Chapter 12: Shock Syndromes

INTRODUCTION

- *Shock* involves a group of syndromes that cause acute, generalized circulatory failure associated with inadequate tissue and organ perfusion. Shock is characterized by systolic blood pressure (SBP) <90 mm Hg (or reduction of at least 40 mm Hg from baseline) or mean arterial blood pressure (MAP) <70 mm Hg with tachycardia and organ perfusion abnormalities.
- Classes of shock based on etiologic mechanisms include (1) hypovolemic, (2) cardiogenic, (3) obstructive, and (4) vasodilatory/distributive. Patients may have components of more than one shock syndrome upon presentation.

PATHOPHYSIOLOGY

- Circulatory shock develops when the cardiovascular system is unable to deliver an adequate oxygen supply to meet tissue demands, resulting in cellular dysfunction, a shift in cellular metabolism to anaerobic pathways, and elevated blood lactate concentrations.
- *Hypovolemic shock* is caused by inadequate venous return because of internal or external loss of intravascular fluids (eg, trauma, surgery, hemorrhage), resulting in insufficient cardiac preload and decreased stroke volume.
- *Cardiogenic shock* results from loss of pump function because of decreased cardiac contractility (eg, acute myocardial infarction [AMI]), acute valvular abnormality, or arrhythmia (eg, ventricular tachycardia).
- *Obstructive shock* results from extracardiac obstruction to blood flow into or out of the heart, such as tension pneumothorax, cardiac tamponade, or pulmonary embolism.
- *Vasodilatory/distributive shock* is characterized by loss of vascular tone; this involves tissue hypoperfusion due to decreased systemic vascular resistance (or hypoperfusion despite normal or elevated cardiac output). Distributive shock is a subset of vasodilatory shock characterized by maldistribution of blood flow in organ microcirculation. Most cases of vasodilatory shock result in distributive shock. Almost all cases of septic shock result in vasodilatory/distributive shock.
- The body responds to an abrupt decrease in tissue perfusion with subsequent restoration of perfusion, leading to a systemic inflammatory response syndrome (SIRS) with release of numerous mediators that interact to cause further injury. This “ischemia-reperfusion injury” results in edematous obstruction of capillaries, oxygen free-radical damage of cell membranes, activation of cellular (eg, white blood cells, platelets) and humoral (eg, procoagulants, anticoagulants, complement, kinins) components, release of other inflammatory mediators, and formation of microthrombi.
- As part of the stress response, anti-inflammatory pathways are also activated to counterbalance the proinflammatory effects on tissues. Vagal nerve-mediated release of acetylcholine leads to suppression of proinflammatory cytokines by macrophages. The renin–angiotensin–aldosterone and hypothalamic–pituitary–adrenocortical systems are activated, with release of angiotensin II, vasopressin, and cortisol to maintain blood pressure (BP) via vasoconstriction and renal sodium and water retention. Cortisol and catecholamine release from the adrenal glands also inhibits proinflammatory cytokine production.

CLINICAL PRESENTATION

- Patients may report dizziness, lightheadedness, confusion, and low urine production.
- Symptoms related to the underlying shock etiology will be present (eg, cough, fever, malaise with pneumonia; chest pain with AMI).

- Vital signs may reveal tachycardia (eg, >120 bpm), tachypnea (eg, >30 breaths/min), hypotension (eg, SBP <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. Temperature may be elevated if infection is present (eg, >38.3°C [101°F]).
- Physical exam findings of tissue hypoperfusion may include neurologic (eg, confusion, obtundation), cutaneous (eg, warm skin with vasodilation and cool, clammy skin with vasoconstriction), and renal (eg, low urine production) system abnormalities. Capillary refill is usually impaired.
- Laboratory test abnormalities may include elevated blood lactate concentration (>2 mmol/L), increased blood urea nitrogen (BUN) and serum creatinine and decreased urine output (<0.5 to 1 mL/kg/hour) with renal dysfunction, elevated transaminase levels with hepatic dysfunction, decreased hemoglobin/hematocrit with hemorrhage, and elevated cardiac troponin concentration with AMI. In septic shock, the white blood cell (WBC) count is usually >12,000 cells/mm^3 (12×10^9/L), and thrombocytopenia may occur. In hemorrhagic and septic shock, the prothrombin time (PT) and international normalized ratio (INR) may increase over time.

