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Chapter e42: Shock Syndromes

Seth R. Bauer; Robert MacLaren; Brian L. Erstad

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 12, Shock Syndromes.

KEY CONCEPTS

KEY CONCEPTS

1. Shock is a clinical syndrome characterized by inadequate global tissue perfusion. Low blood pressures are not required to define shock.
2. Shock is typically classified into one of four etiologic mechanisms: (1) hypovolemic, (2) cardiogenic, (3) obstructive, or (4) vasodilatory/distributive.
3. Shock syndromes can be differentiated based on the evaluation of preload, cardiac output, and afterload or assessment of surrogate markers.
4. Inadequate oxygen delivery leads to organ damage in critical illness.
5. Blood lactate should be measured in all patients in whom shock is suspected.
6. Treatment of the patient with circulatory shock can be divided into four phases: salvage, optimization, stabilization, and de-escalation. Each phase has different but sometimes overlapping goals and therapeutic strategies.
7. Crystalloid solutions are the first-line fluid of choice for forms of circulatory insufficiency that are associated with hemodynamic instability.
8. Vasopressors and inotropes are required in patients with shock when volume resuscitation fails to maintain adequate blood pressure and tissues remain hypoperfused.
9. The choice of a particular vasopressor or inotrope agent depends on the underlying shock pathophysiology, goals of therapy, and clinical pharmacology.
10. Norepinephrine is the preferred initial vasopressor for shock.

BEYOND THE BOOK

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Develop a table that has two columns, one titled *crystalloid solutions* and one titled *colloid solutions.* In each column, list at least four potential advantages and four potential disadvantages of the solution. There are several crystalloid and colloid solutions commercially available, so you will need to be specific about the solutions included in the table. The purpose of this exercise is to help students choose a preferred resuscitation fluid for a critically ill patient based on patient-specific data.

INTRODUCTION

Circulatory shock is a medical emergency requiring prompt recognition and treatment because it can quickly lead to serious consequences, including death. Shock is a broad term for a heterogeneous group of syndromes that cause an acute, generalized circulatory failure associated with inadequate oxygen utilization by the cells.[1] Typically, shock is characterized as systolic blood pressure (SBP) <90 mm Hg (or acute reduction of at least 40 mm Hg from baseline) or mean arterial blood pressure (MAP) <70 mm Hg with tachycardia and organ perfusion abnormalities.[2] The key feature of all shock syndromes is inadequate tissue and organ perfusion.

Learners are strongly encouraged to read **Chapter e29** "Evaluation of Cardiovascular Function" and **Chapter 142** "Sepsis and Septic Shock" to augment their understanding of the content in this chapter.

EPIDEMIOLOGY

Hemodynamic compromise necessitating the use of vasopressors is common in the intensive care unit (ICU), with about one-third of critically ill patients receiving vasopressors during their clinical course.[3] Shock is not a reportable cause of death to state and federal agencies and, thus, the true incidence is unknown. Reported mortality of patients with shock in clinical studies from the 1980s exceeded 70% but now ranges from 20% to 55%.[4–7] However, estimates of deaths due to shock are complicated by differences in definitions and classification systems. Normal compensatory mechanisms may reverse the processes leading to irreversible organ dysfunction. However, progressive circulatory insufficiency may result in the loss of these compensatory responses. Identification of when this occurs can be problematic as this varies from patient to patient and is not always readily apparent during the initial patient presentation. Therefore, forms of shock, such as hemorrhagic shock, are often subsumed by more readily identifiable categories of death, such as accidental injuries and homicides.

ETIOLOGY

1 The presence of circulatory shock is indicated by inadequate global tissue perfusion. Circulatory shock develops when the cardiovascular system is unable to deliver an adequate oxygen supply to meet tissue oxygen demands, resulting in cellular dysfunction. This cellular dysoxia leads to a shift in cellular metabolism to anaerobic pathways and results in elevated blood lactate concentrations. Physiologically, tissue metabolic requirements are met by both adequate MAP and adequate oxygen delivery (Do_2). The MAP is the driving pressure for peripheral blood flow and end-organ perfusion. Tissue blood flow cannot be directly measured; therefore, MAP is used as a surrogate estimate. Because the components of blood pressure are cardiac output (CO) and systemic vascular resistance (SVR) and because CO is a determinant of DO_2, blood pressure is integrally related to DO_2. However, compensatory mechanisms such as vasoconstriction may preserve blood pressure while tissue perfusion is inadequate. Therefore, while low blood pressure is commonly present in patients with shock, it is not required to define shock.[1]

2 Shock is typically classified into one of the four etiologic mechanisms: (1) hypovolemic, (2) cardiogenic, (3) obstructive, or (4) vasodilatory/distributive. Vasodilatory/distributive is the most commonly encountered shock syndrome, which accounts for about two-thirds of all shock cases requiring vasopressors. Cardiogenic and hypovolemic shock are both encountered in about 16% of cases, while obstructive shock is rarely encountered (about 2% of cases).[2] Notably, patients may have components of more than one shock syndrome on presentation (the categories are not mutually exclusive) and patients can transition from one shock type to another (eg, a patient with cardiogenic shock may subsequently develop septic shock, or a patient with septic shock may develop cardiogenic shock from a myocardial infarction). Hypovolemic, cardiogenic, and obstructive shock are all characterized by low CO, but the mechanism for low CO is different in each shock state. Hypovolemic shock is caused by inadequate venous

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return, from internal or external loss of intravascular fluids (eg, trauma, surgery, or hemorrhage), resulting in insufficient cardiac preload and decreased stroke volume. Cardiogenic shock results from a loss in pump function, through decreased cardiac contractility (eg, myocardial infarction), acute valvular abnormality, or an arrhythmia (eg, ventricular tachycardia). Obstructive shock results from an extracardiac obstruction to blood flow into or out of the heart, such as tension pneumothorax, cardiac tamponade, or pulmonary embolism.

Vasodilatory/distributive shock is distinctly different than the other three forms of shock because it is characterized by a loss of vascular tone. Vasodilatory shock is a general term that describes tissue hypoperfusion due to a decrease in SVR (or hypoperfusion despite a normal or elevated CO). Technically, distributive shock is a subset of vasodilatory shock characterized by maldistribution of blood flow in the microcirculation (consisting of arterioles, capillaries, and venules) or at the organ level. However, since most cases of vasodilatory shock result in distributive shock, the terms are often used interchangeably. Septic shock causes vasodilatory/distributive shock in 96% of cases, but this shock type can also be caused by several conditions, including neurogenic shock (typically secondary to acute spinal cord injury), immune-mediated (ie, anaphylactic), or nonimmunologic (ie, anaphylactoid) reactions, adrenal insufficiency, pancreatitis, acute liver failure, or as a component of ischemia-reperfusion injury (eg, after cardiopulmonary bypass or return of spontaneous circulation after cardiac arrest).

PATHOPHYSIOLOGY

Each shock syndrome has a different etiology and resultant pathophysiology. However, since all shock syndromes lead to inadequate tissue perfusion and cellular dysoxia, they have the same effect on cellular metabolism. Figure e42-1 provides a simplified view of the pathophysiology of circulatory insufficiency assuming the acute insult causing shock did not result in immediate patient death. Cell damage and death may occur from the primary insult or from ischemia-reperfusion injury. While the primary insult for shock leads to initial harm, the host response can also result in deleterious effects. Ischemia-reperfusion injury is a consequence of the host response to an abrupt decrease in tissue perfusion with subsequent restoration of perfusion, leading to a systemic inflammatory response syndrome with the release of a multitude of mediators that have complex interactions to further injury. In addition to edematous obstruction of capillaries and oxygen-free radical damage of cell membranes, several cellular (eg, white blood cells and platelets) and humoral (eg, procoagulants, anticoagulants, complement, and kinins) components are activated, causing the release of other inflammatory mediators and the formation of microthrombi. The resulting reperfusion injury may range from readily reversible organ dysfunction to multiple-organ failure and death. Cells have varying responses to hypoxia, ranging from astrocytes that quit functioning almost immediately to other cells that may tolerate more prolonged periods of hypoperfusion. Left unmitigated, cell death occurs with prolonged injury and is usually heralded by vasodilation and acidosis.

FIGURE e42-1

The pathophysiology of shock—detrimental outcomes versus recovery. (CO, cardiac output.) *(Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2018. All rights reserved.)*

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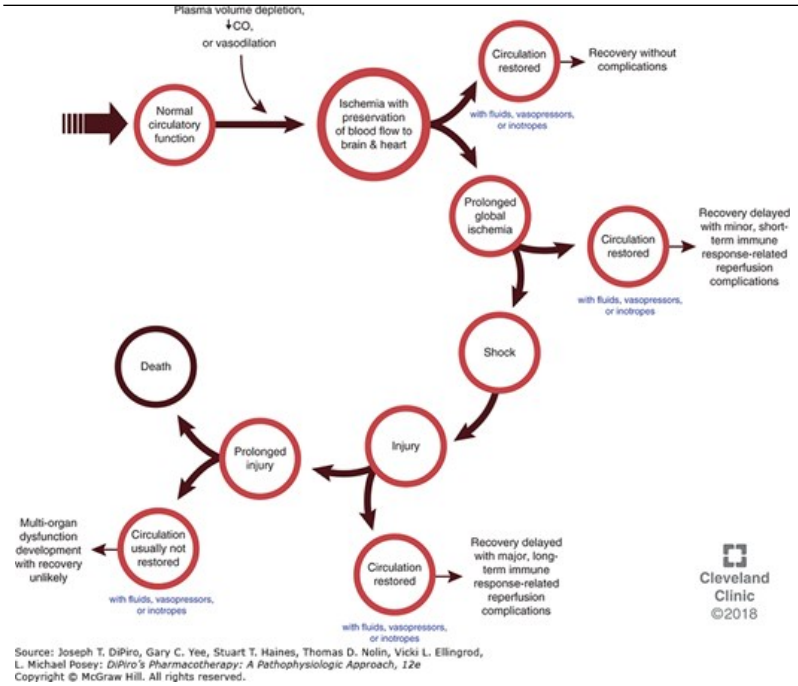

Most patients admitted to the ICU with circulatory shock have some level of systemic inflammatory response syndrome, which is the body's response to tissue injury. This syndrome is defined by several hypermetabolic changes reflected in the patient's temperature, white blood cell count and differential, and respiratory and heart rates. The stress response involves complex interactions between the nervous system and immunomodulating substances and has similar (if not the same) harmful and helpful consequences described with reperfusion following shock. As part of the stress response, anti-inflammatory pathways are also activated to counterbalance the pro-inflammatory effects on local tissues. Vagal nerve-mediated release of acetylcholine leads to suppression of pro-inflammatory cytokines by macrophages.[8] Additionally, the renin-angiotensin-aldosterone and hypothalamic-pituitary-adrenocortical systems are activated, with angiotensin II, vasopressin, and cortisol released to maintain blood pressure through vasoconstriction and concomitantly retain sodium and water in the kidneys to increase cardiac preload. Cortisol and catecholamine release from the adrenal gland also inhibit pro-inflammatory cytokine production.[8] If the underlying problems are left untreated, the patient may develop multiple-organ dysfunction syndrome during the final stages of illness.

3 Conceptually, shock syndromes can be differentiated based on the evaluation of preload, cardiac output, and afterload (Fig. e42-2).[2,9] For example, while hypovolemic and cardiogenic shocks both result in a decreased cardiac output, hypovolemic shock is caused by low cardiac preload, and cardiogenic shock results in an elevated cardiac preload. Because cardiogenic shock and obstructive shock have the same profile in this conceptual model, some experts consider the causes of an obstructive shock to be etiologies of cardiogenic shock. Vasodilatory/distributive shock is typically described as a hyperdynamic shock state from low SVR, but a high cardiac output only develops after venous return is restored (typically with fluid resuscitation).[9,10] For this reason, vasodilatory/distributive shock may be divided into two stages: pre-resuscitation and post-resuscitation.

FIGURE e42-2

Circles indicate primary dysfunction in shock state. (CO, cardiac output)

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Shock State	Preload	CO	Afterload
Hypovolemic	↓	↓	↑
Cardiogenic	↑	↓	↑
Obstructive	↑	↓	↑
Vasodilatory/Distributive			
Pre-resuscitation	↓	↓	↓
Post-resuscitation	↑	↑	↓

Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*
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Hypovolemic shock is extracellular volume depletion that may result from blood loss (plasma and red blood cells) due to trauma, surgery, or internal hemorrhage, or plasma loss due to fluid sequestered within the body or lost from the body. The body attempts to compensate for volume depletion beginning with autoregulatory vasoconstriction of smaller blood vessels. When the cause of circulatory insufficiency continues unabated, local mechanisms eventually fail to provide adequate compensation, and macrocirculatory changes ensue. With increasing volume depletion, blood flow to the heart (preload) is decreased, resulting in lower CO and subsequent activation of baroreceptors and chemoreceptors leading to sympathetic discharge. Also, fluid shifting from the interstitial space to the intravascular space occurs through a phenomenon known as transcapillary refill, and hormones (eg, adrenocorticotropic hormone, angiotensin, catecholamines, and vasopressin) that cause sodium and water retention by the kidneys are released. The phenomenon of transcapillary refill means that the body can have fluid losses exceeding normal plasma volume. These responses cause increases in stroke volume, heart rate, and SVR to maintain blood pressure and tissue perfusion. However, if the initial insult is significant enough, the endogenous response is overcome, and circulatory shock ensues. In the case of hemorrhage leading to hypovolemic shock (ie, hemorrhagic shock), prompt attention must be given to cellular as well as plasma losses. Red blood cells lost during the bleeding episode may compound ischemic damage in vital organs. Clotting factors and platelets are also lost in hemorrhage. The resulting bleeding problems may be aggravated by the dilutional effect of fluid resuscitation on clotting factor activity. This coagulopathy in hemorrhagic shock is typically accompanied by acidosis and hypothermia, referred to as the lethal triad.

Cardiogenic shock is inadequate CO from an intracardiac cause leading to tissue hypoperfusion. In about 80% of cases, cardiogenic shock is caused by acute myocardial infarction leading to left ventricular dysfunction.[11] Mechanical irregularities complicating acute myocardial infarction, such as acute mitral regurgitation or ventricular septal or free wall rupture may also lead to cardiogenic shock. Less frequent causes include acute-on-chronic valvular heart disease, arrhythmias, and myocarditis. Isolated right ventricular cardiogenic shock is rare and will not be discussed. In the setting of acute myocardial infarction, coronary ischemia leads to an abrupt reduction in CO, which causes a decrease in blood pressure and further impairs coronary perfusion. Sympathetic nervous system activation leads to compensatory tachycardia and vasoconstriction. While endogenous catecholamine release initially maintains blood pressure, it also increases myocardial oxygen demand, which can worsen ischemia and create a vicious cycle. As an adaptive mechanism, the left ventricle also dilates to maintain stroke volume. This leads to increased cardiac preload, pulmonary venous hypertension, and subsequent pulmonary edema. Patients with cardiogenic shock may also have cytokine-mediated vasodilation and microcirculatory dysfunction.[11]

The source of obstructive shock is an extracardiac obstruction to cardiovascular flow, which may lead to impaired diastolic filling (eg, tension pneumothorax or cardiac tamponade) or impaired systolic contraction (eg, pulmonary embolism or acute-on-chronic pulmonary hypertension). In cases where the diastolic filling is impaired, ventricular preload is decreased. However, in impaired systolic contraction, ventricular afterload is abruptly increased, leading to ventricular failure. Both etiologies of an obstructive shock lead to decreased CO and similar compensatory mechanisms as with cardiogenic shock ensue.

Vasodilatory/distributive shock is caused by systemic vasodilation. While sepsis is the most common etiology of vasodilatory/distributive shock, other causes include anaphylaxis, spinal cord injury, pancreatitis, and acute liver failure. The deficiency of vascular smooth muscle cell constriction may be from activation of vasodilatory mechanisms or a failure of vasoconstrictive pathways. In septic shock, the host response to the infecting pathogen leads to the release of proinflammatory cytokines, which activate endothelial cells to increase expression of inducible nitric oxide synthase (iNOS) resulting in NO production. Nitric oxide subsequently causes vasodilation through the cyclic guanosine monophosphate pathway. Additionally, lactate

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and intracellular acidosis activate adenosine triphosphate (ATP)-sensitive potassium channels, which causes potassium efflux and cellular hyperpolarization. This hyperpolarization impairs calcium influx through voltage-gated calcium channels even in the presence of vasoconstrictor ligands (eg, catecholamines, vasopressin, and angiotensin II), which impedes cellular depolarization and vasoconstriction. Consequently, the effectiveness of endogenous and exogenous vasoconstrictors is reduced. Prolonged exposure of vascular endothelial tissue to catecholamines may also promote receptor downregulation and "desensitization" to catecholamines. Systemic vasodilation causes ineffective circulating plasma volume through an increase in venous capacitance (venous pooling), which is exacerbated by the loss of intravascular volume through capillary leak.[8,10] Decreased venous return leads to decreased cardiac preload and decreased CO. Fluid resuscitation and catecholamine administration can restore effective circulating plasma volume and a high CO state ensues in the setting of low left ventricular afterload. Many patients with septic shock may also have myocardial dysfunction after fluid resuscitation through multiple mechanisms, including intramyocardial inflammation.[12,13] Furthermore, microthrombi and dysfunction of the microcirculation can lead to heterogeneous distribution of delivered oxygen and altered tissue perfusion despite macrocirculatory (eg, blood pressure and CO) goal attainment.[14]

4 Inadequate DO_2 leads to organ damage in critical illness. In normal individuals, oxygen consumption (VO_2) depends on DO_2 up to a certain critical level (VO_2 flow dependency). At this point, tissue oxygen requirements apparently are satisfied and further increases in DO_2 will not alter VO_2 (VO_2 flow independence). The point that VO_2 becomes dependent on DO_2 represents a pathologic transition from aerobic to anaerobic cellular metabolism and lactate production.[15,16] Although animal models of sepsis substantiate this relationship, studies in critically ill humans show a continuous, pathologic dependence relationship of VO_2 with DO_2. The apparent linear relationship between DO_2 and VO_2 has been questioned because both share variables, and this mathematical coupling can produce artifactual relationships between variables.[15] Inconsistent relationships between DO_2 and VO_2 are observed when VO_2 is measured independently by indirect calorimetry. While the systematic assessments of DO_2 and VO_2 and their dependence are rarely practiced, the concepts of ensuring adequate DO_2 are frequently applied. The DO_2 and VO_2 parameters are calculated as follows:

$$\begin{matrix} DO_2 = CO \times CaO_2 \\ VO_2 = CO \times (CaO_2 - CvO_2) \end{matrix}$$ DO2=CO×CaO2VO2=CO×(CaO2−CvO2)

where CO = cardiac output, CaO_2 = arterial oxygen content determined by hemoglobin concentration and arterial oxygen saturation, and CvO_2 = venous oxygen content determined by hemoglobin concentration and venous oxygen saturation (SvO_2).

