tr>
<tr>
<td>PT/INR</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>^PTT</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>TT</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ECT</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-Xa</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Reversal strategy</td>
<td>• Kcentra</td>
<td>• Dialysis</td>
<td>• Activated charcoal (&lt; 6 hours)</td>
<td>• Activated charcoal (&lt; 2 hours)</td>
</tr>
</tbody>
</table>

^PTT = activated partial thromboplastin time; CI = contraindicated; CrCl = creatinine clearance; ECT = ecarin clotting time; TT = thrombin time.

Table 9. Kcentra Dosing for the Reversal of Warfarin Therapy

<table>
<thead>
<tr>
<th>INR 2–4</th>
<th>INR 4–6</th>
<th>INR &gt; 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of Kcentra (factor IX units/kg)</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>Maximum dose (factor IX units)</td>
<td>2500</td>
<td>3500</td>
</tr>
</tbody>
</table>

Patient Cases
6. A 29-year-old man (weight 85 kg, height 72 inches) is admitted to the burn unit with a 40% total body surface area burn to the lower extremities and buttocks after a fall into a molten slag at work in a steel mill. He received 500 mL of NS during transfer to the hospital. On the patient’s presentation to the burn unit, the surgical resident asks for your help in calculating the patient’s fluid resuscitation needs. Which is the best option for resuscitation?

A. 15 L of LR over 24 hours; initiate at 1000 mL/hour for the first 12 hours, followed by 250 mL/hour, titrating to goal urine output of 1 mL/kg/hour.
B. 13 L of LR over 24 hours; initiate at 813 mL/hour for the first 8 hours, followed by 406 mL/hour, titrating to goal urine output of 0.5 mL/kg/hour.
C. 12 L of LR over 12 hours; initiate at 1000 mL/hour, titrating to goal urine output of 0.5 mL/kg/hour.
D. 24 L of LR over the first 24 hours; initiate at 1000 mL/hour, titrating to goal urine output of 0.5 mL/kg/hour.
Patient Cases (continued)

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 LR. His vital signs on admission to the ED are as follows: BP 92/48 mm Hg, HR 118 beats/minute, RR 25 breaths/minute, and temperature 35°C. On examination, he has 8/10 pain and appears drowsy and incoherent after being administered morphine 2 mg intravenously. Which is the best option for resuscitative strategies?

A. Administer LR 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 LR 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 LR to normal mentation.

D. Administer LR at 1000 mL/hour to maintain a urine output greater than 30 mL/hour, an SBP greater than 90 mm Hg, and normal mentation.

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 pulmonary hypertension [PH] or aortic dissection).

2. Obstructive shock is relatively rare, and only about 2% of patients requiring vasoactive medications have this shock type.

B. Pathophysiology

1. The pathophysiologic hemodynamic hallmark of obstructive shock is decreased CO.

2. The specific pathophysiologic derangements are dependent 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 (pulmonary vascular resistance [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 ➞ systemic hypotension ➞ reduced RV tissue perfusion (decreased right coronary artery perfusion) ➞ RV free wall ischemia ➞ reduced RV free wall contractility and further impairment of RV CO (a viscous cycle). In addition, acute RV pressure overload leads to a shift of the intraventricular septum toward the LV ➞ impaired LV diastolic filling (because of intraventricular dependence) ➞ 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 generally 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 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.
      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 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. Not defined 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 (HR less than 40 beats/minute with signs of shock)
(b) Moderate 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) Low risk: Acute PE not meeting the definition for massive or submassive PE

iii. A scientific statement and a practice guideline recommend the administration of thrombolytics for patients with massive PE and an acceptable risk of bleeding complications. These recommendations are supported by a meta-analysis that found, 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]).

iv. 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 ability of investigators to break the blinding of treatment allocation in the study. Bleeding was not 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 frequently 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 frequently 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% confidence intervals 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.

v. A scientific statement and a guideline both recommend thrombolytics for patients with submassive PE and a low risk of bleeding.

vi. The risks and benefits of thrombolytics are best determined on a case-by-case basis by the bedside clinician.