DIAGNOSIS AND MONITORING

- Rapid assessment by cardiac echocardiography is indicated when the shock etiology is unclear. Transthoracic echocardiograms can lead to rapid (within 5 minutes) diagnosis of the shock type.
- Initial monitoring in suspected circulatory shock should include vital signs, blood lactate concentration, urine production, and physical examination, including mental status.
- Advanced hemodynamic monitoring (eg, central venous catheterization) may be needed to measure central venous pressure (CVP), obtain venous samples for laboratory testing (including central venous oxygen saturation or $ScvO_2$), and administer drugs (including vasopressors) or fluids directly into the central circulation.
- Tissue metabolic requirements are met by both adequate MAP and adequate oxygen delivery (Do_2). MAP is the driving pressure for peripheral blood flow and end-organ perfusion and is a surrogate estimate of tissue blood flow. Because the components of BP are cardiac output (CO) and systemic vascular resistance (SVR) and CO is a determinant of Do_2, BP is integrally related to Do_2. However, compensatory mechanisms such as vasoconstriction may preserve BP while tissue perfusion is inadequate. Therefore, while low BP is commonly present in patients with shock, it is not required to define shock.
- 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 are satisfied and further increases in Do_2 will not alter Vo_2 (Vo_2 flow independency). The point that Vo_2 becomes dependent on Do_2 represents a pathologic transition from aerobic to anaerobic cellular metabolism and lactate production. However, studies in critically ill patients show a continuous, pathologic dependence relationship of Vo_2 with Do_2. The parameters are calculated as follows:

  $Do_2 = CO \times Cao_2$ and $Vo_2 = CO \times (Cao_2 - CVo_2)$ Do2=CO×Cao2 and Vo2=CO×(Cao2−CVo2)
  where CO = cardiac output, Cao_2 = arterial oxygen content determined by hemoglobin concentration and arterial oxygen saturation (Sao_2), and Cvo_2 = mixed 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. 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. When hemoglobin, Sao_2, and Vo_2 are stable, Svo_2 or $Scvo_2$ values reflect CO. Thus, venous oximetry may be used as a surrogate for CO and can be useful in shock state differentiation.
- Generally, Svo_2 values >70% (0.70) are considered adequate and normal. However, Svo_2 values <50% (0.50) are low and may approach the critical O_2ER where anaerobic metabolism occurs and lactate concentrations increase. High Svo_2 (>80% [0.80]) can represent a high CO but may also be a

poor prognostic sign indicating adequate Do_2 but poor capacity of tissues to extract oxygen.