Venous oximetry (ie, venous oxygen saturations) reflects the adequacy of tissue oxygenation.[16] SvO_2 and central venous oxygen saturation ($ScvO_2$) are the oxyhemoglobin saturation of venous blood obtained from the pulmonary artery and a central vein in the thorax, respectively, and are expressed as a percentage. When tissue oxygen demand exceeds supply, the oxygen extraction ratio (O_2ER) increases and values of SvO_2 and $ScvO_2$ are low. Rearranging the equations above shows that when hemoglobin, arterial oxygen saturation, and VO_2 are stable, SvO_2 or $ScvO_2$ values reflect CO. Thus, venous oximetry may be utilized as a surrogate for CO and can be useful to differentiate shock states. Although SvO_2 and $ScvO_2$ are not equivalent, they correlate well in most circumstances and $ScvO_2$ is a reasonable approximation of SvO_2. Generally, SvO_2 values above 70% (0.70) are considered adequate and normal. However, SvO_2 values below 50% (0.50) are low and may approach the critical O_2ER where anaerobic metabolism occurs and lactate concentrations will increase. In isolation, firm conclusions about the O_2ER cannot be made from SvO_2 values between 50% (0.50) and 70% (0.70), and other markers of tissue perfusion should be utilized to interpret values in this range. High venous oximetry values (above 80% [0.80]) can represent a high CO but may also be a poor prognostic sign indicating adequate DO_2 but the poor capacity of tissues to extract oxygen.[16]

Hemodynamic parameters obtained from monitoring devices are critical to shock syndrome identification, therapeutic intervention selection, and monitoring a patient's response to therapy. Importantly, one hemodynamic parameter cannot show the complete hemodynamic profile. Instead, hemodynamics must be interpreted in the context of multiple parameters.[1] Also, a monitoring device by itself cannot improve patient-centered outcomes and the information obtained must be combined with evidence-based therapies. The type of shock may be clear based on the patient's presenting symptoms and physical examination. For example, a patient who presents after a motor vehicle collision with frank blood loss most likely has hypovolemic shock (hemorrhagic shock subtype). However, concomitant shock states may occur, such as cardiac tamponade due to hemopericardium from chest trauma in the above example. When additional information is needed to evaluate the type of shock, echocardiography is suggested over more invasive methods (such as central venous or pulmonary artery catheters).[1] Critical care clinicians are frequently and increasingly

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trained to perform and evaluate transthoracic echocardiograms, which can lead to a rapid (within 5 minutes) and noninvasive diagnosis of the shock type.[14,17] A rapid assessment by cardiac echocardiography includes evaluation of left and right ventricular chamber size and function, pericardial appearance, and vena cava size with and without respiration. Additional assessments of valve structure/function and measurement of the left ventricular outflow tract velocity-time integral (which can be used to calculate stroke volume and CO) may also be performed.[2,17] Ventricular chamber size and function are the most crucial components for shock differentiation because they reflect ventricular filling and contractility, respectively.

Advanced hemodynamic monitoring may be necessary to augment the diagnosis or treatment of a patient with shock. Importantly, there is no high-level evidence to support the routine use of a central venous catheter in patients with shock. A central venous catheter placed in the internal jugular or subclavian vein may be used to measure the central venous pressure (CVP), to obtain venous samples for laboratory testing (including $ScvO_2$), and to administer drugs (including vasopressors) or fluids directly to the central circulation. A triple-lumen catheter is frequently used, whereby drugs with known incompatibility can be administered. The CVP may be used as an estimate of preload for shock state differentiation but should not be utilized as a resuscitation goal.[1,18,19] In summary, estimates or surrogates for hemodynamic parameters that may be used include ventricular size on echocardiography or CVP as estimates for preload, and SvO_2, $ScvO_2$, or ventricular contractility on echocardiography as surrogates for CO.

The general goal of therapy during initial resuscitation from shock is to achieve and maintain MAP consistently above 65 mm Hg while ensuring adequate perfusion to the critical organs.[1,2] Hemodynamic and perfusion monitoring can be categorized into two broad areas: global and regional monitoring. Global parameters, such as systemic blood pressure, venous oximetry, and lactate, assess perfusion and oxygen utilization of the entire body. Regional monitoring techniques focus on tissue-specific oxygen delivery and subsequent changes in functional indices of individual organs. These measurements include coagulation abnormalities (disseminated intravascular coagulation), altered renal and/or hepatic function, altered gastrointestinal perfusion, cool extremities, cardiac ischemia, and altered sensorium. Although none of these indices alone is a reliable indicator of adequate resuscitation, they offer immediate detection and may be prognostic of recovery when combined and defined at the level of organ function. As a result, these indices are frequently used as surrogate endpoints for the goals of resuscitation. While it is assumed that normalization of these parameters infers benefit, the clinician must first treat the patient rather than relying solely on data from continuous monitoring to guide therapy.

5 Blood lactate should be measured in all patients in whom shock is suspected.[1,2,20] Because lactate production is increased under anaerobic conditions, blood lactate concentration can be used as a diagnostic tool for tissue hypoperfusion.[21,22] However, not all lactate elevations are from Type A hyperlactatemia where oxygen demand exceeds supply. Type B hyperlactatemia is not related to tissue hypoxia but instead is associated with an underlying disease (eg, malignancy or sepsis), a medication-related cause (eg, epinephrine, metformin, or linezolid), or inborn errors of metabolism.[22] Increased lactate production, reduced lactate elimination (commonly termed “clearance”), or the combination of these two mechanisms may lead to hyperlactatemia. Because lactate is predominantly metabolized by the liver, patients with severe liver dysfunction may have impaired lactate elimination accentuating lactate concentration elevations in shock. Additionally, regional tissue hypoperfusion (eg, arterial thrombosis leading to critical limb ischemia or mesenteric ischemia) may also produce elevated lactate concentrations. Thus, if an elevated blood lactate concentration (>2 mmol/L) does not normalize after initial resuscitation the cause must be investigated and not assumed to be due to tissue hypoxia.

Blood pressures, CO, blood lactate, and venous oximetry parameters do not offer information about perfusion to individual organs. Organ-specific hypoxia may be evident by coagulopathy as indicated by thrombocytopenia (platelet count <100,000/μL [100×10^9/L]) and/or prolonged clotting times (international normalized ratio >1.5 or activated partial thromboplastin time at least 1.5-fold the upper limit of normal), impaired renal function, urine production (<0.5 mL/kg/hr and/or increased serum concentrations of blood urea nitrogen and creatinine), altered hepatic function (substantially increased serum concentrations of transaminases and bilirubin), altered gastrointestinal perfusion (ileus and diminished bowel sounds), cool extremities, cardiac ischemia (elevated troponin levels and electrocardiogram or echocardiography changes), pulmonary ischemia with worsening partial pressure of arterial oxygen ([PaO_2]), and altered sensorium.[1,2,8] The success of resuscitation should be based on the combination of blood pressure, organ-specific parameters of regional perfusion, and global perfusion measurements.

The microcirculation plays a key role in tissue oxygenation because it is where oxygen release occurs. Microcirculatory blood flow is often altered in patients with shock (particularly in patients with septic shock) and improvements in microcirculatory blood flow are associated with improved patient outcomes.[23] Monitoring and resuscitation strategies have typically focused on global (macrocirculatory) hemodynamics, which cannot predict microcirculatory blood flow.[24] Microcirculatory evaluations (eg, sidestream darkfield imaging of sublingual blood flow) are typically not undertaken in clinical practice because proper measurements require user experience and time to analyze the results. With technical advances, though, markers of

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microcirculatory perfusion may be used more commonly.

Receptor Pharmacology

Comparative receptor activities of endogenous and exogenous catecholamines, vasopressin, and angiotensin II are summarized in Table e42-1.[25–32] Endogenous catecholamines are responsible for the regulation of vascular and bronchiolar smooth muscle tone and myocardial contractility. These effects are mediated by sympathetic adrenergic receptors of the autonomic nervous system located in the vasculature, myocardium, and bronchioles. Postsynaptic adrenoceptors are located at or near the synaptic junction. These receptors can be activated by naturally circulating or exogenous catecholamines (eg, norepinephrine, epinephrine, and phenylephrine), whereas presynaptic adrenoceptors are stimulated by locally released neurotransmitters (eg, norepinephrine) and are controlled by a negative feedback mechanism.

TABLE e42-1

Adrenergic, Dopaminergic, Vasopressin, and Angiotensin Receptor Pharmacology and Organ Distribution

Effector Organ	Receptor Subtype	Physiologic Response
Heart		
Sinoatrial node	β_1, β_2, AT-1	Increased heart rate
Atria	β_1, β_2	• Increased contractility • Increased conduction velocity
Atrioventricular node	β_1, β_2, AT-1	• Increased automaticity • Increased conduction velocity
His-Purkinje system	β_1, β_2, AT-1	• Increased automaticity • Increased conduction velocity
Ventricles	• α_1, AT-1 • β_1, β_2	• Increased contractility • Increased contractility • Increased conduction velocity • Increased automaticity • Increased rate of idioventricular pacemaker cells
Arterioles		
Coronary	α_1, α_2, V1, AT-1; β_2, D1, V2 (via NO)	Constriction; dilation
Skin and mucosa	α_1, α_2, V1, AT-1	Constriction
Skeletal muscle	α_1, V1, AT-1; β_2, AT-2	Constriction; dilation
Cerebral	α_1, V1, AT-1; V2 (via NO)	Constriction (slight); dilation

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Pulmonary	α_1; β_2, V2 (via NO)	Constriction; dilation
Abdominal viscera (mesentery)	α_1, V1; β_2, D1	Constriction; dilation
Renal	α_1, α_2, V1, AT-1; β_1, β_2, D1, AT-2	Constriction; dilation
Veins (systemic)	α_1, α_2; β_2	Constriction; dilation
Lungs		
Tracheal/bronchial smooth muscle	β_2	Relaxation
Bronchial glands	α_1; β_2	Decreased; increased secretion
Stomach		
Motility and tone	α_1, α_2, β_1, β_2	Decreased (usually)
Sphincter	α_1	Contraction (usually)
Secretions	α_2	Inhibition
Intestine		
Motility and tone	α_1, α_2, β_1, β_2, V_1	Decreased (usually)
Sphincters	α_1	Contraction
Secretions	α_2	Inhibition
Kidney		
Aldosterone secretion	AT-1	Increased
Renin secretion	α_1; β_1	Decreased; increased
Reabsorption of water	V2, AT-1	Increased

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Sodium reabsorption and H^+ excretion	AT-1; AT-2	Increased; decreased
Skeletal muscle	β_2	Increased contractility, glyconeogenesis, potassium uptake
Liver	α_1, β_2	Glycogenolysis and gluconeogenesis
Fat cells	$\alpha_1, \beta_1, \beta_2$	Lipolysis (thermogenesis)
Pituitary	V3, AT-1	Adrenocorticotropic hormone secretion
Hypothalamus	AT-1	Vasopressin secretion
Nervous	AT-1	Enhanced norepinephrine secretion
Immune		
Pro-inflammatory cytokine release, macrophage, and T-cell activation	β_2, AT-1; AT-2	Increased; decreased
Coagulation system		
	V1	Thromboxane synthesis (platelet aggregation)
	AT-1	Release of plasminogen activator inhibitor-1, platelet activation

AT, angiotensin; D, dopamine; NO, nitric oxide; V, vasopressin.

The signal transduction pathways associated with catecholamine-, vasopressin-, and angiotensin II-induced effects in the heart and blood vessels are illustrated in Fig. e42-3.[25–31] Agonists of β-adrenoceptors and dopamine (D_1) receptors stimulate adenylate cyclase by a G-protein (G_s)–dependent mechanism (Fig. e42-3, top). Adenylate cyclase generates cyclic adenosine monophosphate (cAMP) from ATP. cAMP-dependent protein kinase A, which is activated by elevations in intracellular cAMP, phosphorylates target proteins to modify cellular function. Through these mechanisms, β_1-adrenoceptor activation exerts positive inotropic and chronotropic effects in the heart, and β_2-adrenoceptor and D_1-receptor activation induce vascular smooth muscle relaxation. Agonists of α_1-adrenoceptors stimulate phospholipase C-β (PLC-β) through a G-protein (G_q)–dependent process (Fig. e42-3, bottom). PLC-β produces inositol trisphosphate and diacylglycerol from cell membrane phosphatidylinositol bisphosphate. Diacylglycerol activates protein kinase C, an enzyme that phosphorylates several key proteins (eg, extracellular signal-regulated kinases, c-Jun NH_2-terminal kinases, and mitogen-activated protein kinases) that modify cellular function (eg, hypertrophy). Inositol trisphosphate elicits the release of calcium from intracellular stores, such as the sarcoplasmic reticulum. Calcium forms a complex with calmodulin, which then activates calcium/calmodulin-dependent protein kinases (CaMK). CaMKs phosphorylate target proteins to alter cellular function. Myosin light-chain kinase is an example of a CaMK. Its action of phosphorylating myosin light chain leads to vascular smooth muscle contraction.

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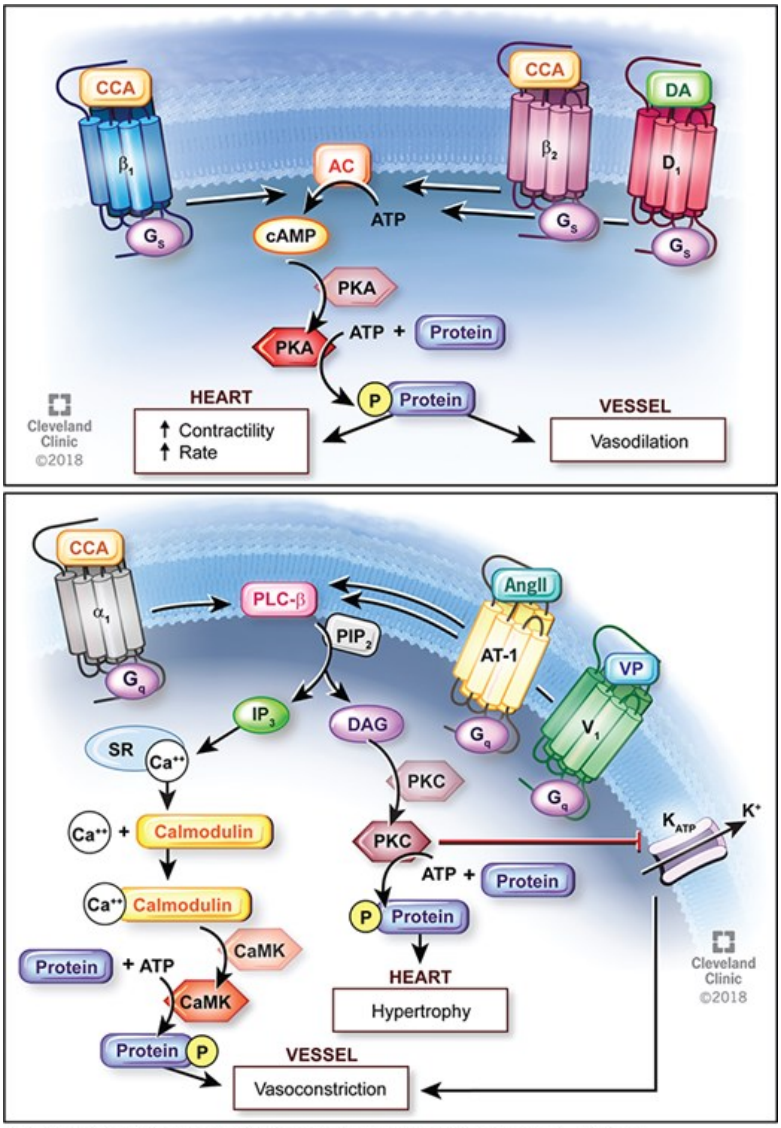
FIGURE e42-3

Top: Catecholamine (CCA)-induced effects mediated in heart (β_1) or vascular smooth muscle (β_2, D_1). (AC, adenylate cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PKA, cAMP-dependent protein kinase.) Bottom: CCA (α_1), angiotensin II (AngII), and vasopressin (VP)-induced actions in vascular smooth muscle. (Ca++, calcium ion; CaMK, calcium/calmodulin-dependent protein kinase; DAG, diacylglycerol; IP_3, inositol trisphosphate; K_{ATP}, ATP-sensitive potassium channel; P, phosphorus; PIP_2, phosphatidylinositol bisphosphate; PKC, protein kinase C; PLC-β, phospholipase C-β; SR, sarcoplasmic reticulum.) These pathways have been extensively simplified, and denoted cellular effects represent one of many produced. *(Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2018. All Rights Reserved.)*



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The heart contains primarily postsynaptic β_1-receptors, which cause increased rate and force of contraction when stimulated. This effect is mediated by activation of adenylate cyclase and subsequent generation and accumulation of cAMP. Stimulation of postsynaptic cardiac α_1 receptors causes a significant increase in contractility without an increase in rate, an effect mediated by PLC rather than adenylate cyclase. The increased contractility is more pronounced at lower heart rates and has a slower onset and longer duration in comparison with the β_1-mediated inotropic response.

Presynaptic α_2-adrenoceptors also are found in the heart and are activated by norepinephrine released by the sympathetic nerve itself. Their activation inhibits further norepinephrine release from the nerve terminal.

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Both presynaptic and postsynaptic adrenoceptors are present in the vasculature. Postsynaptic α_1- and α_2-receptors mediate vasoconstriction, whereas postsynaptic β_2-receptors induce vasodilation. Presynaptic α_2 receptors inhibit norepinephrine release in the vasculature, also promoting vasodilation. Presynaptic β_1-adrenoceptors promote neurotransmitter release. Stimulation of peripheral D_1 receptors produces renal, coronary, and mesenteric vasodilation and a natriuretic response. Stimulation of D_2 receptors inhibits norepinephrine release from sympathetic nerve endings, sequesters prolactin, and aldosterone, and may induce nausea and vomiting. D_1- and D_2-receptor stimulation also suppresses peristalsis and may precipitate ileus.

Vasopressin-induced vasoconstriction occurs through a variety of direct and indirect mechanisms.[27–29] Stimulation of vascular vasopressin (V_1)-receptors causes vasoconstriction by receptor-coupled activation of PLC and calcium release from intracellular stores via secondary messengers similar to α_1-adrenergic stimulation (Fig. e42-3, bottom). Vasopressin also inhibits vascular potassium-sensitive ATP channels via activation of protein kinase C, indirectly leading to vasoconstriction (Fig. e42-3, bottom). V_1-receptor stimulation inhibits the actions of interleukin (IL)-1β and thereby further facilitates vasoconstriction. Vasopressin also increases the activity of adrenergic receptors. The greatest vasoconstriction occurs in the skin and soft tissue, skeletal muscle, fat tissue, pancreas, and thyroid gland. In contrast, vasopressin causes vasodilation in the cerebral, pulmonary, coronary, and selected renal vascular beds by enhancing endothelial NO release through V_1- and V_2-receptor stimulation in these tissues.[27–29] Vasopressin has minimal to no direct inotropic or chronotropic effects.