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 "contraindications" noted in the product labeling, other than active internal bleeding, may be considered “relative contraindications” by some clinicians for thrombolytic administration.
Table 10. Risk Factors for Bleeding After Administration of Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Alteplase package insert contraindications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Active internal bleeding</td>
<td>Recent intracranial or intraspinal surgery or trauma</td>
</tr>
<tr>
<td>History of cerebrovascular accident (intracranial hemorrhage or ischemic stroke)</td>
<td>Severe uncontrolled hypertension&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Malignant intracranial neoplasm, arteriovenous malformation, or aneurysm</td>
<td>Known bleeding diathesis&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alteplase package insert warnings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent major surgery</td>
<td>Significant closed-head or facial trauma with radiographic evidence of bony fracture or brain injury within 3 weeks</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Recent GI or genitourinary bleeding</td>
</tr>
<tr>
<td>Hemostatic defects (including those secondary to severe hepatic or renal disease)</td>
<td>Hypertension (systolic blood pressure ≥ 175 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg)</td>
</tr>
<tr>
<td>Acute pericarditis</td>
<td>Subacute bacterial endocarditis</td>
</tr>
<tr>
<td>Recent trauma</td>
<td>Significant hepatic dysfunction</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>Needle puncture at noncompressible site</td>
</tr>
<tr>
<td>Left heart thrombus</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Septic thrombophlebitis or occluded arteriovenous cannula at seriously infected site</td>
<td>Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions</td>
</tr>
<tr>
<td>Recent receipt of oral anticoagulants</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bleeding risk factors reported in published literature</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent internal bleeding</td>
<td>Suspected aortic dissection</td>
</tr>
<tr>
<td>Poorly controlled hypertension at baseline</td>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>Cardiopulmonary resuscitation &gt; 10 minutes</td>
</tr>
<tr>
<td>Stool occult blood positive</td>
<td>Bilirubin level &gt; 3 mg/dL</td>
</tr>
<tr>
<td>Presence of an intra-aortic balloon pump</td>
<td>Dementia</td>
</tr>
<tr>
<td>African American race</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Undefined for pulmonary embolism, but noted as > 185 mm Hg systolic or > 110 mm Hg diastolic for acute ischemic stroke.

<sup>b</sup>Undefined for pulmonary embolism, but noted as INR > 1.7 or platelet count < 100 x 10<sup>9</sup>/L (< 100 x 10<sup>3</sup>/mm<sup>3</sup>) for acute ischemic stroke.


viii. Patients with a massive or submassive PE who (1) have an unacceptably high risk of being administering thrombolytics, (2) remain unstable despite thrombolytic administration, or (3) have shock likely to cause death within hours (before the onset of systemic thrombolytics) should be considered for surgical embolectomy or catheter thrombectomy.

ix. 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. If anticoagulation is contraindicated, an IVC filter should be placed.
Patient Case

8. S.L. is a 48-year-old woman (weight 75 kg) who 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: HR 118 beats/minute, BP 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

(Septic shock will be discussed in detail in the Infectious Diseases II chapter.)

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 frequent 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), 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 (as noted earlier, septic shock will be covered in detail in the Infectious Diseases II chapter), immune-mediated (“anaphylactic”) shock, and neurogenic shock, which will be the focus of this section.

4. Vasodilatory shock is the most commonly encountered shock type, with about 66% of patients having this shock type requiring vasoactive medications. 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 levels of endogenous vasoconstrictors (e.g., norepinephrine, epinephrine, and angiotensin II).
2. Potential mechanisms of vasodilation
   a. Activation of cellular ATP (adenosine triphosphate)-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 levels 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-κB, which leads to the transcription of both proinflammatory cytokines (e.g., interleukin-1β, 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 re-exposure 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 preload and CO.

C. Resuscitation and Treatment
   1. 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.
2. Treatment goals and end points of resuscitation are generally similar to those listed in section IV, 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.

3. Initial resuscitation
   a. The treatment of choice is intravenous fluids, which restore effective circulating volume.
      i. Crystalloids (e.g., LR or NS) 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 generally 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 there are no compelling data to 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.