TREATMENT

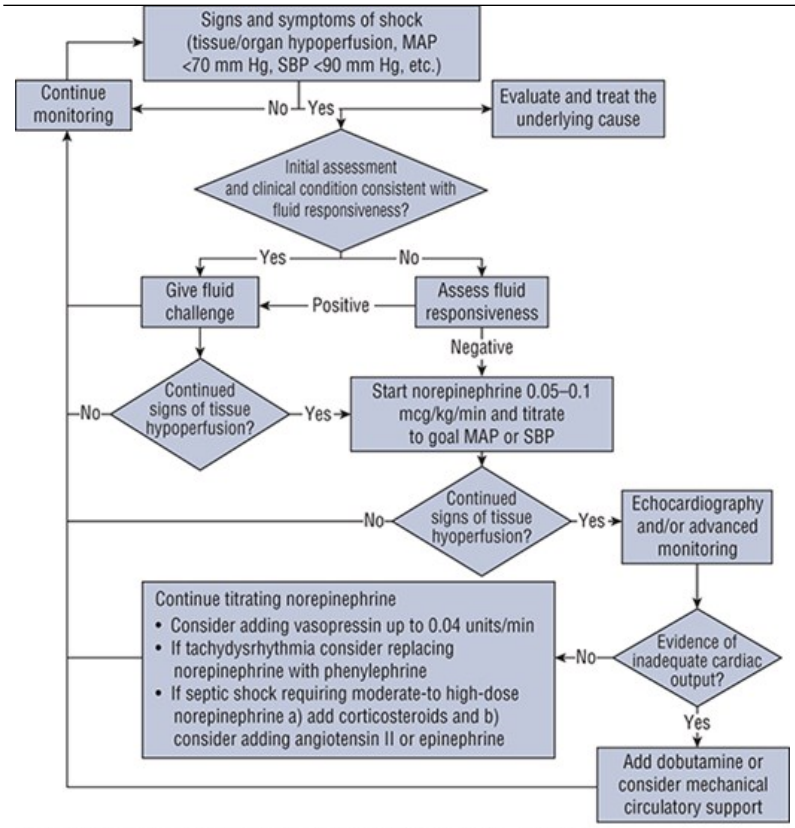
- Goals of Treatment: The desired outcome is to reduce morbidity and mortality by preventing organ damage and, to the extent possible, halt or reverse existing organ dysfunction. Treatment of circulatory shock can be divided into four phases, each with different (but sometimes overlapping) treatment goals and strategies: (1) *Salvage*, with goals of obtaining a minimum perfusion pressure and CO to ensure survival and treating the underlying shock etiology (eg, hemostasis, antimicrobials, coronary revascularization); (2) *optimization*, ensuring adequate organ perfusion and Do_2; (3) *stabilization*, to prevent further end-organ dysfunction; and (4) *de-escalation*, which targets patient recovery with goals of weaning (or stopping) vasoactive medications and fluids. This chapter focuses on salvage and optimization, but recognizing the phase of a patient's circulatory shock is necessary to establish treatment goals and therapeutic approaches.

General Approach

- **Figure 12-1** presents an algorithm for managing patients with shock using a stepwise approach to optimize MAP, first with crystalloid fluid resuscitation followed by the vasopressor norepinephrine if appropriate.
- Hospitalization is indicated for patients with circulatory insufficiency that does not respond readily to fluid resuscitation.
- Venous access is generally obtained during the initial examination process. Large-bore peripheral IV lines are preferred over central lines for initial fluid resuscitation, but vasopressors should preferentially be administered via a central venous catheter.
- The stabilization phase should include general supportive care measures such as assessment and management of pain, anxiety/agitation, delirium, immobility, sleep disturbances, nutrition, glycemic control, and thromboembolism prophylaxis.
- A goal MAP >65 mm Hg is often targeted to maintain adequate perfusion to critical organs.
- Consider patient-specific characteristics when establishing a BP goal and determining an adequate perfusion response to resuscitation.
- If MAP or SBP remains below goal, then initiate vasopressors to ensure tissue perfusion.
- Determine adequacy of Do_2 by assessing markers of end-organ perfusion (eg, urine production) and lactate concentrations. Obtain serial lactate concentrations in the early treatment phases because lactate clearance and normalization correspond with improved global tissue perfusion.
- After the salvage treatment phase, give fluids only to patients with ineffective tissue perfusion who are predicted or known to be fluid responsive. The benefits of continued fluid administration (improved CO and tissue perfusion) must be balanced against the risks of fluid overload (eg, pulmonary edema).

FIGURE 12-1

Algorithm for the management of patients with shock.



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

Nonpharmacologic Therapy

- Give all patients the basic life support measures of a secure airway with appropriate oxygenation.
- For hypovolemic shock, additional measures may include surgery, control of blood loss, blood component transfusion, and prevention of heat loss with hypothermia or cooling measures with heat exposure (eg, heat stroke).
- For patients with thermal injuries, cover wound sites with cool, moist sterile dressings until more definitive care can be provided.
- Patients with cardiogenic shock secondary to AMI should undergo emergent coronary revascularization and be considered for CO augmentation via mechanical device (eg, intra-aortic balloon pump or extracorporeal life support).
- Measures for obstructive shock may include pericardiocentesis or surgical evacuation of fluid for cardiac tamponade, needle decompression and/or chest tube thoracostomy for tension pneumothorax, and surgical or catheter thrombectomy for pulmonary embolism.
- Patients with vasodilatory/distributive shock secondary to septic shock should have infectious source control with consideration given to fever control via external cooling.