V_2 receptors located in the kidneys are responsible for the antidiuretic properties of vasopressin.[27–29] Stimulation of V_2 receptors facilitates the integration of aquaporins into the luminal cell membrane of distal tubules and collecting duct capillaries to increase permeability and thus retain intravascular volume. However, vasopressin stimulation of V_1-receptors causes vasoconstriction of renal efferent arterioles and relative vasodilation of renal afferent arterioles to increase glomerular perfusion pressure and filtration rate to enhance urine production.

Vasopressin rapidly increases serum cortisol concentration by stimulating V_3 receptors in the pituitary gland to enhance the release of adrenocorticotropic hormone (ACTH).[27–29] Cortisol helps regulate pro-inflammatory states and increases blood pressure through several mechanisms, including inhibition of iNOS to reduce NO production, reversal of adrenergic receptor desensitization, and increased intravascular volume through retention of sodium and water.

Angiotensin II also causes vasoconstriction through both direct and indirect mechanisms.[30,31] When angiotensin II binds to angiotensin (AT)-1 receptors on arterioles, a G-protein (G_q)–dependent process with PLC-β activation is initiated, which results in vasoconstriction. This is a similar mechanism to α_1-adrenoceptor- and V_1-receptor–mediated vasoconstriction. Stimulation of AT-1 receptors in the hypothalamus and pituitary also leads to vasopressin and ACTH secretion, respectively, further enhancing vasoconstriction. AT-1 receptors are also present in the kidney and lead to multiple effects, including aldosterone secretion, sodium reabsorption, and H^+ excretion. In the renal vasculature, AT-1 receptors are present on efferent renal arterioles but not afferent renal arterioles, resulting in increased glomerular filtration pressure. Coagulation factors are also affected by AT-1, with increased expression of plasminogen activator inhibitor-1 (leading to inhibition of the fibrinolytic pathway) and platelet activation.[30,31] Several immune mediators are also influenced by AT-1 stimulation, including pro-inflammatory cytokine release, and macrophage and T-cell activation. Some of the effects of AT-1 are counterbalanced by AT-2; stimulation of AT-2 receptors leads to vasodilation (including skeletal muscle and afferent renal arterioles) and anti-inflammatory activity.

Adrenoreceptor Function

Most of the work describing receptor function and associated clinical pharmacology has been performed in animal models or human volunteers. In critically ill patients with shock, derangements in adrenergic receptor activity may result in resistance to exogenously administered catecholamine.[25–28] This “desensitization” is frequently characterized by myocardial and vascular hyporesponsiveness to high dosages of inotropes and vasopressor agents. Prolonged exposure of vascular endothelial tissue to vasopressor drugs (α-adrenergic agonists) or endogenous catecholamines may promote additional receptor downregulation.[26] Increased endogenous catecholamine concentrations have been reported in endotoxemic and other critically ill patients, suggesting an acquired adrenergic receptor defect and desensitization of adrenergic receptors, and alteration in voltage-sensitive calcium

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channels. The problem in critically ill patients may be related to decreased receptor activity or density. However, in patients with septic shock, catecholamine concentrations are even higher, so abnormalities in adrenergic receptor function are greater, with associated reductions in the concentrations of intracellular signal transduction mediators. The worsened receptor abnormality may be explained by defects distal to the receptor site, such as uncoupling of adrenergic receptors from adenylate cyclase or PLC, or dysfunction in the regulatory G-protein unit of signal transduction pathways. Hypoxemia and acidosis may further worsen receptor adrenergic activity.

In addition to catecholamines, circulating inflammatory cytokines may be partly responsible for distal alterations.[26,28,29] Macrophage-derived IL-1β and tumor necrosis factor (TNF)-α produce impaired coupling of β-adrenoceptors to adenylate cyclase resulting in myocardial hyporesponsiveness to various vasopressors and inotropes.[14,26,29] Additionally, IL-1β and TNF-α suppress gene expression of α_1-adrenoceptors, resulting in fewer receptor proteins. Cytokine-mediated iNOS expression leads to overproduction of NO, which directly contributes to vasodilation. NO also indirectly produces vasodilation by combining with superoxide to form peroxynitrite, a highly toxic reactive species that causes endothelial dysfunction, uncoupling of α_1-adrenoceptors to PLC, and deactivation of catecholamines. The result of inflammation is a system that promotes adrenergic receptor dysfunction to limit myocardial performance and accentuate vasodilation and shock.[14,26,29] However, the clinical response to vasopressors and possibly inotropic agents is variable over time because α- and β-adrenergic receptor derangements will change with the dynamic inflammatory process.[14,20,26–29] Therefore, these drugs should be dosed to clinical endpoints and not to arbitrary maximal dosages; high dosages are frequently required.

Vasopressin, Cortisol, and Angiotensin II

Endogenous arginine vasopressin, a peptide hormone also known as antidiuretic hormone, is important for osmoregulation under normal physiologic conditions. Vasopressin is produced in the hypothalamus, stored in the posterior pituitary, and released from magnocellular neurons of the hypothalamus.[28,29] Increased serum osmolality and hypovolemia are the major stimuli for vasopressin release.[29] Other stimuli commonly associated with shock are dopamine, histamine, angiotensin II, prostaglandins, pain, hypoxia, acidosis, hypotension, hypercarbia, and α_1-adrenergic receptor stimulation. Vasopressin release is inhibited by NO, natriuretic peptides, γ-aminobutyric acid, β-adrenergic receptor stimulation, and α_2-adrenergic receptor stimulation.[29]

Normal serum vasopressin concentrations are <4 pg/mL (3.7 pmol/L).[29] Serum vasopressin concentrations are elevated with hypotension. Vasopressin response in septic shock is biphasic. During the initial hours of septic shock, serum concentrations of vasopressin are appropriately high to help maintain blood pressure and organ perfusion. Thereafter, serum vasopressin concentrations decline dramatically over the next 96 hours to physiologically normal but inappropriately low values, resulting in a state of “relative deficiency.” A similar pattern has been observed in patients with hypovolemic (hemorrhagic) shock secondary to trauma.[33] In contrast, serum vasopressin concentrations remain elevated in patients with cardiogenic shock. Administration of vasopressin at 0.01 to 0.07 units/min produces concentrations similar to those observed in early septic shock and other shock states; however, the correlation between vasopressin concentrations and blood pressure is unclear.[29] Administration of vasopressin augments the decline of inflammatory mediators and improves arterial pressure while minimizing the dosage of catecholamine vasopressors.[29,34]

The mechanism of vasopressin insufficiency in septic and hypovolemic shock is not well understood. Neurohypophyseal stores in the posterior lobe of the pituitary gland are depleted during shock, likely as a result of excessive and continuous baroreceptor stimulation that eventually exhausts the limited vasopressin secretory stores. In addition, secretion of vasopressin is inhibited by enhanced endothelial production of NO, high circulating concentrations of adrenergic agonists (both endogenous and exogenous), and tonic inhibition by stretch receptors in response to volume replacement and mechanical ventilation.[29]

As with vasopressin, during sepsis, a state of “relative adrenal insufficiency” is produced by continuous activation of the hypothalamic-pituitary-adrenal axis by IL-1β, IL-6, and TNF-α that causes depletion of cortisol in the adrenal glands.[35] Administration of corticosteroids improves arterial pressure while minimizing the dosage of catecholamine vasopressors. Proposed mechanisms of the vasoconstrictor effect of corticosteroids include increasing the number and function of α_1- and β-adrenergic receptors and attenuating the production of vasodilatory inflammatory mediators.

The use of corticosteroids for the treatment of septic shock has been a topic of controversy for many years. Interest in corticosteroid use is driven by the awareness of critical illness-related corticosteroid insufficiency.[36] Relative adrenal insufficiency, a component of critical illness-related corticosteroid insufficiency, has been defined as a random cortisol concentration <10 μg/dL (280 nmol/L) or an increase of <9 μg/dL (250 nmol/L)

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following a dose of synthetic ACTH irrespective of the initial serum cortisol concentration. Although absolute insufficiency is rare, relative adrenocortical insufficiency is present in 50% to 70% of patients with septic shock and is associated with a poor outcome.[36]

Conversely, an elevated random cortisol concentration (>34 µg/dL [940 nmol/L]) is also a predictor of mortality.[36] Mortality is further increased if cortisol response to ACTH is <9 µg/dL (250 nmol/L), suggesting that the risk of mortality is greatest in situations of adrenal gland "fatigue" (ie, degree of stress is not matched by sufficient cortisol production by the adrenal glands despite operating at maximal functional capacity).

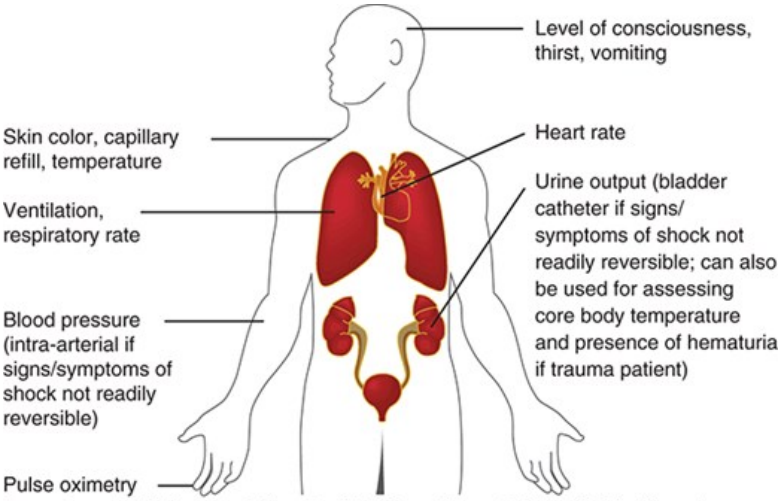
Angiotensin II concentrations may also be low in patients with vasodilatory shock resulting in a "relative deficiency." Typically, angiotensin II concentrations are elevated in patients with effective hypovolemia (ie, hypovolemic shock and vasodilatory shock) because of renin secretion. However, pro-inflammatory cytokines (eg, IL-1β and TNF-α) can lead to downregulation of AT-1, which leads to low aldosterone concentrations despite high concentrations of renin and angiotensin II.[31] Additionally, reduced sensitivity of AT-1 to angiotensin II as well as the impaired conversion of angiotensin I to angiotensin II via angiotensin-converting enzyme has been observed.[31]

CLINICAL PRESENTATION

The initial presentation of patients with circulatory shock can vary markedly. A patient's first contact with the healthcare setting is commonly a result of the underlying etiology such as fever and malaise associated with infection or chest pain associated with acute myocardial infarction. However, patients may also present with overt signs of tissue hypoperfusion. Regardless of patient age or preexisting conditions, the initial monitoring of a patient with suspected circulatory shock should include the following non-invasive parameters: vital signs, urine production, mental status, and physical examination (Fig. e42-4). Clinical manifestations of tissue hypoperfusion may be apparent at the bedside, including neurologic (eg, confusion or obtundation), cutaneous (eg, warm skin in states of vasodilation and cool, clammy, or mottled skin in states of vasoconstriction), and renal (eg, low urine production) abnormalities. However, signs of tissue hypoperfusion must be interpreted in the context of concomitant therapies (eg, sedative administration) and the patient's history (eg, chronic end-stage renal disease with anuria).

FIGURE e42-4

Clinical parameters—evaluation and monitoring of patients in shock.



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Although the presenting signs and symptoms of circulatory insufficiency are variable, patients usually have decreased blood pressure, increased heart and respiratory rates, and a normal or low-normal temperature (eg, 36°C–37°C [96.8°F–98.6°F]) in the absence of infection, exposure to extremes of temperature, and medications that impair thermoregulation. However, patients with infection may have an elevated temperature (eg, above 38.3°C [101°F]). As mentioned earlier, recordings of vital signs must be interpreted in light of known or suspected baseline conditions. For example, alcohol, β-blockers, diuretics, and medications with anticholinergic effects may impair thermoregulation. Medications such as β-blockers and calcium channel blockers or disease states like cirrhosis may alter resting blood pressure and heart rate, as well as the subsequent response to therapeutic

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interventions. Although a blood pressure of 110/70 mm Hg (systolic/diastolic) may be acceptable in many patients, it may be inadequate in a patient with preexisting hypertension who normally has a blood pressure of 170/105 mm Hg. At the other extreme, patients with low blood pressure may have inaudible or inaccurate determinations with cuff (sphygmomanometric) measurements. Chapters 1 and e29 detail blood pressure measurement (eg, cuff size and position). In this case, intra-arterial monitoring is indicated. The respiratory rate may be elevated because of anxiety or as a compensatory mechanism for the metabolic acidosis caused by lactic acidosis. Pulse or arterial oxygen saturation may be decreased because of pulmonary edema.

Mental status changes associated with circulatory shock may range from subtle fluctuations in mood or mild confusion to unconsciousness. Although the latter finding typically is indicative of more severe tissue hypoperfusion, less dramatic findings should not be interpreted as indicating the absence of shock. Similar interpretation difficulties must be considered when performing the initial physical examination. While capillary refill (rapid return of blood flow to the extremity after removal of compression) is usually impaired, an orderly progression from warm, reddish skin with appropriate capillary refill to cold, cyanotic discoloration with impaired refill may not occur.

Although the kidneys continually produce urine, the bladder stores the urine for intermittent elimination. For the initial diagnosis and management of acute circulatory insufficiency, a catheter can be inserted into the bladder for measurement of urine production. In contrast to thirst, which is a relatively insensitive indicator of volume depletion, urine production is generally diminished with inadequate kidney perfusion and increases with appropriate resuscitation. This presumes, of course, that acute kidney insufficiency or medications such as diuretics are not altering the expected response. Adults should produce at least 0.5 to 1 mL/kg/hr of urine.

Increased blood lactate concentration (above 2 mmol/L) is typically present. End organ dysfunction may be reflected in laboratory testing, such as elevated serum creatinine with renal dysfunction or elevated transaminase levels with hepatic dysfunction. The complete blood count can be variable. In the absence of infection, it may be normal. But, in septic shock, the white blood cell count is usually increased (above 12,000 cells per microliter [12×10^9/L]). In hemorrhagic shock, hemoglobin and hematocrit decrease over time; septic shock may lead to decreased platelet count. In shock, the prothrombin time and international normalized ratio may increase over time. Cardiac troponin concentrations may be increased in the setting of myocardial ischemia.

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CLINICAL PRESENTATION: Shock Syndromes

General

- Initial presentation can vary markedly, but the symptoms are typically a result of the underlying etiology of shock.

Symptoms

- Patients may report dizziness, light-headedness, confusion, or low urine production.
- Symptoms consistent with underlying shock etiology, such as cough, fever, and malaise secondary to pneumonia or chest pain secondary to acute myocardial infarction, will be present.

Signs

- Increases in heart rate (eg, >120 beats/min) and respiratory rate (eg, >30 breaths/min)
- Low blood pressure (eg, systolic blood pressure <90 mm Hg) and low or normal body temperature (eg, 36°C–37°C [96.8°F–98.6°F]) in the absence of infection. If an infection is present body temperature may be elevated (eg, above 38.3°C [101°F]).
- Impaired capillary refill time (eg, >3 seconds)
- With severe hypoperfusion, altered mental status to the point of obtundation may be observed.

Laboratory Tests

- Blood lactate concentration is typically elevated (>2 mmol/L).
- Evidence of end-organ hypoperfusion may be present (eg, elevated serum creatinine).
- Hemoglobin and hematocrit may be decreased in a bleeding patient.
- Elevated cardiac troponin concentration will be observed with acute myocardial infarction.

Other Diagnostic Tests

- Rapid assessment by cardiac echocardiography is indicated when the shock etiology is unclear.
- Advanced hemodynamic monitoring (eg, central venous catheterization) may be needed for diagnosis or treatment.

TREATMENT

6 Treatment of the patient with circulatory shock can be divided into four phases, with each having different (but sometimes overlapping) goals of treatment and therapeutic strategies.[2] The first phase focuses on salvage, where a minimum perfusion pressure and CO must be obtained to ensure the patient's survival. Concomitant treatment of the underlying etiology of the shock state should occur during this phase. Some of these treatments can be lifesaving measures. Examples include surgical/interventional procedures to achieve hemostasis, initiation of antimicrobials and source control to treat sepsis, and coronary revascularization to treat acute myocardial infarction. The second phase is optimization, where the goals shift to ensuring adequate organ perfusion and DO_2. Stabilization is the third phase, where the goal is preventing (further) end-organ dysfunction. In the fourth phase of de-escalation, facilitation of patient recovery is targeted where goals include weaning (or cessation) of vasoactive medications and fluid elimination. Although this chapter focuses on the salvage and optimization phases, recognizing the phase of a patient's circulatory shock is necessary to establish treatment goals and corresponding therapeutic approaches. The desired outcome is to reduce morbidity and mortality by preventing organ damage and, to the extent possible, reverse or halt existing organ dysfunction.

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General Approach to Treatment

Hospitalization is indicated for patients with circulatory insufficiency that does not readily respond to fluid resuscitation. If access to the circulatory system for administration of fluids and medication is not obtained prior to hospitalization, this should be a priority. Venous access generally is obtained during the preliminary examination process. Whenever large-volume fluid resuscitation is expected, as in cases of hemorrhagic or septic shock, at least two intravenous (IV) catheters are desirable. Because flow is a function of tubing length and catheter diameter, large-bore peripheral IV lines are preferred over longer central lines for initial resuscitation. Emergent and short-term peripheral IV administration of vasopressors may be necessary, but long-term administration of these medications via a central venous catheter is preferred. Unfortunately, vascular access in some patients may be problematic, and other routes such as intraosseous infusion may be necessary. Historically, using the intraosseous route to administer fluids and medications in the United States was mostly restricted to children with poor IV access but is increasingly used in adult patients. In the stabilization phase of circulatory shock treatment, general supportive and preventative care measures are necessary. Examples include appropriate assessment and management of pain, anxiety/agitation, delirium, immobility, sleep disturbances, nutrition, glycemic control, and thromboembolism risk.