4. 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. Clinical controversy exists regarding the use of high-dose corticosteroids in the setting of acute spinal cord injury, and they are not considered part of standard care (patient selection must be individualized).

Note: Cardiogenic shock will be discussed in the Cardiology chapter.
REFERENCES

Introduction


Monitoring Techniques


Differentiation of Shock States


Resuscitation Parameters and End Points


Agents Used to Treat Shock – Fluids and Vasoactive Agents


Hypovolemic Shock


Obstructive Shock


Vasodilatory and Distributive Shock


ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: B**
The patient has hypovolemic shock caused by his upper GI hemorrhage and is manifesting 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 $D_O$ (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 left ventricular diastolic dysfunction), tachycardia will increase (not decrease) $D_O$ (Answer C is incorrect). Leukocytosis does not impede $D_O$ until it reaches an exorbitant threshold (greater than 75 L/mm$^3$) (Answer D is incorrect). When examining the Fick equation for $D_O$, acute anemia is the determinant that is adversely affecting $D_O$ (Answer B is correct).

2. **Answer: C**
The patient’s calculated SVR is 541 dynes•s•cm$^{-5}$, which, together with relatively high central venous pressure and PCWP values and a high CO, is consistent with vasodilatory shock (Answer C is correct). 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 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 the patient is still fluid responsive (Answer D is incorrect). Data from a large randomized trial of patients with heterogeneous shock types did not show a 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 (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 $\beta_1$-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 $\beta_1$-adrenergic properties, it primarily increases BP through vasoconstriction secondary to its $\alpha_1$-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: B**
Using the Parkland formula for burn resuscitation, the 24-hour fluid requirement would be 13 L, to be segmented into the first 8 hours of resuscitation and the remaining 16 hours. Calculating fluid requirements according to weight and total burn body surface area to target a urine output goal of greater than 0.5 mL/kg/hour would be correct (Answers A, C, and D are incorrect). Answer B is correct because the total volume requirement, the titration of fluid rates, and the target urine output are appropriate.
7. **Answer: D**
   It is important to recognize that this patient has class II hypovolemic shock after blood loss caused by penetrating trauma (HR greater than 100 beats/minute, RR 20–30 breaths/minute, and confused on examination). In this case, the appropriate resuscitative strategy should focus on the selection of 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, B, and C are incorrect).
ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: C**
   This elderly patient presents with septic shock. Shock is a syndrome of impaired $\text{DO}_2$, 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 is suggestive of the presence of a shock syndrome in the setting of impaired $\text{DO}_2$.

2. **Answer: B**
   Oxygen delivery is best shown by the Fick equation for $\text{DO}_2$. According to this equation, $\text{DO}_2$ depends on CO and arterial oxygen content. Cardiac output depends on HR and SV. Typically, an elevated HR will lead to an increase in CO and $\text{DO}_2$. If a patient has atrial fibrillation, though, ventricular filling is impaired and the SV is decreased. This leads to a decrease in CO and $\text{DO}_2$ (Answer B is correct). Lactate does not impede $\text{DO}_2$ but is a by-product of impaired $\text{DO}_2$ (Answer A is incorrect). Similarly, $\text{DO}_2$ is not impaired by acute kidney injury (Answer C is incorrect). Finally, fever is an inflammatory response that increases oxygen consumption but does not impair $\text{DO}_2$.

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). Similarly, 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 (Answer B is incorrect). Hydroxyethyl starch solution 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 $\text{ScVO}_2$ 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 $\text{FiO}_2$, a reliable predictor of fluid responsiveness should be used to guide fluid therapy instead of administering fluid without regard 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 on 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 $\text{SeVO}_2$ (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 [suggesting 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 arterial oxygen content (PRBCs) and CO (dobutamine and milrinone) should not be initiated unless the patient has inadequate Do₂ and is not fluid responsive (Answers A, B, and 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 is probable. According to the extent of confusion, oliguria, tachycardia, and tachypnea, this patient has class III hemorrhage (Answers A, B, and D incorrect).

8. **Answer: A**  
The patient has a massive PE, as evidenced by pulselessness. 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 management (Answers B and C are incorrect). Although a transthoracic echocardiogram 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).