Pharmacologic Therapy

Intravenous Fluids and Blood Products

- The goal of administering IV fluids is to increase venous return in order to increase stroke volume, cardiac output, Do_2, and BP. Blood products may also be administered to replace cellular and plasma losses with the added benefit of increasing venous return.

Crystalloids

- Isotonic (or near isotonic) crystalloid solutions (eg, **lactated Ringer's** and **0.9% sodium chloride** [normal saline]) are the initial fluid of choice for resuscitation, and large volumes should be administered (except for patients with cardiogenic shock). Balanced salt solutions (eg, lactated Ringer's) and **multiple electrolytes injection** (eg, Plasma-Lyte A) and normal saline have similar efficacy in expanding plasma volume, but balanced salt solutions may be safer. Excess chloride administration with normal saline may be more likely to lead to hyperchloremic metabolic acidosis and possibly acute kidney injury (AKI). However, balanced salt solutions may aggravate preexisting hyperkalemia or exacerbate cerebral edema in brain-injured patients. If there are signs of tissue hypoperfusion and the clinical syndrome is consistent with a shock state that is fluid responsive (eg, hypovolemic), administer an initial fluid challenge of at least 500 mL of crystalloid.

- **3% sodium chloride** (hypertonic saline) causes redistribution of fluid from the intracellular space, resulting in rapid expansion of the intravascular compartment; however, its use is not associated with improved outcomes when used for initial fluid resuscitation in shock. In addition, potential dosing and administration errors can lead to adverse events, and dramatic fluid shifts may be associated with hypernatremia, metabolic acidosis from hyperchloremia, and peripheral vein damage due to high osmolality (1026 mOsm/L).

Colloids

- **Albumin** (**5%** or **25%**), **hydroxyethyl starch**, and **dextran** are large molecular weight solutions that have a prolonged intravascular retention time compared to crystalloid solutions; colloids remain in the intravascular space for hours or days, depending on the size of the colloid molecules and capillary permeability. However, colloids are expensive and have been associated with fluid overload, renal dysfunction, and bleeding. When compared with alternative resuscitation solutions, hydroxyethyl starch was associated with increased mortality, AKI, and need for renal replacement therapy. Consequently, the US product labeling was changed in 2013 to state that starch products are contraindicated in critically ill patients; therefore, they should not be used for fluid resuscitation.

Blood products

- Some patients require blood products (**packed red blood cells**, **fresh frozen plasma**, **platelets,** or **cryoprecipitate**) to ensure maintenance of O_2-carrying capacity, as well as clotting factors and platelets for blood hemostasis. Blood products may be associated with circulatory overload, transfusion-related reactions, virus transmission (rarely), hypocalcemia from added citrate, increased blood viscosity from supranormal hematocrit elevations, and hypothermia from failure to appropriately warm solutions before administration.

Fluid Resuscitation in Distributive (Septic) Shock

- The initial fluid challenge volume is unclear; the Surviving Sepsis Campaign recommends 30 mL/kg crystalloids given within the first 3 hours of shock recognition, but supporting evidence for this specific volume is of low quality. Several approaches exist for fluid resuscitation during the first 6 hours: (1) liberal fluid administration (50–75 mL/kg) while reserving vasopressors; and (2) relatively restrictive initial fluid administration (≤30 mL/kg) with earlier vasopressor use to maintain tissue perfusion. More than 30 mL/kg of crystalloid fluids 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 is unlikely to cause a substantial change in BP or acid–base balance. Therefore, multiple fluid boluses are often needed 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. Because intravenous medication diluents can contribute significantly to total fluid volume, the total fluid administration should be accounted for, and dynamic fluid response with clinical assessment should occur frequently after each fluid challenge.