Arterial blood pressure is the commonly used endpoint of therapy; however, restoration of adequate perfusion pressure is the primary criterion of effectiveness.[1,2,20] Profound hypotension (MAP <60 mm Hg) is associated with pressure-dependent decreases in coronary, cerebral, and renal blood flow and may rapidly produce myocardial, cerebral, and renal ischemia. Therefore, a goal MAP above 65 mm Hg is often targeted to maintain perfusion; however, patient-specific characteristics must be considered in establishing a blood pressure goal and determining an adequate perfusion response to resuscitation. Indeed, in patients aged 65 years or older with vasodilatory shock, a goal MAP of 60 to 65 mm Hg decreases vasopressor exposure without increasing adverse drug reactions.[37] In contrast, a goal MAP 80 to 85 mm Hg for patients with chronic hypertension leads to a less-frequent need for renal replacement therapy.[38] In order to limit further bleeding in patients with hemorrhagic shock, the blood pressure goal is SBP of 80 to 90 mm Hg with a restricted volume replacement strategy until major bleeding has been controlled.[1,39] If MAP or SBP remains below goal, then vasopressors should be initiated to ensure tissue perfusion.

Blood pressure is an insensitive parameter of resuscitation because it is affected by several hemodynamic variables (eg, blood pressure may be within the goal range when CO is inadequate). As such, additional resuscitation goals should be utilized to ensure end-organ perfusion and DO_2 are optimized. Adequate DO_2 can be ensured through evaluating CO, SvO_2, or $ScvO_2$. Instead of considering a specific CO, SvO_2, or $ScvO_2$ value as high or low based on absolute values, it is best to interpret these values as adequate, inadequate, or trend them relative to clinical response.[16] Adequacy is determined by concomitantly assessing markers of end-organ perfusion (eg, urine production), lactate concentrations, and capillary refill time. Targeting absolute values of DO_2 or its surrogates in isolation is not recommended.[1] Serial lactate concentrations are recommended in the early phases of shock treatment because lactate clearance and normalization correspond with improved global tissue perfusion.[1,22] Since blood lactate measurement does not require invasive hemodynamic monitoring, targeting lactate clearance or normalization is an attractive endpoint. Capillary refill time is a completely non-invasive peripheral perfusion marker that rapidly changes in response to treatment. Although controversial, compared with a resuscitation strategy targeting lactate decrease by 20% every 2 hours, incorporating capillary refill time normalization (<3 seconds; evaluated every 30 minutes until normalization) as a resuscitation goal decreases organ dysfunction and may improve mortality in patients with septic shock.[40,41]

After the salvage treatment phase, fluids should only be given to patients with ineffective tissue perfusion who are predicted or demonstrated to be fluid responsive. Because only about half of hemodynamically unstable patients respond to a fluid challenge,[18,19] the benefits of fluid administration (improved CO and tissue perfusion) must be balanced against the risks of fluid overload (eg, pulmonary edema). This risk/benefit determination is informed by determining fluid responsiveness, defined as demonstration or prediction of an increase in stroke volume or CO by >10% with a rapid fluid bolus.[18,19] Importantly, blood pressure change (or lack thereof) does not reliably indicate CO response to a fluid challenge.[19] Evaluating fluid responsiveness is most crucial in patients in whom the risk of detrimental fluid effects is not acceptable (eg, a patient with refractory hypoxemia). Such patients must have evidence of hypoperfusion and a reasonable likelihood of benefitting from fluids. Although commonly used, cardiac filling pressures (eg, CVP and pulmonary artery occlusion pressure [PAOP]) poorly predict fluid responsiveness; therefore, dynamic markers of fluid responsiveness should be utilized instead.[18–20] Dynamic markers of fluid responsiveness include assessments based on heart-lung interactions in mechanically ventilated patients (eg, pulse pressure variation, stroke volume variation, and inferior vena cava dimension variation) or response to the passive leg raising test (which can be used in all patients). Each of these dynamic markers has limitations to their reliability, which should be

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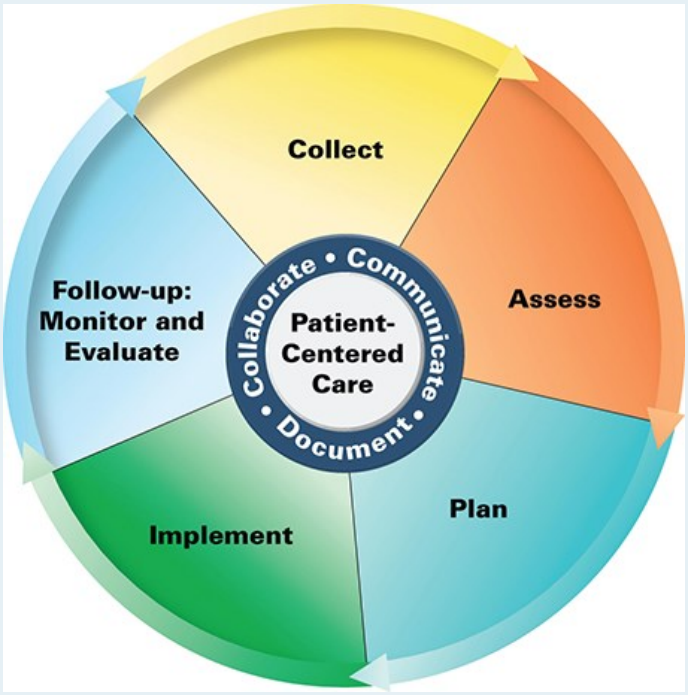
recognized prior to their employment.[19] If fluid administration is indicated, a fluid challenge technique should be utilized where the type of fluid, rate of administration, goals to be achieved, and safety limits are outlined prior to initiation.[20,42]

Non-pharmacologic Therapy

Non-pharmacologic therapy for shock is dependent on the inciting event, although the basic life support measures such as a secure airway with appropriate oxygenation apply to all patients. For patients with hypovolemic shock, additional measures would include surgery (including stabilization of fractures and surgical control of bleeding), control of blood loss by physical compression or endoscopy, and blood component transfusion. Prevention of heat loss is also warranted since hypothermia may aggravate other problems such as coagulopathy and bleeding. For patients with heat exposure (eg, heatstroke), cooling measures are indicated. Patients with thermal injuries should have the wound sites covered with cool, moist sterile dressings until more definitive care can take place. Those with cardiogenic shock secondary to acute myocardial infarction should undergo emergent coronary revascularization and be considered for CO augmentation via a mechanical device (eg, temporary percutaneous circulatory support). Non-pharmacologic therapy is frequently the treatment of choice for obstructive shock, including pericardiocentesis or surgical evacuation of fluid for cardiac tamponade, and needle decompression and/or chest tube thoracostomy for tension pneumothorax. Surgical or catheter thrombectomy are also potential treatment options for obstructive shock secondary to pulmonary embolism. Patients with vasodilatory/distributive shock secondary to septic shock should have infectious source control and consideration should be given to fever control via external cooling. Those with immune-mediated shock should have the potentially offending agent(s) discontinued and, if possible, clearance augmented.

PATIENT CARE PROCESS

Patient Care Process for Shock Syndromes



Collect

- Reason(s) for hospitalization
- History of present illness
- Patient characteristics (eg, age, sex, pregnant)
- Past medical history

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- Social history (eg, tobacco/ethanol use)
- Medication history, including intravenous fluids that have been administered
- Review of systems and physical examination findings
- Objective data (Fig. e42-4)
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Laboratory findings including lactate, hemoglobin, platelets, serum creatinine, activated partial thromboplastin time, prothrombin time
  - Capillary refill time
  - Urine production if catheterized
  - Presence of visually evident bleeding
  - Other hemodynamic or advanced monitoring data (echocardiography) if available

Assess

- Hemodynamic stability/instability (eg, systolic BP <90 mm Hg, HR >110 bpm, O_2-sat <90% [0.90])
- Non-invasive measures of circulatory insufficiency (eg, skin color, capillary refill time, and temperature; level of consciousness; urine production if catheterized)
- Dynamic markers of fluid responsiveness and advanced monitoring parameters if available
- Change in baseline organ function as evidenced by laboratory or other measures of circulatory insufficiency
- Risk for bleeding or ongoing bleeding based on objective data
- Need for vasopressors
- Type of shock syndrome (Fig. e42-2)
- Goals and wishes of patient or healthcare surrogate decision maker's goals and wishes for the patient if the patient cannot express their goals and wishes

Plan

- Surgery or procedure if needed (eg, non-compressible bleeding, coronary revascularization, and debridement of infected tissue)
- Initial focus on fluid resuscitation with type and amount of fluid based on patient-specific data (Table e42-2)
- Administer blood products as needed for hemorrhagic forms of shock (Table e42-4)
- Initiation of vasoactive medications when the patient is not responding to fluid resuscitation as is commonly seen in patients with vasodilatory/distributive forms of shock (Table e42-5)
- Temporary percutaneous mechanical circulatory support for cardiac output augmentation
- Referrals or consults to specialist providers (eg, infectious diseases providers, and hematology providers) when appropriate

Implement*

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- Ensure that all members of the interprofessional care team and patient's family/friends are aware of the plan for care
- Plan for transfer to step down unit or hospital ward after stabilization in ICU

Follow-up: Monitor and Evaluate

- Ongoing signs and symptoms of circulatory insufficiency (multiple times daily) and organ function status (at least once daily)
- Presence of adverse drug reactions
- Schedule possible follow-up visit(s) based on the status upon discharge

**Collaborate with patient, caregivers, and other healthcare professionals.*

Pharmacologic Therapy

Intravenous Fluids and Blood Products

Because IV fluids are utilized as the initial treatment for most shock syndromes, they will be considered as pharmacologic agents for this discussion. The goal of administering IV fluids is to increase venous return to subsequently increase stroke volume, cardiac output, DO_2, and blood pressure. IV fluids are typically classified as crystalloids or colloids, each with advantages and disadvantages. Blood products may also be administered to replace cellular and plasma losses with the added benefit of increasing venous return. This section reviews IV fluids and blood products, the relative advantages and disadvantages of each, and provides guidance for the clinical use of these agents.

Consensus statements for the treatment of shock and hemodynamic monitoring have been published by the European Society of Intensive Care Medicine.[1] Recommendations for shock associated with trauma are available as part of the Advanced Trauma Life Support course (http://www.facs.org/trauma/atls/) and from the Eastern Association for the Surgery of Trauma.[43] Guidelines specific to the management of major bleeding and coagulopathy after trauma, and fluid therapy in neurointensive care patients are also available.[39,44] The Surviving Sepsis Campaign also has published international guidelines for the management of patients with sepsis and septic shock.[20] Other evidence relative to fluid choice for resuscitation is available from systematic reviews,[45–47] a consensus statement on colloid use in critically ill patients,[48] and a guideline pertaining to shock resuscitation in burn patients.[49] Taken as a whole, the recommendations from all of these sources are consistent in that isotonic (or near isotonic) crystalloid solutions are the initial fluid of choice for resuscitation in patients with shock and relatively large volumes should be administered (with the notable exception of patients with cardiogenic shock).

Crystalloid solutions

7 Isotonic crystalloid (sodium-containing) solutions are the first-line fluid of choice for forms of circulatory insufficiency that are associated with hemodynamic instability. Solutions with sodium concentrations approximating normal serum sodium values usually are indicated because they cause greater expansion of the intravascular and interstitial spaces compared with dextrose solutions (Table e42-2). Lactated Ringer's and 0.9% sodium chloride ("normal saline") solutions are examples of such crystalloid solutions. Balanced salt solutions (eg, lactated Ringer's solution and multiple electrolytes injection [eg, Plasma-Lyte A; multiple products available]) and 0.9% sodium chloride have similar efficacy in expanding plasma volume but balanced salt solutions may be safer. Excess chloride administration with infusions of 0.9% sodium chloride may lead to hyperchloremic metabolic acidosis and possibly acute kidney injury, which may be less likely to occur with balanced salt solutions. Large pragmatic, cluster-randomized, multiple-crossover studies of critically ill and non-critically ill patients suggest that balanced salt solutions are less frequently associated with major adverse kidney events within 30 days (a composite outcome of death from any cause, new renal-replacement therapy, or serum creatinine level at least 200% of the baseline level).[50,51] In these studies, the effect size of major adverse kidney events was small (about 1% absolute risk difference between groups) and no single component of the composite outcome was significantly different between groups. The study in 15,802 critically ill patients showed less renal dysfunction and numerically lower mortality (but not statistically significant) with balanced salt solutions compared to 0.9% sodium chloride, although the effects sizes were small for both outcomes.[51] Serum chloride concentrations were consistently lower and serum bicarbonate concentrations were consistently higher with balanced crystalloids over the first week of study. A large trial randomized critically ill patients to receive

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balanced salt solution or 0.9% sodium chloride for all fluid needs in the ICU, including fluid challenges, maintenance fluids, and drug admixtures (up to 100 mL), and found similar 90-day mortality rates.[52] Importantly, because balanced salt solutions may exacerbate cerebral edema in brain-injured patients, a pre-specified subgroup analysis was performed in patients with traumatic brain injury. This subgroup analysis found higher mortality in patients randomized to balanced salt solution; therefore, balanced salt solutions should be used with extreme caution in brain-injured patients (Table e42-3). Despite conflicting results of large trials, no study has shown the superiority of 0.9% sodium chloride over balanced salt solutions, and practice is shifting toward balanced salt solutions. Concerns have been raised relative to the administration of balanced salt solutions in patients with pre-existing hyperkalemia (because the solutions contain potassium), but these concerns have not been substantiated in clinical trials.[53]

TABLE e42-2

Fluid Distribution and Major Indications[a]

Fluid	Intracellular	Interstitial	Intravascular	Major Indication
0.9% Sodium chloride, lactated Ringer's, or multiple electrolytes (eg, Plasma-Lyte A)	None	750 mL	250 mL	Intravascular volume expansion
3% Sodium chloride	→	750 mL+	250 mL+	Small boluses (eg, 150-300 mL) and/or intermittent infusions used for patients with elevated intracranial pressure or those with symptomatic hyponatremia
5% Dextrose / 0.45% sodium chloride	333 mL	500 mL	167 mL	Maintenance fluid in euvolemic or dehydrated (sodium and water loss) patients with mild signs/symptoms of volume depletion
5% Dextrose	667 mL	250 mL	83 mL	Dehydration (primarily water loss) in patients with mild signs/symptoms of volume depletion
5% Albumin	None	None	1,000 mL[b]	Intravascular volume expansion
25% Albumin	→	→	1,000 mL+++[b]	Given by intermittent infusion to expand the intravascular volume via recruitment of volume from the interstitial space (eg, after large-volume paracentesis)

[a]Based on the administration of 1 L of each solution *for comparative purposes only.* This amount of fluid, particularly for 3% saline and 25% albumin, would be inappropriate and likely harmful if given over a short period of time. Numbers are approximations and are likely not reflective of actual fluid distribution in critically ill patients; arrows indicate the direction of fluid shift and plus signs indicate fluid pulled from other compartments.

[b]After distribution and attainment of steady-state conditions, 60% of albumin (and associated fluid) is in the interstitial compartment and 40% is in the intravascular compartment.

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TABLE e42-3

Adverse Effects of Plasma Expanders

Balanced salt solutions (lactated Ringer's or multiple electrolytes [eg, Plasma-Lyte A]) • Primarily extensions of pharmacologic actions (eg, fluid overload, dilutional coagulopathy) • Hyponatremia with lactated Ringer's (has 130 mEq/L [mmol/L] of sodium); because multiple electrolytes (eg, Plasma-Lyte A) has 140 mEq/L (mmol/L) of sodium, this is not a concern with this solution
0.9% Sodium chloride ("normal saline") • Primarily extensions of pharmacologic actions (eg, fluid overload, dilutional coagulopathy) • Hyperchloremic metabolic acidosis (contains 154 mEq/L [mmol/L] of chloride) • Hypernatremia (contains 154 mEq/L [mmol/L] of sodium) • Acute kidney injury (from hyperchloremia)
3% Sodium chloride ("hypertonic saline") • Primarily extensions of pharmacologic actions (eg, fluid overload, dilutional coagulopathy, and intracellular volume depletion) • Hypernatremia (contains 513 mEq/L [mmol/L] of sodium) • Hyperchloremia (contains 513 mEq/L [mmol/L] of chloride)
Albumin • Primarily extensions of pharmacologic actions (eg, fluid overload; dilutional coagulopathy) • Amino acid profile and catabolism alterations (clinical significance?); potential protein overload if given with exogenous protein (eg, parenteral nutrition) • Anaphylactoid/anaphylaxis reactions (life-threatening reactions rare; higher in patients with immunoglobulin A deficiency) • Interactions with medications and nutrients (clinical significance varies) • Renal dysfunction with hyperoncotic albumin

Although lactated Ringer's solution contains lactate, it does not cause substantial elevations in circulating lactate concentrations when used as a resuscitation solution.[54] Once adequate plasma volume has been restored by fluid administration, the body can readily clear the blood of the excess lactate that has accumulated from both anaerobic metabolism and lactated Ringer's solution. However, blood samples for lactate determinations drawn through catheters (arterial and venous) that have not been cleared appropriately may have spurious increases or decreases in lactate concentrations because of retained lactated Ringer's and nonlactated solutions (eg, varying concentrations of dextrose-in-water or sodium chloride), respectively. Therefore, blood samples for lactate concentration determinations should be drawn from a catheter that has been cleared adequately (eg, 5 mL) of infusate after temporarily stopping the fluid infusion.

Alternative Fluid Treatments

Hypertonic sodium chloride solutions have been studied as alternatives to isotonic crystalloid solutions for hypovolemic shock, particularly in patients with traumatic brain injuries. By causing redistribution (ie, pulling fluid) from the intracellular space, hypertonic solutions cause rapid expansion of the intravascular compartment, which is essential for vital organ perfusion. In head-injured patients, it has been postulated that this redistribution should decrease intracranial pressure because the vessels of the brain are more impermeable to sodium ions than are vessels in other areas of the body. Additionally, hypertonic sodium chloride solutions have beneficial immunomodulating actions when compared with more isotonic solutions in experiments with animals. Unfortunately, the theoretical benefits associated with hypertonic sodium chloride solutions have not translated into improved outcomes when used for the initial resuscitation of patients with shock.

From a safety standpoint, hypertonic sodium chloride is a high-risk concentrated electrolyte solution. Potential dosing and administration errors and

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related adverse events can occur when hypertonic sodium solution is ordered and administered by clinicians relatively unfamiliar with its use. Potential adverse events include cellular crenation and damage caused by the dramatic fluid shifts associated with hypernatremia, metabolic acidosis from hyperchloremia, and peripheral vein destruction from high osmolality. The osmolarity of 3% sodium chloride is 1,026 mOsm/L. Although there are some notable exceptions (eg, peripheral parenteral nutrition solutions often approach 1,000 mOsm/L), IV solutions with osmolarity values above 600 mOsm/L are usually recommended to be administered through a central line. In the limited number of studies conducted in humans to date, adverse effects have been uncommon with short-term administration of hypertonic (2-3%) sodium solutions administered through a peripheral line.

Larger-molecular-weight solutions (ie, >30,000 Da) known as *colloids* have been recommended in conjunction with or as replacements for crystalloid solutions, although their use is controversial.[20] The major theoretical advantage of these compounds is their prolonged intravascular retention time compared with crystalloid solutions. In contrast to isotonic crystalloid solutions that have substantial interstitial distribution within minutes of IV administration, colloids remain in the intravascular space for hours or days, depending on factors such as the size of the colloid molecules and capillary permeability. Examples of colloids used as plasma expanders in the United States include albumin, hydroxyethyl starch, and much less commonly, dextran. In the absence of increased capillary permeability, the theoretical benefit of colloids over crystalloids is that their increased molecular weight increases intravascular oncotic pressure, leading to enhanced intravascular volume expansion and longer retention time.

However, even in patients with intact capillary permeability, small and intermediate size colloid molecules, such as albumin, eventually leak through capillary membranes, with a few notable exceptions (eg, those in the central nervous system and glomeruli). In the case of albumin with a distribution half-life of 15 hours in normal subjects, approximately 60% of administered albumin molecules (and associated fluid) shifts to the interstitial space within 3 to 5 days of exogenous administration. In patients with altered vascular permeability (eg, sepsis), the leakage of albumin from the intravascular to the interstitial space may occur within hours, not days. The primary adverse effect concern of all colloids is fluid overload, which is an extension of their pharmacologic action. Excessive fluid administration has been shown to increase capillary permeability through disruption of the endothelial glycocalyx. Another adverse effect of increasing concern is renal dysfunction that seems to be related to hyperoncotic (eg, 25%) albumin and other starch and dextran products. The mechanism of this adverse effect may be related to alteration of normal glomerular oncotic pressure differences or formation of lesions in the kidney.[55]

Albumin is available in the United States in 5% and 25% concentrations. Plasma protein fraction has oncotic actions similar to a 5% albumin solution, which is not surprising because albumin is the predominant protein in this product. When given in equipotent amounts, albumin is much more costly than crystalloid solutions. Additionally, the 5% and 25% albumin solutions typically are priced such that no cost savings are associated with dilution of the 25% product to make a 5% concentration. Dilution should be avoided because of the possibility of preparation errors. Hemolysis and death have occurred when 25% albumin was inappropriately diluted with sterile water for injection, due to a dramatic lowering of effective osmolarity.[56] The 5% albumin solution is relatively *iso-oncotic*, which means that it does not pull fluid into the compartment in which it is contained. In contrast, 25% albumin is referred to as *hyperoncotic* albumin, because it tends to pull fluid into the compartment containing the albumin molecules. In general, the 5% albumin solution is used for shock states with inadequate venous return. The 25% solution should not be used for acute circulatory insufficiency unless it is used in combination with other fluids or it is being used in patients with excess total body water but intravascular depletion as a means of pulling fluid into the intravascular space. An example of the latter condition is cirrhosis with ascites in which total body water is substantially increased, but the patient is hypotensive because of a lack of intravascular volume. For this approach to be cost-effective, one must presume that excess water (eg, interstitial fluid accumulation in the lungs) is associated with adverse effects, and albumin remains in the intravascular space long enough to be beneficial. Albumin has a variety of functions beyond plasma expansion, such as binding properties, inflammatory gene modification, and antioxidant and free radical scavenging effects, which have been used to justify its administration instead of less-expensive crystalloid or other colloid products. Although appealing theoretically, improved patient outcomes related to these properties have not been documented in sufficiently powered, randomized controlled trials. Additionally, the clinician must realize that the properties of commercially available albumin products are not biologically identical to those of native albumin. For example, denaturation of the products may lead to inefficient binding and decreased oncotic activity.

From a historical perspective, the so-called crystalloid versus colloid debate was intensified when a meta-analysis found an overall increase in mortality associated with albumin using pooled results of randomized investigations.[57] With the notable exception of trauma patients, a subsequent and more comprehensive systematic review did not find increased mortality attributable to albumin.[58] These conflicting findings prompted the design and completion of a landmark investigation in critically ill patients, which did not detect a statistically significant difference in 28-day mortality between patients treated with 0.9% sodium chloride or 4% albumin.[59] In a subset of patients with severe traumatic brain injury, mortality in those receiving

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albumin was significantly higher at 24 months, an effect that seemed to be confined to patients with severe injury.[60] This multicenter, randomized, double-blind investigation, the Saline versus Albumin Fluid Evaluation (SAFE) study, involved a heterogeneous group of ICU patients and was not sufficiently powered to look at various subsets. So clinicians must be cautious when extrapolating the results to more specific patient populations. Additionally, the assigned study fluid was used throughout the 28-day study period for volume expansion; therefore, this study was not exclusively an evaluation of the initial phase of fluid resuscitation and the implications of the study findings in that setting are unclear. The results of meta-analyses that include this large study are conflicting with regard to a survival benefit associated with colloid administration; however, they are in agreement that resuscitation with albumin achieves higher values of CVP and MAP more rapidly than crystalloid fluids with a lower overall fluid balance.[61–64] A randomized study of patients with sepsis also showed that albumin 20% achieved higher MAP despite a lower net fluid balance compared to crystalloid solutions but mortality rates were similar.[65]

Colloids are expensive solutions and whether these beneficial outcomes confer cost-benefit over crystalloids has not been established. While the use of albumin in specific patient populations (eg, septic shock) is still debated, a systematic review and meta-analysis found that when compared with alternative resuscitation solutions, hydroxyethyl starch was associated with increased mortality, increased acute kidney injury, and increased use of renal replacement therapy.[66] In light of these studies, US product labeling of all medications in the class was changed to state they are contraindicated in critically ill patients; therefore, starch products should not be used for fluid resuscitation.

Blood Products

In the case of a patient with hemorrhage, prompt attention must be given to cellular as well as plasma losses. Red blood cells lost during the bleeding episode may lead to ischemic damage in vital organs. Packed red blood cell transfusions may be needed to increase the oxygen-carrying capacity of the blood because oxygen transport is a function not only of CO but also of hemoglobin concentration and saturation, and of hemoglobin affinity for oxygen. Red blood cells contain hemoglobin that delivers oxygen to tissues. Neither crystalloids nor colloids perform this function. Although a small group of trauma patients respond to the initial fluid bolus and remain stable, most patients respond initially and then deteriorate. The latter patients, as well as patients with blood loss associated with surgery and those with gastrointestinal hemorrhage, frequently need blood components such as packed red blood cells (Table e42-4).

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TABLE e42-4

General Indications and Concerns for Blood Products and Prothrombin Complex Concentrates[a]

Product	Major Indication	Major Concerns
Packed red blood cells	Increase oxygen-carrying capacity of blood. Usually indicated in patients with continued deterioration after volume replacement or obvious exsanguination	Hypocalcemia, hyperkalemia, hyperphosphatemia, circulatory overload, ARDS (lowest risk among blood products), immunomodulation, transfusion reactions, hypothermia, and virus transmission
Fresh frozen plasma	Replacement of clotting factors. Overused; indicated if ongoing hemorrhage in patients with PT/PTT >1.5 times normal, prolonged initial fibrin formation (R value) on viscoelastic testing, severe hepatic disease, or other bleeding diathesis	Hypocalcemia, circulatory overload, ARDS (highest risk among blood products, particularly transfusions from female donors), immunomodulation, transfusion reactions, hypothermia, and virus transmission
Platelets	Used for bleeding due to severe thrombocytopenia (ie, platelet count <20,000/μL [20×10^9/L]), rapidly dropping platelet counts as would occur with massive bleeding, or decreased clot strength (maximum amplitude value) on viscoelastic testing	Hypocalcemia, circulatory overload, ARDS, immunomodulation, transfusion reactions, hypothermia, and virus transmission
Cryoprecipitate	Contains concentrated fibrinogen, von Willebrand factor, factor VIII, and factor XIII. Not indicated in acute hemorrhage but rather used after specific deficiencies are identified (eg, decreased rate of clot formation [alpha value] on viscoelastic testing)	Hypocalcemia, circulatory overload, ARDS, immunomodulation, transfusion reactions, hypothermia, and virus transmission
Prothrombin complex concentrates (PCCs)	The most commonly used product contains inactivated factors II, VII, IX, and X, and Proteins C and S. Another product contains activate factors. Used for reversal of antithrombotic agents in the setting of acute major bleeding or prior to urgent surgery/invasive procedure.	Thrombosis (arterial and venous), anaphylactic reactions, and viral transmission. Some products contain heparin and should not be given to patients with heparin-induced thrombocytopenia

ARDS, acute respiratory distress syndrome; PT, prothrombin time; PTT, partial thromboplastin time.

[a]Although whole blood can be used for large-volume blood loss, most hospitals use component therapy, and use crystalloids or colloids for plasma expansion.

Administration of excessive blood products may be counterproductive. In the case of red blood cells, attempts to raise the hemoglobin to high-normal or supranormal concentrations may decrease oxygen delivery by increasing blood viscosity. Stored red blood cells undergo biochemical alterations to reduce oxygen dissociation at the tissue level which may explain why studies do not demonstrate increased end-organ DO_2. Additionally, there are concerns of hyperkalemia, hyperphosphatemia, and immunomodulation with red blood cell administration. Many institutions curtailed a more liberal transfusion strategy (transfusion threshold less than 10 g/dL [100 g/L; 6.21 mmol/L]) following the publication of a randomized, multicenter trial of critically ill patients that found 30-day mortality to be similar between this strategy and the use of a lower hemoglobin concentration threshold for transfusion (less than 7 g/dL [70 g/L]; 4.34 mmol/L).[67] Although the investigators were cautious about extrapolating the results of this investigation, subsequent studies performed in patients with acute upper gastrointestinal hemorrhage, septic shock, and those undergoing cardiac surgery found similar results with a restrictive transfusion strategy (transfusion threshold of hemoglobin concentration ≤7 g/dL [70 g/L; 4.34 mmol/L]).[68–70] In fact, liberal transfusion strategies were associated with increased bleeding in patients with acute upper gastrointestinal hemorrhage and higher mortality in critically ill patients with lower severity of illness. Furthermore, even in patients with acute myocardial infarction, a transfusion threshold hemoglobin concentration ≤8 g/dL (80 g/L; 4.97 mmol/L) was non-inferior to a transfusion threshold hemoglobin concentration ≤10 g/dL (100 g/L; 6.21 mmol/L) in preventing major adverse cardiac events at 30 days.[71] With the exception of the critically ill or perioperative patients with acute exsanguination, there is little justification for a liberal transfusion strategy based solely on hemoglobin concentrations.

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Clotting factors may be lost from bleeding or consumed through hemostatic mechanisms requiring replacement. Laboratory parameters or viscoelastic testing (eg, thromboelastography) may guide blood product administration.[39] Blood products that contain clotting factors include fresh frozen plasma, platelets, and cryoprecipitate (Table e42-4). Concentrated products available as a lyophilized powder for reconstitution (eg, prothrombin complex concentrates or fibrinogen concentrate) are increasingly used as alternatives to traditional blood products because they are not associated with hypervolemia or immunomodulation. However, they may enhance the risk of thromboembolic events. Reversal agents for antithrombotic-associated bleeding may also be administered (eg, prothrombin complex concentrates for warfarin, idarucizumab for dabigatran, and andexanet alfa for factor Xa inhibitors).

Blood products have risks beyond immunomodulation. There is a rare but important risk of virus transmission (eg, human immunodeficiency virus and hepatitis). Citrate that is added to stored blood products to prevent coagulation may bind to calcium, resulting in hypocalcemia. In patients receiving large amounts of blood products, prophylactic calcium administration may be warranted until levels are available. Potassium and phosphate concentrations often are elevated in stored packed red blood cells, particularly when hemolysis has occurred during storage. Additionally, blood product administration may be associated with acute respiratory distress syndrome (particularly with fresh frozen plasma and platelets) or circulatory overload. Other issues that must be considered with blood product administration include monitoring for transfusion-related reactions and attention to appropriate warming, particularly when large volumes are given to pediatric patients because hypothermia is associated with increased fluid requirements and mortality.

Fluid Resuscitation in Distributive (Septic) Shock

In patients with distributive shock, the initial fluid challenge volume is unclear. While the Surviving Sepsis Campaign guidelines suggest 30 mL/kg crystalloids given within the first 3 hours of shock recognition, the evidence to support this specific volume for administration is low quality.[20] Multiple approaches exist for fluid resuscitation during the first 6 hours of therapy. One initial approach includes liberal fluid administration (50-75 mL/kg) while reserving vasopressors, and another approach includes relatively restrictive initial fluid administration (≤30 mL/kg) with earlier use of vasopressors to maintain tissue perfusion. Both approaches have rational because early aggressive fluid resuscitation can restore effective venous return (and thus increase cardiac output) but can also contribute to edema within organs that impairs their function. A comparison of these initial resuscitation approaches is ongoing.[72] Greater than 30 mL/kg of crystalloid fluids in total may be needed to obtain goal MAP, reverse global hypoperfusion (lactate clearance, $ScvO_2$ ≥70% [0.70]), or achieve clinical indication of regional organ-specific perfusion (eg, urine production). An isolated bolus (eg, 250-500 mL) in an adult patient with shock is unlikely to cause a substantial change in blood pressure or acid-base balance. Therefore, multiple fluid boluses are often needed in such patients to achieve hemodynamic stability. However, excessive fluid administration has been associated with higher mortality and overly aggressive fluid administration should be avoided, especially in patients with heart failure or impending pulmonary edema.[55] Also, IV medication diluents can contribute significantly to total fluid volume administration during a patient's ICU stay and, when 0.9% sodium chloride is utilized, can contribute to hyperchloremia and possibly acute kidney injury.[73] Therefore, total fluid administration should be accounted for, and dynamic fluid response with clinical assessment should occur frequently following each fluid challenge.[20]

Fluid Resuscitation in Hypovolemic (Hemorrhagic/Traumatic) Shock

The need for immediate treatment of hemorrhagic shock with plasma expanders (ie, crystalloids or colloids) seems obvious, but no large, well-controlled trials conducted in humans have supported this practice. To the contrary, fluid resuscitation beyond minimal levels (ie, mean arterial pressure ≥60 mm Hg) is harmful in patients with penetrating abdominal trauma due to hemodilution and clot destabilization. One prospective study of adult patients with gunshot or stab wound injuries to the torso and an SBP of 90 mm Hg or less found that delayed fluid resuscitation until the operation was associated with increased survival and discharge from the hospital.[74] Since concerns were expressed about the comparability of the immediate and delayed resuscitation groups, particularly because true randomization did not take place, a follow-up randomized trial was conducted to verify the findings. There were no differences in survival (four deaths in each group) in the second trial regardless of whether systolic blood pressure was titrated to ≥100 mm Hg or 70 mm Hg.[75] Both studies were conducted in populated urban areas with approximately 2 hours from the time of injury to operation. Therefore, the results may not be applicable to rural areas with extended transport times. There also is a concern in applying the results of these investigations to patients with certain kinds of single-system injuries, particularly head trauma, where cerebral perfusion pressure is of primary importance.

The administration of hypertonic sodium chloride solutions requires less overall fluid than isotonic solutions; therefore, it stands to reason those

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concerns regarding the dilutional effect of isotonic solutions could be minimized with hypertonic saline solutions. In order to address ongoing questions of efficacy, hypertonic sodium chloride solutions with or without a colloid (ie, 7.5% sodium chloride or 7.5% sodium chloride in 6% dextran 70) for prehospitalized trauma patients with shock and traumatic brain injury were evaluated in two trials conducted by a network of sites known as the Resuscitation Outcomes Consortium. Both the parallel trials were stopped when it was determined that the hypertonic sodium chloride solutions were no better than 0.9% sodium chloride ("normal saline") and further enrollment would not change the outcomes.[76,77] Therefore, isotonic crystalloids are the fluid of choice since they are equal in efficacy with a lower risk of adverse effects compared with hypertonic solutions that are high-risk electrolyte solutions. Balanced salts solutions may be used as an alternative solution to 0.9% sodium chloride but should be avoided in patients with severe traumatic brain injury because it may worsen cerebral edema.[39] Given their relatively poor intravascular expansion and association with poor outcome in animal models of closed head injury, hypotonic solutions should be avoided in this population.

Although the applicability of the aforementioned studies to other populations and settings is debatable, the *presumption* of benefits from immediate plasma expansion in all preoperative patients with circulatory insufficiency caused by hemorrhage is no longer valid. Instead, the initial priority should be surgical control of the bleeding source. Until this is possible, fluids should be given in small aliquots to yield a palpable pulse and to maintain MAP no more than 60 mm Hg and SBP no more than 90 mm Hg based on accurate measurements (eg, arterial monitoring). Approaches also should be used to avoid or decrease acute traumatic coagulopathy, which is the result of the combination of bleeding-induced shock, tissue injury-related thrombin-thrombomodulin-complex generation, and activation of anticoagulant and fibrinolytic pathways.[39]

The periodic shortages, high costs, and adverse effects related to blood products have prompted investigations of alternative "bloodless" strategies. In addition to the use of more restrictive transfusion thresholds, as mentioned previously, these strategies have included hemoglobin-based oxygen carriers and perfluorocarbon compounds to deliver oxygen to tissues. Other strategies have aimed at reducing blood loss using improved procedural and surgical techniques, as well as the administration of hemostatic medications. Reversal of antithrombotic agents (eg, prothrombin complex concentrates for patients receiving warfarin) should be considered in the context of the patient's degree of bleeding or operative plan and their indication for antithrombotic therapy. However, the only hemostatic medication with a proven mortality benefit is the antifibrinolytic agent tranexamic acid. The best evidence for efficacy was data from a multicenter trial involving adult trauma patients with significant bleeding (or risk for significant bleeding) who were randomized to IV tranexamic acid 1 g over 10 minutes followed by 1 g over 8 hours by infusion or matching placebo within 8 hours of injury.[78] There was a significant reduction in all-cause mortality with tranexamic acid compared with placebo with no increase in vascular or other adverse events. A more in-depth review of the results of this trial suggests that the beneficial effects are most likely to occur if tranexamic acid is given within the first 3 hours of injury. In a subsequent trial of patients with traumatic brain injury, the same tranexamic acid dosing strategy given within 3 hours of injury reduced head injury-related death within 28 days in patients with a mild-to-moderate head injury, but not in patients with a severe head injury.[79] These studies are relatively unique in that an intervention other than surgery and blood product administration reduced mortality.

In the bleeding patient, once hemostasis has been achieved, a more restrictive transfusion strategy (ie, transfusion if hemoglobin ≤7 g/dL [70 g/L; 4.34 mmol/L]) is indicated.[39] Additional blood product administration should be guided by laboratory parameters (eg, PT/INR and platelets) or viscoelastic testing (eg, thromboelastography).[39] Reversal of antithrombotic therapy (eg, prothrombin complex concentrates for warfarin) may also be utilized for severe bleeding.

Vasopressors and Inotropes

8 Vasopressors and inotropes are required in patients with shock when volume resuscitation is not indicated or fails to maintain adequate blood pressure (MAP ≥65 mm Hg) and organs and tissues remain hypoperfused.[1,2,8,20,27] In addition, vasopressors may be needed temporarily to treat life-threatening hypotension when tissue perfusion is inadequate despite ongoing aggressive fluid resuscitation. Inotropes are frequently used to optimize DO_2 in cases of septic shock and cardiac function in cases of cardiogenic shock.[1,2,11,20] The clinician must decide on the choice of agent, therapeutic endpoints, and safe and effective doses of vasopressors and inotropes to be used. This section provides guidance for the clinical use of adrenergic agents, optimization of pharmacotherapeutic outcomes, and minimization of adverse drug reactions in critically ill patients. Vasopressin, angiotensin II, and corticosteroids, as they relate to shock, also are emphasized because they have pharmacologic interactions with catecholamine vasopressors, possess hemodynamic effects, and are frequently used.

9 The choice of a particular vasopressor or inotrope agent depends on the underlying shock pathophysiology, goals of therapy, and clinical

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pharmacology of the agent(s).[27] Table e42-5 lists receptor selectivity, typical dosage ranges, and potential adverse drug reactions of commonly used vasopressors and inotropes.[26–29,80] In most shock syndromes, limited literature exists to guide optimal agent selection. Dosages for norepinephrine, epinephrine, and phenylephrine may be weight based (μg/kg/min) or non-weight based (μg/min). Although controversial, there does not appear to be an effectiveness or safety difference between these dosage strategies.[81] The dosage strategy utilized is typically based on institutional preference. Only dopamine and dobutamine are commercially available as premixed ready-to-use solutions that can be stored in automated dispensing systems for rapid initiation. The use of other vasopressors and inotropes requires preparation time. Institutions may stock compounded admixtures in preparation for administration but they must follow sterile compounding and storage regulations.

Catecholamine vasopressors may result in adverse peripheral vasoconstrictive, metabolic, and arrhythmogenic effects that limit or outweigh their positive effects on the central circulation.[26–29] Excessive peripheral vasoconstriction with catecholamine vasopressors may cause ischemia or necrosis of already poorly perfused tissues, such as the skin and the mesenteric and splanchnic circulations. Some of these profound vasoconstrictive effects may be compounded by under-resuscitation with fluid administration prior to initiating the vasopressor. Vasopressor catecholamines also have the potential to cause extravasation-associated tissue damage if infusions infiltrate during peripheral administration. In the event of infiltration, an α-receptor antagonist such as phentolamine (5 or 10 mg in 10 mL saline) should be injected intradermally or nitroglycerin paste applied topically to reverse local vasoconstriction. β_1 cardiac stimulation may produce myocardial ischemia and atrial and ventricular arrhythmias, especially in patients with coronary artery disease, atherosclerosis, cardiomyopathies, left ventricular hypertrophy, congestive heart failure, or underlying dysrhythmias. All catecholamine vasopressors, especially epinephrine, stimulate β2-adrenergic receptors on immune cells, leading to immunomodulatory actions. Catecholamines inhibit the production of inflammatory cytokines (eg, IL-6, TNF-α), may enhance anti-inflammatory cytokines (eg, IL-4 and IL-10), suppress oxygen-free radical production from neutrophils, and direct proapoptotic effects. These anti-inflammatory effects may be either beneficial (by dampening harmful effects of oxygen-free radical-mediated tissue injury) or deleterious (by reducing neutrophilic defense against bacteria). While epinephrine is most associated with these immunomodulatory effects, the clinical significance of these actions remains unknown.

Clinical Pharmacology and Pharmacodynamic Effects

Norepinephrine

Norepinephrine has combined strong α_1-activity and less potent β_1-agonist effects while maintaining weak vasodilatory effects of β_2-receptor stimulation. It produces vasoconstriction primarily via its more prominent α-effects on all vascular beds, thus increasing SVR.[26–28,80] Norepinephrine administration produces a small (10%-15%) increase in stroke volume.[27] Several meta-analyses have demonstrated improved MAP and mortality in ICU patients with severe hypotension treated with norepinephrine either as first-line therapy or after therapeutic failure with fluid resuscitation treatment.[1,20,80,82]

Norepinephrine 0.05 to 2 μg/kg/min reliably and predictably improves hemodynamic parameters to “normal” values in most patients with shock. As with other vasopressors, norepinephrine dosages exceeding those recommended by most references are frequently needed in critically ill patients with shock to achieve goals. A significant increase in MAP is caused by an increase in SVR. Heart rate generally decreases with norepinephrine because of reflex bradycardia from increased SVR.[26–28,80] Increasing norepinephrine doses may increase heart rate, cardiac index, DO_2, and cutaneous blood flow but these results are inconsistent. Older patients may benefit from the combined α- and β-adrenergic effects of norepinephrine, given the higher prevalence of coronary disease and compromised ventricles in this patient population. By virtue of restored MAP and hence coronary perfusion, the cardiac index is increased in older patients, whereas in younger patients with less coronary artery disease and a higher cardiac index at baseline, norepinephrine acts primarily as a vasoconstrictor. Norepinephrine can increase cardiac filling pressures (eg, CVP) by increasing venous return through vasoconstriction, but this effect is inconsistent.[83–85]

The effect of norepinephrine on oxygen transport parameters is variable and depends on baseline values and concurrently administered vasoactive agents. In most studies of norepinephrine alone, either an increase or no change in DO_2 is seen with no change in O_2ER, particularly when DO_2 values were “supranormal” prior to therapy. Splanchnic blood flow and fractional blood flow are higher with norepinephrine than dopamine or epinephrine despite higher CO with the two latter agents.

Epinephrine

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Epinephrine exerts combined α- and β-agonist effects.[26–28,82] At low dosages (0.01-0.05 µg/kg/min), β-adrenergic effects predominate with an increase in stroke volume and CO. For this reason, low dosages of epinephrine may be utilized as an inotrope after cardiac surgery. When higher epinephrine dosages are used α-adrenergic effects are predominantly observed and SVR and MAP are increased. Epinephrine is an acceptable choice for hemodynamic support for patients with shock because of its combined vasoconstrictor and inotropic effects.[26–28,82,86] It is as effective as norepinephrine for MAP response in vasodilatory/distributive shock. Epinephrine dosages of 0.04 to 1 µg/kg/min alone increase hemodynamic and oxygen transport variables to "supranormal" values in shock patients without coronary artery disease. Large dosages (0.5-3 µg/kg/min) often are required, particularly for patients with septic shock. Smaller dosages (0.1-0.5 µg/kg/min) are effective when epinephrine is added to other vasopressors and inotropes. In addition, younger patients respond better to epinephrine, possibly due to greater β-adrenergic reactivity.

Despite a linear dose-response curve with rapid improvement of hemodynamic variables and DO_2, epinephrine has deleterious effects on regional hemodynamics and oxygen utilization. Although DO_2 increases mainly as a function of increases in the CO, a more variable increase in SVR is observed, VO_2 may not increase, and O_2ER may fall. A decrease in gastric mucosal perfusion may be seen during epinephrine administration but this effect can be counteracted in part by dobutamine. This may be explained by the vasodilatory effect of dobutamine on gastric mucosal microcirculation resulting in a redistribution of blood flow toward the mucosa. When compared with a combination of norepinephrine and dobutamine, epinephrine preferentially decreases splanchnic DO_2 without increasing VO_2. The effects of epinephrine on absolute and fractional splanchnic blood flow are more pronounced during severe shock. However, epinephrine, in contrast to dopamine, increases the proportion of total CO delivered to the splanchnic circulation, although VO_2 is not increased sufficiently. As a result, O_2ER values are usually lower with epinephrine than with other vasopressors but the concomitant administration of dobutamine helps maintain O_2ER.

In contrast to other vasopressors, lactate concentrations frequently rise during epinephrine therapy resulting in variable arterial pH values. The increase in lactate may be a result of worsened DO_2 to the liver (and subsequent anaerobic metabolism) or to the hepatosplanchnic circulation, a direct increase in calorigenesis, and breakdown of glycogen (enhanced aerobic lactate production via β_2-adrenergic receptor stimulation), or lactate mobilization. Of all the vasopressors, epinephrine exhibits the most pronounced capacity to induce hyperglycemia by increased gluconeogenesis and glycogenolysis with α-mediated suppression of insulin secretion.

Phenylephrine

Phenylephrine is essentially a pure α_1-agonist and increases blood pressure primarily through vasoconstriction.[26–28,82] Given the presence of cardiac α_1-receptors, phenylephrine also may increase contractility and CO, although variable effects on CO are observed. It is a therapeutic option in hypotensive patients experiencing a tachyarrhythmia when a vasopressor with minimal to no β_1-agonist activity is indicated.[27,28]

Phenylephrine is a selective α_1-agonist with primarily vascular effects.[26–28,82] As with other vasopressors, phenylephrine dosages required to achieve goals of therapy are significantly higher than dosages traditionally recommended for use. Phenylephrine 0.5 to 9 µg/kg/min, used alone or in combination with dobutamine or low dosages of dopamine, improves blood pressure and myocardial performance in fluid-resuscitated patients with vasodilatory/distributive shock. Incremental doses of phenylephrine result in linear dose-related increases in SVR and MAP when administered alone in stable, normotensive but hyperdynamic, volume-resuscitated surgical ICU patients. In septic shock, phenylephrine does not significantly impair the cardiac index, PAOP, or peripheral perfusion. Phenylephrine improves MAP by increasing SVR and stroke index through an enhanced venous return to the heart.

In septic shock, phenylephrine increases global tissue oxygen use, although data regarding the relationship of the oxygen-transport variables with increases in MAP and cardiac index are conflicting. Increases in VO_2 are dissociated from DO_2, representing an increase in O_2ER, as the cardiac index remains unchanged. Increases in VO_2 may result from redistribution of blood flow to previously under perfused areas, improving oxygen use because of changes in MAP and SVR. Evidence of globally improved peripheral tissue perfusion is observed as lactic acid concentration declines or remains unchanged and urine production increases significantly at increased or maximal VO_2. An increased O_2ER may contribute to improved tissue response.

Few data regarding the effect of phenylephrine on regional hemodynamics and oxygen transport variables are available. When phenylephrine

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replaced norepinephrine in patients with septic shock, phenylephrine selectively reduced splanchnic blood flow, DO_2, and lactate uptake rate without changing the overall splanchnic VO_2. Concomitantly, arterial lactate concentrations increased. Because all these parameters normalized when norepinephrine was reinstated, these data suggest that exogenous β-adrenergic stimulation (with norepinephrine) may determine hepatosplanchnic perfusion and oxygen availability but not utilization in septic shock. Phenylephrine and norepinephrine demonstrate similar short-term hemodynamic profiles and indices of global and regional perfusion when used as an initial vasopressor in septic shock.[26–28]

Dopamine

Dopamine has been described as having dose-related receptor activity at D_1-, D_2-, β_1-, and α_1-receptors.[26–29,80] This dose-response relationship has not been confirmed in critically ill patients. In patients with shock, a significant overlap of hemodynamic effects occurs, even at dosages as low as 3 µg/kg/min. Historically, dopamine was frequently utilized but is no longer considered a first-line therapy for shock.[20,27]

Dopamine is a natural precursor to norepinephrine and epinephrine and is generally not as effective as these two agents for achieving goal MAP in patients with shock.[26–28,80] Most studies of patients with septic shock have shown that dopamine at dosages of 5 to 10 µg/kg/min increases CO by improving contractility and heart rate, primarily from its β_1 effects. At higher dosages (>10 µg/kg/min), it increases MAP because of both increased CO and SVR due to its combined β_1 and α_1 effects.

The clinical utility of dopamine as a vasopressor in the setting of shock is limited because large dosages are frequently necessary to maintain CO and MAP. At dosages exceeding 20 µg/kg/min, further improvement in cardiac performance and regional hemodynamics is limited. The effect of dopamine on global oxygen-transport variables parallels the hemodynamic effects. Although dopamine improves global DO_2, it may compromise O_2ER in the splanchnic and mesenteric circulations by α_1-mediated vasoconstriction. Splanchnic blood flow and DO_2 increase with dopamine, but with no preferential increase in splanchnic perfusion as a fraction of CO and systemic increases in DO_2. Large doses of dopamine cause a decrease or lack of change in regional VO_2 and a decrease in tissue O_2ER. Dopamine at low or vasopressor dosages directly impedes gastric motility in critical illness and may aggravate gut ischemia in shock. Similar to high-dose administration, low-dose dopamine increases splanchnic blood flow but lowers splanchnic VO_2 in sepsis. Therefore, dopamine at all dosages impairs hepatosplanchnic metabolism despite an increase in regional perfusion. Low dosages (eg, 2 µg/kg/min) increase renal blood flow and glomerular filtration rate in studies of animals and healthy volunteers, but urine production is similar to placebo in critically ill patients.[87]

Dobutamine

Dobutamine, a synthetic catecholamine, is primarily a selective β_1-agonist with mild β_2- and α_1-activity, resulting in strong positive inotropic activity without concomitant vasoconstriction.[26–28] In comparison with dopamine, dobutamine produces a larger increase in CO and is less arrhythmogenic. α_1-Adrenoceptors in the heart are directly stimulated by the (−) isomer of dobutamine, but β_1 and β_2 activity reside in the (+) isomer. The strong inotropic action of dobutamine is a function of its structure, the additive effect of cardiac α_1- and β_1-agonist activity, and a relatively weak chronotropic effect limited to the (+) isomer action on the β-receptors. Clinically, β_2-induced vasodilation and increased myocardial contractility with subsequent reflex reduction in sympathetic tone lead to a decrease in SVR. Optimal uses of dobutamine in shock are for patients with low CO and high filling pressures (eg, left ventricular dysfunction demonstrated with echocardiography) or ongoing signs of global or regional hypoperfusion despite adequate resuscitation; however, vasopressors may be needed to counteract arterial vasodilation.[20,27]

Dobutamine is an inotrope with vasodilatory properties (an “inodilator”).[26–28] It is used for the treatment of septic and cardiogenic shock to increase the CO, typically by 25% to 50%. In septic shock, left and right ventricular functions are depressed despite a high CO, whereas ventricular volumes and compliance are increased. Dobutamine increases stroke volume, left ventricular stroke work index, and thus cardiac index and DO_2 without increasing PAOP.[26–28] It also enhances the chronotropic effect. The combination of dobutamine and norepinephrine results in a lower increase in heart rate compared with the use of epinephrine alone.

Dobutamine increases DO_2 without affecting VO_2, resulting in decreased O_2ER. Arterial lactate concentrations decrease significantly with

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norepinephrine and dobutamine compared with dopamine and epinephrine infusions. The addition of dobutamine to other vasopressors improves gastric mucosal perfusion even without increases in CO. This effect may relate to blood flow redistribution toward gastric mucosa. Dobutamine may increase the fraction of CO distributed to the global hepatosplanchnic blood flow. Additionally, dobutamine may redistribute blood flow within gastric wall layers toward the mucosa by "stealing" blood from the muscularis secondary to greater β_2-mediated vasodilation. Sublingual microcirculation improves after dobutamine is added to vasopressor-dependent septic shock patients in a manner unrelated to arterial pressure or CO, suggesting that enhanced perfusion is the result of the "steal" phenomenon. Of note, gastric mucosal perfusion and tissue oxygen utilization are most improved with concurrent norepinephrine and dobutamine therapies compared with other vasopressor combinations at the same level of MAP.

Vasopressin

Initiating vasopressin in patients with vasodilatory/distributive shock increases SVR and arterial blood pressure, which allows for reductions in the dosage requirements of catecholamine adrenergic agents.[29,31,82,88–91] Vasopressin's strongest vasoconstrictive action occurs in the skin and soft tissues, skeletal muscles, and fat tissues.[29] Vasopressin decreases heart rate after initiation because of reflex bradycardia from increased SVR.[92] Unlike adrenergic receptor agonists, the vasoconstrictive effects of vasopressin are preserved during hypoxemia, and pulmonary arterial pressures do not increase with vasopressin. After initiation of vasopressin, organ-specific vasodilation may preserve cardiac and renal function. Whereas V_2 stimulation promotes water retention from the distal tubules and collecting ducts, V_1-receptors cause vasoconstriction of efferent renal arterioles and relative vasodilation of afferent arterioles to increase glomerular perfusion pressure and filtration rate, enhancing urine production.[29,93]

Because vasopressin increases SVR through vasoconstriction, it may be utilized as a component of therapy for patients with vasodilatory/distributive shock. Studies involving vasopressin infusion for management of septic shock show rapid and sustained improvement in blood pressure.[29,88–90] These effects are evident with the administration of dosages up to 0.04 units/min. Administration of dosages >0.04 units/min may be associated with negative changes in CO and mesenteric mucosal perfusion; however, these results are inconsistent in studies.[29,33] Cardiac ischemia and reductions in stroke volume are rare when dosages of 0.04 units/min or lower are used.[33] However, higher dosages of vasopressin in patients with septic shock complicated by impaired left ventricular systolic function warrant extreme caution. Although vasopressin may have deleterious effects on mesenteric and skin perfusion, studies report vasodilation of cerebral, pulmonary, coronary, and some renal vasculature beds. The clinical outcomes associated with selective vasodilation are not yet known except for the possibility of enhanced urine production in patients not anuric at baseline.[93]

Angiotensin II

Angiotensin II increases SVR and may be utilized for patients with vasodilatory/distributive shock. Blood pressure rapidly increases after initiation of angiotensin II in patients with low SVR (ie, those with vasodilatory/distributive shock). The starting dosage of angiotensin II is 10 to 20 ng/kg/min with rapid titration (as quickly as every 5 minutes) to MAP goal. In the first 3 hours of treatment, the dosage may be increased up to 80 ng/kg/min; thereafter, the dosage should not exceed 40 ng/kg/min. The effects of angiotensin II on myocardial performance, oxygen transport parameters, and regional organ perfusion are unclear. However, because the risk of lactic acidosis and delirium are higher with angiotensin II, there may be a deleterious effect on regional tissue perfusion.[33,91] Angiotensin II has only been evaluated in patients without depressed CO; therefore, it should also be used with extreme caution in patients with impaired left ventricular systolic function. Angiotensin II also increases glomerular perfusion pressure and filtration, but its effects on kidney function are unclear.[33] Angiotensin II increases heart rate through unclear mechanisms, but likely due to activation of AT-1 receptors in the heart.[32,33]

Comparative Studies of Vasoactive Agents

The results of several observational and randomized studies support norepinephrine as the first-line vasopressor for most shock states, particularly septic shock.[20,27] A meta-analysis showed that norepinephrine was associated with increased survival compared to dopamine.[82] Tachydysrhythmias were less common with norepinephrine. The results of one study contributed to the majority of data. The study randomized patients with shock unresponsive to volume resuscitation to norepinephrine or dopamine and found similar 28-day mortality rates.[4] Despite the theoretical advantages of dopamine in patients with cardiogenic shock, dopamine was not superior to norepinephrine in patients with this shock type. Overall, patients receiving norepinephrine had fewer arrhythmic events and more vasopressor-free days. This study demonstrates that while there is no mortality benefit of norepinephrine over dopamine in heterogeneous shock syndromes, it is more effective in increasing blood pressure and is safer.

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Two randomized, double-blind studies compared epinephrine with norepinephrine in patients with shock.[86,94] Both studies found similar 28-day mortality rates and time to vasopressor withdrawal with epinephrine and norepinephrine. One study found more events of tachyarrhythmias with epinephrine leading to study discontinuation.[86] Both studies also showed that epinephrine was associated with lower arterial pH values and higher serum lactate concentrations over the first days of therapy. Another study compared norepinephrine and epinephrine in patients with cardiogenic shock after acute myocardial infarction.[95] Cardiac index was higher with epinephrine over the first 4 hours of treatment, but there was no difference between groups over the 72-hour study period. The study was stopped early because of a higher incidence of refractory cardiogenic shock in patients receiving epinephrine. Survival was similar between study groups, but the study was not designed or statistically powered to evaluate this outcome. These data suggest that norepinephrine is preferred to epinephrine in patients with cardiogenic shock.

Taken together, norepinephrine is the primary vasopressor of choice in patients in most shock states because of its multiple benefits: (1) norepinephrine may decrease mortality in septic shock; (2) it reverses inappropriate vasodilation and low global oxygen extraction; (3) it attenuates myocardial depression at unchanged or increased CO and increased coronary blood flow; (4) it improves renal perfusion pressure and renal filtration; (5) it enhances splanchnic perfusion; and (6) it is less likely than many other vasopressors to cause tachydysrhythmias.[26–28,80]

Two meta-analyses concluded that adjunctive vasopressin did not produce a survival benefit in patients with vasodilatory/distributive shock,[88,96] while a third meta-analysis showed vasopressin reduced mortality.[89] Furthermore, a meta-analysis utilizing patient-level data of patients with septic shock did not detect a survival benefit with vasopressin.[97] The largest meta-analysis and the individual patient data meta-analysis showed the addition of vasopressin to catecholamine vasopressors was associated with a lower risk for atrial fibrillation and arrhythmias overall.[96,97] The results of one study contributed the majority of data for all meta-analyses. This study randomized patients with septic shock to vasopressin 0.01 to 0.03 units/min or norepinephrine, added to open-label catecholamine therapy, and 28-day mortality rates were similar.[90] Subgroup analyses suggested a mortality benefit with vasopressin in patients with less severe shock. The adverse event profiles were similar between groups and vasopressin therapy expedited the discontinuation of catecholamine vasopressors. Although vasopressin helped preserve renal function in patients with acutely declining urine production,[93] a subsequent randomized study of early vasopressin in patients with septic shock did not detect a difference between norepinephrine and vasopressin in the number of kidney failure-free days.[98] At present, vasopressin should not be used for the sole purpose of improving or maintaining renal function.

A study compared norepinephrine and vasopressin in patients with vasodilatory/distributive shock after cardiac surgery.[99] The incidence of a composite outcome of mortality or severe complications (stroke, requirement for mechanical ventilation for longer than 48 hours, deep sternal wound infection, reoperation, or acute kidney injury) was lower in patients receiving vasopressin. There was a lower incidence of acute kidney injury in patients receiving vasopressin but no difference between groups in mortality or other components of the composite outcome. Vasopressin may be considered as a component of vasopressor therapy for patients with vasodilatory/distributive shock after cardiac surgery.

Few studies to date have evaluated angiotensin II as a therapy for shock. In one study, patients with vasodilatory shock (81% septic shock) requiring a norepinephrine dosage of at least 0.2 μg/kg/min without evidence of a low CO were randomized to angiotensin II or placebo.[91] Compared with those receiving placebo, patients receiving angiotensin II more frequently achieved an MAP of at least 75 mm Hg (higher than recommended by guidelines) without an increase in the dosage of open-label vasopressors after 3 hours. Angiotensin II was also associated with lower open-label vasopressor doses over 3 hours. There was no difference between groups in organ function after 48 hours or mortality at day 28. Although a secondary analysis of the study suggested a mortality benefit with angiotensin II in patients with acute kidney injury treated with renal replacement therapy at study enrollment,[100] angiotensin II should not be started exclusively for this indication.

Several randomized controlled trials of low-dose corticosteroids in vasopressor-dependent septic shock patients have been published.[101,102] The results of meta-analyses are conflicting with regard to a survival benefit associated with corticosteroid administration; however, they are in agreement that corticosteroid use improves hemodynamics with more rapid shock reversal and shorter durations of vasopressor support.[101,102] Studies that showed a mortality benefit included ill patients requiring high-dose vasopressors (average norepinephrine dosages about 1 μg/kg/min); studies that did not detect a mortality benefit enrolled patients who were not as sick (average norepinephrine dosages 0.5 μg/kg/min or below). Discrepancies in study designs and conflicting results have led to an ongoing debate about the optimal use of corticosteroids in patients with septic shock.

TABLE e42-5

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Receptor Pharmacology and Adverse Events of Selected Vasopressor and Inotropic Agents Used in Shock[a]

Agent (Adverse Events)	α_1	α_2	β_1	β_2	D	V_1	V_2	AT-1	AT-2
Angiotensin II (5,000-10,000 ng/mL NS)	Tachycardia, thrombosis, peripheral ischemia, lactic acidosis, bronchospasm, infection								
1.25-80 ng/kg/min	0	0	0	0	0	0	0	++++	++++
Dobutamine (500-4,000 µg/mL D_5W or NS)	Tachycardia, dysrhythmias, hypotension								
2-10 µg/kg/min	+	0	++++	++	0	0	0	0	0
>10-20 µg/kg/min	++	0	++++	+++	0	0	0	0	0
Dopamine (800-3,200 µg/mL D_5W or NS)	Tachycardia, dysrhythmias, decreased PaO_2, mesenteric hypoperfusion, GI motility inhibition, T-cell inhibition								
1-3 µg/kg/min	0	0	+	0	++++	0	0	0	0
3-10 µg/kg/min	0/+	0	++++	+	++++	0	0	0	0
>10-20 µg/kg/min	+++	0	++++	+	0	0	0	0	0
Epinephrine (8-16 µg/mL D_5W or NS)	Tachycardia, dysrhythmias, mesenteric hypoperfusion, increased lactate, hyperglycemia, immunomodulation								
0.01-0.05 µg/kg/min	++	++	++++	+++	0	0	0	0	0
0.05-3 µg/kg/min	++++	++++	+++	+	0	0	0	0	0
Norepinephrine (16-64 µg/mL D_5W or NS)	Mixed effects on myocardial performance and mesenteric perfusion, peripheral ischemia, immunomodulation								
0.02-3 µg/kg/min	++++	+++	+++	+/++	0	0	0	0	0
Phenylephrine (100-400 µg/mL D_5W or NS)	Mixed effects on myocardial performance, peripheral ischemia								
0.5-9 µg/kg/min	+++	+	+	0	0	0	0	0	0
Vasopressin (0.2-1 units/mL D_5W or NS)	Mixed effects on myocardial performance, mesenteric hypoperfusion, peripheral ischemia, thrombocytopenia, hyperbilirubinemia								

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0.01-0.1 units/min	0	0	0	0	0	++++	++++	0	0

AT, angiotensin; D, dopamine; D_5W, dextrose 5% in water; GI, gastrointestinal; NS, normal saline (0.9% sodium chloride); PaO_2, arterial oxygen pressure; V, vasopressin.

[a]Activity ranges from no activity (0) to maximal (++++) activity.

Use of Vasopressors and Inotropes in Distributive (Septic) Shock

The Surviving Sepsis Campaign guidelines outline vasopressor and inotrope selection, and corticosteroid use for patients with septic shock.[20] Other evidence relative to vasopressor and inotrope choice is available from systematic reviews and meta-analyses.[80,82,88,89,96,103,104] Guidelines from the Society of Critical Care Medicine and European Society of Intensive Care Medicine also outline corticosteroid use in patients with septic shock,[36] and systematic reviews and meta-analyses also exist on the topic.[101,102] Overall, the recommendations from all of these sources support norepinephrine as the first-line vasopressor for shock.

In patients with vasodilatory/distributive shock, norepinephrine should be started when an MAP ≥65 mm Hg and/or adequate tissue perfusion is not achieved with fluid resuscitation. Norepinephrine infusions are initiated at 0.05 to 0.1 µg/kg/min and rapidly titrated to preset blood pressure goals (usually MAP ≥65 mm Hg) and/or improvement in global and regional peripheral perfusion (eg, decrease blood lactate or restore urine production). Norepinephrine may be associated with tachydysrhythmias, with higher doses more likely to cause this adverse drug reaction.

Epinephrine is considered as adjunctive therapy to norepinephrine because it is associated with tachydysrhythmias and lactate elevation.[26–28,82,86] Epinephrine-associated clinically important dysrhythmias or cardiac ischemia occur at variable rates irrespective of age or underlying cardiac status.[26–28,82,86] Nevertheless, caution must be exercised before considering epinephrine for managing hypoperfusion in patients with coronary artery disease and inadequate CO, in whom ischemia, chest pain, or myocardial infarction may result. Epinephrine is commonly used in countries where other agents may not be readily available or are relatively expensive. It may also be used as an inotrope after cardiac surgery, particularly in patients with revascularized coronary circulation.

Despite its use in refractory shock, little information is available regarding the clinical efficacy of phenylephrine. It improves myocardial performance in hyperdynamic, normotensive patients with sepsis but worsens myocardial performance in patients with cardiogenic shock as a result of a decrease in CO and an increase in SVR. Therefore, phenylephrine use warrants caution and should not be used as an initial vasopressor in shock patients with impaired myocardial performance. The available data on hemodynamics, oxygen-transport variables, and mortality with phenylephrine in shock patients may not be generalizable because of the small numbers of patients evaluated. Tachydysrhythmias are notably infrequent with phenylephrine, particularly when it is used as a single agent or at higher doses, because phenylephrine exerts little activity on β_1-adrenergic receptors. Whether the beneficial effects can be sustained with longer administrations of phenylephrine is unclear. Phenylephrine may be a useful alternative in patients who cannot tolerate tachycardia or tachydysrhythmias with use of norepinephrine or epinephrine.[82]

The use of dopamine as a first-line vasopressor is no longer recommended. Its clinical use is frequently hampered by tachycardia and tachyarrhythmias, which may lead to myocardial ischemia.[4] Although tachyarrhythmias theoretically should not be expected to occur until the administration of dopamine 5 to 10 µg/kg/min, β_1 effects are observed with dosages as low as 3 µg/kg/min. While dopamine may improve hemodynamic function, the use of dopamine for shock is questionable because regional hemodynamics, oxygen-transport variables, and functional parameters of improved organ perfusion are not consistently enhanced in a sustained manner and may be negatively impacted.[6] Low-dose dopamine did not demonstrate improved renal function in a randomized, placebo-controlled study of critically ill patients with early renal dysfunction.[87] A meta-analysis confirmed that low-dose dopamine fails to enhance renal function or survival in critically ill patients.[105] The negative findings of low-dose dopamine use and the deleterious effects of inotropic and vasopressor dosages of dopamine on regional hemodynamics, oxygen transport, and functional performance of organ perfusion raise concern over whether dopamine should even be considered in patients with shock.[20,87,105]

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Current guidelines for patients with septic shock recommend a trial of dobutamine infusion, titrated up to 20 µg/kg/min, in the presence of myocardial dysfunction (elevated cardiac filling pressures, low CO, echocardiography displaying left ventricular dysfunction) or continued signs of global or regional hypoperfusion despite meeting volume and MAP goals.[20] Increased cardiac performance measures in response to adjunctive dobutamine therapy are predictive of survival during sepsis. However, administration of dobutamine purely to achieve a normal CO, DO_2, or $ScvO_2$ in the absence of other signs of tissue hypoperfusion (eg, low urine production) is not recommended. The achievement of supranormal oxygen transport values with dobutamine is of little value compared with treatment to normal values. In addition, administration of dobutamine to achieve these high values may increase mortality rate and/or the incidence of adverse drug reactions.

Dobutamine should be started at dosages ranging from 2.5 to 5 µg/kg/min. Dosage increments of dobutamine beyond 20 µg/kg/min are limited by tachycardia, myocardial ischemia, hypertension, and tachyarrhythmias despite the absence of preexisting cardiac abnormalities. Although a dose-response may be seen, dosages >5 µg/kg/min may provide limited beneficial effects on oxygen transport values and hemodynamics and may increase adverse cardiac effects. If given to patients who have an inadequate venous return, dobutamine will result in hypotension and a reflexive tachycardia. Because dobutamine increases myocardial oxygen demand, it should be used cautiously in patients with cardiogenic shock, particularly those with acute myocardial infarction who have not undergone coronary revascularization.[11] Doses should be guided by clinical endpoints, echocardiography, and global perfusion goals. Dobutamine, like other inotropes, is usually given until improvement in myocardial function occurs or dose-limiting adverse drug reactions are observed.

Additional vasoactive agents (eg, vasopressin and/or angiotensin II and/or corticosteroids) may be added to improve MAP or decrease catecholamine requirements. However, specific catecholamine dosage thresholds indicating the initiation of these adjunctive agents are unclear.

Adjunctive use of vasopressin to prevent dose escalation of adrenergic agents, decrease norepinephrine dosage, or increase MAP should be considered in patients with vasodilatory/distributive shock. A meta-regression showed a negative correlation between vasopressin and norepinephrine dosages.[88] Small studies of septic shock patients demonstrate that initial therapy with vasopressin achieves blood pressure control as effectively as traditional catecholamine vasopressors but the response is delayed.[29] Therefore, vasopressin therapy should be used as add-on therapy to catecholamine adrenergic agents rather than as first-line therapy.[20,29] In patients with septic shock, dosages are generally fixed at 0.03 or 0.04 units/min with higher doses reserved for salvage therapy (norepinephrine dosage >0.6 µg/kg/min).[20] The results of studies showed that vasopressin markedly reduced the requirements for adrenergic agents.[29,88–90] Therefore, vasopressin should be used when the response to initial adrenergic therapy is inadequate or as a method for reducing the dosage of these therapies.[20] Increased arterial pressure should be evident within the first hour of vasopressin therapy, at which time the dose(s) of adrenergic agent(s) should be reduced while maintaining goal MAP. In patients with vasodilatory shock after cardiac surgery, vasopressin is frequently titrated to the MAP goal with dosages up to 0.1 units/min.[99]

Mesenteric ischemia associated with vasopressin may be clinically relevant. Increased hepatic transaminases and total bilirubin concentrations may occur with vasopressin therapy, suggesting impaired hepatic blood flow or a direct effect on excretory hepatic function.[29,33] While mesenteric vasoconstriction occurs at low vasopressin serum concentrations, studies indicate that only vasopressin dosages exceeding 0.04 units/min worsen gastric mucosal perfusion when it is added to low or high dosages of catecholamine vasopressors.[29] The effect is additive with norepinephrine despite substantially reduced dosages of norepinephrine when vasopressin is initiated. Ischemic skin lesions have also been observed in several studies, with an occurrence rate as high as 30% after vasopressin was added to norepinephrine-resistant shock.[29] Digital ischemia is also significantly more frequent with vasopressin (2% higher absolute risk increase).[96,97] However, meta-analyses concluded that there was no difference in overall serious adverse events between vasopressin and control.[88,89,96,97]

Several studies reported difficulty discontinuing vasopressin therapy. Because vasopressin is often used to replace a physiologic deficiency in patients with septic shock, it stands to reason that the requirement for vasopressin will subside with reversal of the underlying septic process. Whether vasopressin should be stopped prior to or after catecholamine vasopressors is unclear.[33] Long-term administration of vasopressin may be associated with hyponatremia and thrombocytopenia.

The optimal use of angiotensin II is unclear although it is most frequently used as adjunctive therapy to norepinephrine and vasopressin in the treatment of patients with vasodilatory/distributive shock.[106] However, angiotensin II is associated with a number of adverse drug reactions due to its action on angiotensin receptors throughout the body. It increases the risk of thromboembolic events, particularly deep vein thrombosis. This adverse

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drug reaction is likely due to the release of plasminogen activator inhibitor-1 (resulting in inhibition of fibrinolysis) and platelet activation.[31,33] Because of this risk, concurrent thromboembolism prophylaxis should be utilized. Heart rate significantly increases after angiotensin II initiation, and this agent should be used cautiously in those who cannot tolerate an increase in heart rate (eg, older patients with coronary artery disease). Through unclear mechanisms, patients receiving angiotensin II have a higher risk for secondary infection, particularly fungal infection.[33,91] Angiotensin II has been associated with bronchospasm and should be avoided in patients with asthma or current bronchospasm.[31,33]

Treatment of septic shock with corticosteroids improves hemodynamic variables and lowers catecholamine vasopressor dosages with minimal effects on patient safety.[20,36] Corticosteroids should be considered when fluids and vasopressors are unable to restore hemodynamic stability, or when weaning of vasopressor therapy proves futile.[36,101,102] They should also be started in cases of shock when adrenal insufficiency is suspected (eg, patients receiving long-term corticosteroid therapy for other indications prior to the onset of shock); however, assessment of adrenal function to guide therapy is not recommended.[20,36] Adverse events with corticosteroids for shock are few because corticosteroids are administered for a finite period of time, usually 7 days. Studies suggest that short-term, low-dose corticosteroids do not alter the rates of gastrointestinal bleeding and superinfections, but increase the risk for hypernatremia and hyperglycemia, and may increase the risk of neuromuscular weakness.[101,102] Acutely elevated serum concentrations of blood urea nitrogen and white blood cell count may also occur. The reader is referred to Chapter 142 “Sepsis and Septic Shock” for further discussion of this topic.

Use of Vasopressors and Inotropes in Hypovolemic (Hemorrhagic/Traumatic) Shock

Guidelines specific to the management of major bleeding and coagulopathy after trauma also outline vasopressor and inotrope use.[39] In contrast to other forms of shock such as vasodilatory/distributive, medications are a distant alternative to the primary therapy for hypovolemic shock, fluids. In hypovolemic shock, peripheral resistance is high due to compensatory mechanisms aimed at maintaining tissue perfusion. Early or overzealous use of vasopressors in lieu of fluids may exacerbate this resistance to the point that flow is stopped. Vasopressors are only used as a temporizing measure or as a last resort when all other measures to maintain perfusion have been exhausted.[27] Because vasopressors have such a limited role in hypovolemic shock, few studies compare various agents. However, norepinephrine is considered the first-line vasopressor of choice.

Integrated Use of Fluids, Vasopressors, and Inotropes in Shock Therapy

The initial goals of therapy are to restore effective tissue and organ perfusion. Priority should be placed on the ABCs of life support (ie, airway, breathing, and circulation), assessment of vital signs and mental status, and determination of tissue perfusion (eg, urine production after catheterization). The underlying cause of the patient’s tissue hypoperfusion should be evaluated because this leads to the correct treatment approach. For example, in hemorrhagic shock due to trauma, the most important intervention is surgical control of bleeding, and anything that delays this control is likely to increase, not decrease, mortality. If patients have signs of tissue hypoperfusion and their clinical syndrome is consistent with a shock state that is fluid responsive (eg, hypovolemic), an initial fluid challenge of at least 500 mL of crystalloid fluid should be administered.

Current recommendations for patients with sepsis are to measure blood lactate concentration (and remeasure if initial lactate is >2 mmol/L), begin rapid administration of 30 mL/kg crystalloid for hypotension, and obtain MAP ≥65 with vasopressors if patient is hypotensive during or after fluid resuscitation, all started within 1 hour of recognition.[20] Although protocolized initial treatment of patients with septic shock is not better than usual care, usual care must include rapid (ie, within 1 hour of recognition) antibiotic administration and aggressive fluid resuscitation.[20] Figure e42-5 presents an algorithm for the management of patients with shock.[1,2,20,25–28,39] This algorithm suggests a stepwise approach to optimize MAP, first with crystalloid fluid resuscitation then adding norepinephrine. Although albumin is not recommended for the prevention or initial treatment of circulatory insufficiency, its use may be appropriate in patients who are not responding to crystalloids and are developing problems such as interstitial fluid accumulation. Patients with evidence of inadequate CO without fluid responsiveness should have an inotrope initiated or mechanical circulatory support considered. Inotropes may be added for shock states with low CO or left ventricular dysfunction. Occasionally, epinephrine and phenylephrine are used when necessary. Although this approach is empirical, it is used broadly in clinical practice and has been justified by the desire to avoid the adverse events associated with strong vasoconstriction.

Developing a strategy to rapidly restore effective tissue perfusion reduces mortality. Goals of initial resuscitation should include crystalloid fluids if the patient is fluid responsive, vasopressor agents to achieve MAP at least 65 mm Hg (or SBP 80-90 mm Hg in trauma patients), and frequent clinical assessments to meet global and regional perfusion goals (eg, additional fluid challenge or inotropic therapy to achieve lactate clearance ≥20%,

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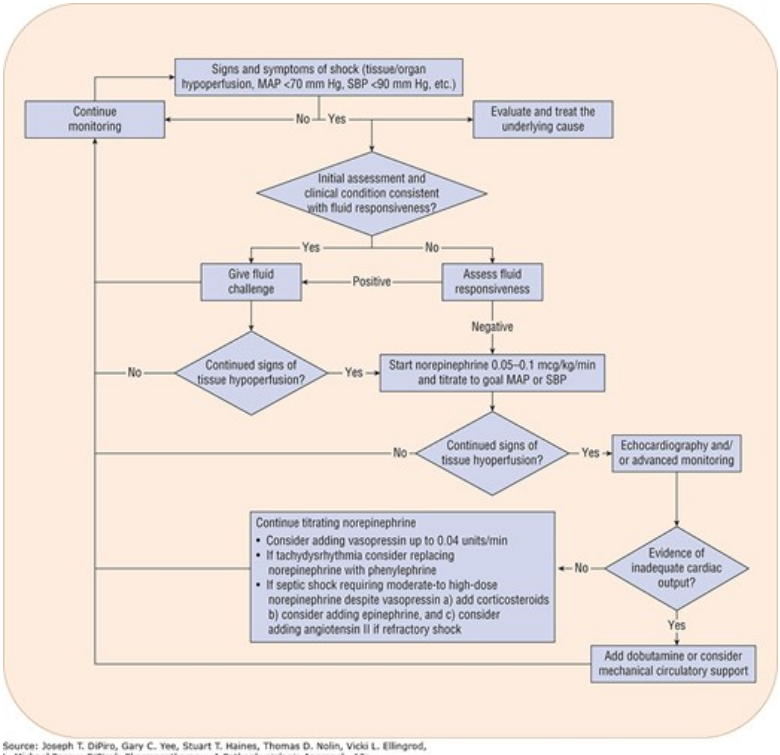
capillary refill time <3 seconds, $ScvO_2$ ≥70% [0.70] or urine production ≥0.5 mL/kg/hr).[1,20] Patients who develop supranormal DO_2 and VO_2 values have lower mortality, but targeting these with exogenous administration of vasopressors/inotropes is not beneficial and cannot be recommended.

Vasopressors should be initiated if tissue perfusion is not responding to fluid challenges. Dosage titration and monitoring of vasopressor and inotropic therapy should be guided by the "best clinical response", lactate clearance, and capillary refill time.[1,2,20,26–28,39] Clinically effective dosing of vasopressors and inotropes in shock often requires dosages much higher than recommended by most references.[1,2,20,26–28,39] These large doses must be tempered with the development of adverse drug reactions. The goal is to use the lowest effective dosage while minimizing evidence of global hypoperfusion (lactate, $ScvO_2$, capillary refill time) and regional hypoperfusion such as myocardial (eg, tachyarrhythmias, electrocardiographic changes, troponin elevations), renal (decreased glomerular filtration rate and/or urine production), splanchnic/gastric (bowel ischemia, elevated transaminases), pulmonary (worsening PaO_2), or peripheral (capillary refill time, cold extremities) ischemia. Therapy with catecholamine vasopressors and inotropes is continued until myocardial depression and/or vascular hyporesponsiveness (ie, blood pressure) of shock improve, usually measured in hours to days.[20,27]

This algorithmic approach (Fig. e42-5) is consistent with the recommendations made in the Surviving Sepsis Campaign guidelines and other guidance for the monitoring and treatment of patients with shock.[1,2,14,20,25–28,39] Personalized pharmacotherapy for hemodynamic support of shock may be rational in certain situations (such as long-standing baseline hypertension, or home corticosteroid use) but may be difficult to achieve because the patient response is variable and the acute nature of emergent resuscitation often necessitates treatment before pharmacotherapy can be personalized. Effectiveness and safety may be influenced by genetic polymorphisms; therefore, future vasopressor therapies may be directed based on pharmacogenomic profiles.

FIGURE e42-5

Treatment algorithm for shock syndromes.



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EVALUATION OF THERAPEUTIC OUTCOMES

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Patients should be frequently monitored for their response to therapy. If perfusion is not restored with the initial treatment approach, then echocardiography should be pursued with additional treatment options implemented based on the findings. Additional hemodynamic monitoring with a pulmonary artery catheter should be considered in complex patients (eg, those with mixed shock states) or when a clinician is questioning the validity of perfusion assessments or measurements from other monitoring devices. The pulmonary artery catheter (ie, a Swan-Ganz catheter) provides multiple cardiovascular parameters, including CVP, pulmonary artery pressure, PAOP (commonly called the "wedge pressure"), CO, SVR, and SvO_2. However, because the pulmonary artery catheter is more invasive (leading to a higher risk of complications) than a central venous catheter and not associated with improved clinical outcomes, it should not be used routinely for patients with shock.[1,107] Semi-invasive and minimally invasive hemodynamic monitoring devices are increasingly utilized in patients with shock but are beyond the scope of this chapter.[108]

Several laboratory tests are indicated for monitoring of shock in the ICU setting. These include assays for assessing possible electrolyte alterations and kidney perfusion (eg, blood urea nitrogen and creatinine). Among other things, a complete blood count will enable assessment of possible infection (white blood cell count), the oxygen-carrying capacity of the blood (hemoglobin, hematocrit), and ongoing bleeding (hemoglobin, hematocrit), and hemostasis potential (platelet count). In bleeding patients, clotting factors are lost and diluted; therefore, concomitant monitoring of coagulation function through laboratory tests (eg, PT/INR and platelets) or viscoelastic tests (eg, thromboelastography) with corresponding measures of support should be initiated.[39] Increasing blood lactate concentration, increasing arterial base deficit, or decreasing bicarbonate concentration are global markers indicative of inadequate perfusion leading to anaerobic metabolism. The value of these surrogate markers for improving patient outcomes is controversial, but they are considered traditional endpoints of resuscitation, particularly for trauma patients. Other tests may be indicated if organ dysfunction is likely. For example, when blood flow to the liver is interrupted because of sustained hypotension, a condition known as shock liver may occur. In this condition, the levels of transaminases on a liver panel may be markedly elevated in the first couple of days after marked hypotension, although the concentrations should decrease over time. Along with laboratory testing, a more extensive history can be obtained during the subacute monitoring period.

In patients responding to initial therapy, discontinuation of vasopressor or inotropic therapy should be executed slowly; therapy should be "weaned" to avoid a precipitous worsening in regional and systemic hemodynamics. Careful monitoring of global and regional endpoints also should be geared toward discontinuation of vasopressors and inotropes as soon as the patient is hemodynamically stable. This requires constant observation. Because vasopressors and inotropes often are started while the patient is not yet optimally volume resuscitated, clinicians should reevaluate fluid responsiveness frequently so that the patient can be weaned from the vasopressor as soon as possible. Dosages should be titrated downward approximately every 10 minutes to determine if the patient can tolerate gradual withdrawal and eventual discontinuation of the vasopressor and/or inotrope. Discontinuation of agents may occur only minutes to hours after their initiation, or it may take days to weeks. Shock requiring vasopressor and/or inotropic support usually resolves within several days to 1 week.

CONCLUSION

The presence of circulatory shock is indicated by inadequate global tissue perfusion. Shock syndromes are typically classified into hypovolemic, cardiogenic, obstructive, or vasodilatory/distributive shock. Differentiation of these syndromes is conceptually based on the evaluation of preload, cardiac output, and afterload. Patients require close monitoring, including assessment of organ and tissue perfusion, adequate DO_2, and fluid responsiveness.

Crystalloids and norepinephrine are the recommended first-line fluid and vasopressor, respectively, for shock.[2,20,27,39] Balanced salt solutions may be preferred to 0.9% sodium chloride as the initial crystalloid solution. The choice of additional fluids, vasopressors, or inotropic agents should be made according to the clinical needs of the patient and the data obtained from hemodynamic and global and regional perfusion monitoring.[1,2,20,25–28,39]

ABBREVIATIONS

ACTH	adrenocorticotropic hormone
AT	angiotensin

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ATP	adenosine triphosphate
BP	blood pressure
CaMK	calcium/calmodulin-dependent protein kinases
cAMP	cyclic adenosine monophosphate
CaO_2	arterial oxygen content
CI	confidence interval
CO	cardiac output
CvO_2	venous oxygen content
CVP	central venous pressure
D	dopamine
DO_2	oxygen delivery
HR	heart rate
ICU	intensive care unit
IL	interleukin
iNOS	inducible nitric oxide synthase
MAP	mean arterial blood pressure
NO	nitric oxide
O_2ER	oxygen extraction ratio
PaO_2	partial pressure of arterial oxygen
PAOP	pulmonary artery occlusion pressure
PLC	phospholipase C
RR	respiratory rate
SBP	systolic blood pressure
$ScvO_2$	central venous oxygen saturation
SvO_2	(mixed) venous oxygen saturation
SVR	systemic vascular resistance

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TNF	tumor necrosis factor
V	vasopressin
VO_2	oxygen consumption

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SELF-ASSESSMENT QUESTIONS

1. Which of the following conditions can result in a lowering of blood pressure in critically ill patients?
   A. Increased cardiac output
   B. Increased cardiac preload
   C. Systemic vasodilation
   D. Systemic vasoconstriction
2. The “lethal triad” associated with substantial blood loss is comprised of which of the following parameters?
   A. Acidosis, hyperthermia, coagulopathy
   B. Acidosis, hypothermia, coagulopathy

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C. Alkalosis, hyperthermia, apoptosis

D. Alkalosis, hypothermia, necrosis

3. Which of the following hemodynamic profiles is typically observed in a patient with obstructive shock?

A. Low preload, low cardiac output, low afterload

B. Low preload, low cardiac output, high afterload

C. High preload, low cardiac output, low afterload

D. High preload, low cardiac output, high afterload

4. Based on efficacy and cost considerations, which of the following is the initial fluid of choice for the initial resuscitation of a patient with hypovolemic shock?

A. Lactated Ringer's solution

B. Dextrose 5%

C. Albumin 5%

D. Albumin 25%

5. If given in large but equivalent volumes, which of the following fluids is most likely to yield hyponatremia?

A. 0.9% sodium chloride

B. Lactated Ringer's solution

C. Albumin 5%

D. Albumin 25%

6. Stimulation of the beta-adrenergic receptor by agonists results in a physiologic response mediated by which of the following?

A. Inositol trisphosphate

B. Cyclic AMP

C. Cyclic GMP

D. Diacylglycerol

7. Which of the following drugs predominantly stimulates alpha-adrenergic receptors with minimal effects on beta-adrenergic receptors?

A. Dopamine

B. Phenylephrine

C. Epinephrine

D. Norepinephrine

8. Which of the following explains the development of lactic acidosis by a catecholamine?

A. Enhanced vasodilation in peripheral arteries

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B. Enhanced glycogenolysis

C. Increased DO_2 to the liver

D. Increased cardiac output

9. Which of the following catecholamines is preferred as the initial agent when treating hypotension in a patient with septic shock?

A. Norepinephrine

B. Dobutamine

C. Dopamine

D. Phenylephrine

10. Which adverse drug effect is *not* observed with dobutamine?

A. Tachycardia

B. Bradycardia

C. Hypotension

D. Dysrhythmias

11. Which of the following is *least likely* to cause a tachyarrhythmia?

A. Epinephrine

B. Dopamine

C. Norepinephrine

D. Vasopressin

12. Which of the following adverse effects has been observed with angiotensin II?

A. Bradycardia

B. Thrombosis

C. Hyperbilirubinemia

D. Dysrhythmias

13. Which of the following is *true* regarding the use of vasopressin?

A. Studies have shown that it reduces mortality in patients with vasodilatory/distributive shock after cardiac surgery.

B. Studies have shown that it reduces organ dysfunction when initiated as the first-line agent for septic shock.

C. Studies have shown that it increases blood pressure while reducing the dose of other vasopressors when it is added to vasopressors.

D. Studies have shown that it increases the risk for atrial fibrillation.

14. Which of the following best summarizes current evidence comparing blood pressure control and tachyarrhythmias between dopamine and norepinephrine in patients with septic shock?

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A. Dopamine may achieve better blood pressure control, tachyarrhythmias are less frequent.

B. Norepinephrine may achieve better blood pressure control, tachyarrhythmias are less frequent.

C. Norepinephrine may achieve better blood pressure control, tachyarrhythmias are more frequent.

D. Both agents achieve good blood pressure control, tachyarrhythmias are rare.

15. Which of the following receptors is most likely to cause an increase in heart rate when stimulated?

A. AT-2

B. β_1

C. V_1

D. α_1

16. Extravasation of a vasopressor catecholamine can be treated with intradermal injections of which of the following agents?

A. Phentolamine

B. Phenylephrine

C. Nitric oxide

D. Vasopressin

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** A lowering of blood pressure may be caused by any of reduced cardiac preload, reduced cardiac output, or decreased cardiac afterload (from systemic vasodilation) or a combination of these factors. See the "Pathophysiology" section for more information.

2. **B.** The "lethal triad" of hemorrhagic shock includes acidosis, hypothermia, and coagulopathy. See the "Pathophysiology" section for more information.

3. **D.** Obstructive shock is typically associated with a hemodynamic profile of high preload, low cardiac output, and high afterload. See the "Pathophysiology" section and Fig. e42-2 for more information.

4. **A.** Isotonic crystalloid solutions (such as lactated Ringer's solution) are the initial fluid of choice for resuscitation based on efficacy and cost considerations. Dextrose 5% is not an isotonic crystalloid solution and does not effectively expand the intravascular space; therefore, it is not considered a fluid for resuscitation. See the "Treatment" (Pharmacologic Therapy) section and Table e42-2 for more information.

5. **B.** Lactated Ringer's solution has 130 mEq/L (mmol/L) of sodium and therefore may cause hyponatremia if given in large volumes. See the "Treatment" (Pharmacologic Therapy) section and Table e42-3 for more information.

6. **B.** Beta-adrenergic receptor agonism is mediated through cyclic AMP. See the "Treatment" (Pharmacologic Therapy) section and Fig. e42-4 for more information.

7. **B.** Phenylephrine predominantly stimulates alpha-adrenergic receptors with minimal beta-adrenergic effects. The other agents stimulate beta-adrenergic receptors with at least moderate activity. See the "Treatment" (Pharmacologic Therapy) section and Table e42-5 for more information.

8. **B.** Potential mechanisms for catecholamine-associated lactic acidosis include enhanced vasoconstriction in peripheral arteries, enhanced glycogenolysis, and mobilization of lactate from peripheral tissues. See the "Treatment" (Pharmacologic Therapy) section for more information.

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9. **A.** Norepinephrine is the preferred initial agent for most shock states, including septic shock. See the "Treatment" (Pharmacologic Therapy) section for more information.

10. **B.** Dobutamine has been associated with each of the listed adverse drug reactions except bradycardia. See the "Treatment" (Pharmacologic Therapy) section and Table e42-5 for more information.

11. **D.** Vasopressin does not have chronotropic effects and is, therefore, the least likely of the agents listed to cause a tachyarrhythmia. See the "Treatment" (Pharmacologic Therapy) section and Table e42-5 for more information.

12. **B.** Angiotensin II has been associated with thrombosis. See the "Treatment" (Pharmacologic Therapy) section and Table e42-5 for more information.

13. **C.** When vasopressin is added to other vasopressors it has been shown to improve blood pressure and decrease the dose of other vasopressors. See the "Treatment" (Pharmacologic Therapy) section for more information.

14. **B.** Norepinephrine is associated with better blood pressure control and less frequent tachyarrhythmias than dopamine. See the "Treatment" (Pharmacologic Therapy) section for more information.

15. **B.** Stimulation of β_1 (and AT-1) receptors is likely to cause an increase in heart rate. See the "Treatment" section and Table e42-1 for more information.

16. **A.** Phentolamine is an α-receptor antagonist that can be used to treat the extravasation of a vasopressor catecholamine. See the "Treatment" (Pharmacologic Therapy) section for more information.

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