Fluid Resuscitation in Hypovolemic (Hemorrhagic/Traumatic) Shock

- Immediate treatment of hemorrhagic shock with plasma expanders (crystalloids or colloids) seems logical, but no large, well-controlled clinical trials have supported this practice. In fact, some evidence suggests that fluid resuscitation beyond minimal levels (ie, MAP ≥60 mm Hg) is harmful in patients with abdominal trauma due to hemodilution and clot destabilization.

- Instead of immediate plasma expansion in all preoperative patients with circulatory insufficiency caused by hemorrhage, 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 values no more than 60 mm Hg and SBP no more than 90 mm Hg.

- Isotonic crystalloids are the fluid of choice because they are equal in efficacy to hypertonic sodium chloride solutions with a lower risk of adverse effects. Lactated Ringer's solution may be used as an alternative to normal saline but should be used cautiously in patients with traumatic brain injury because it may worsen cerebral edema. Hypotonic solutions should be avoided in this population given their relatively poor intravascular expansion and association with poor outcomes in animal models of closed head injury.

- Once hemostasis has been achieved in a patient with hemorrhage, a relatively restrictive transfusion strategy (ie, transfusion if hemoglobin ≤7 g/dL [70 g/L; 4.34 mmol/L]) is indicated unless a patient has active cardiac ischemia. Additional blood product administration should be guided by laboratory parameters (eg, PT/INR, platelets) or viscoelastic testing (eg, thromboelastography). Reversal of antithrombotic therapy (eg, prothrombin complex concentrates for warfarin) may also be used for severe bleeding.

Vasopressors and Inotropes

- Vasopressors and inotropes are required when volume resuscitation fails to maintain adequate BP (MAP ≥65 mm Hg) and organs and tissues remain hypoperfused. Vasopressors may also 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 septic shock and cardiac function in cardiogenic shock.

- **Table 12-1** lists the usual dosage range, receptor selectivity, and potential adverse effects of vasopressors and inotropes used in shock.

- **Norepinephrine** has combined strong α_1-agonist 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; it also produces a small (10%–15%) increase in stroke volume. Norepinephrine is the vasopressor of choice in patients in most shock states because (1) it 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. Norepinephrine 0.1–2 mcg/kg/min 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 predetermined goals. A significant increase in MAP is caused by an increase in SVR. Heart rate generally decreases because of reflex bradycardia from increased SVR. Increasing doses to maintain higher MAPs may increase heart rate, cardiac index, Do_2, and cutaneous blood flow, but these results are inconsistent. Norepinephrine may be associated with tachydysrhythmias, which is more common with higher doses. The primary limitation to use is that norepinephrine is not commercially available as premixed ready-to-use solutions, so its use requires preparation time.

- **Epinephrine** has combined α- and β-agonist effects. At low doses (0.01–0.05 mcg/kg/min) β-adrenergic effects predominate with an increase in stroke volume and CO. For this reason, low doses may be used as an inotrope after cardiac surgery. When higher dosages are used, α-adrenergic effects are predominant and SVR and MAP are increased. Epinephrine is an acceptable choice for hemodynamic support of patients with shock because of its combined vasoconstrictor and inotropic effects. It is as effective as norepinephrine for MAP response in vasodilatory/distributive shock. Epinephrine doses of 0.04–1 mcg/kg/min alone increase hemodynamic and oxygen-transport variables to “supranormal” values in shock patients without coronary artery disease. Large doses (0.5–3 mcg/kg/min) are often required, particularly for patients with septic shock. Smaller doses (0.1–0.5 mcg/kg/min) are effective when epinephrine is added to other vasopressors and inotropes. In addition, younger patients appear to respond better to epinephrine, possibly due to greater β-adrenergic reactivity. Despite rapid improvement of hemodynamic variables and Do_2, it can have deleterious effects on the splanchnic circulation. Like norepinephrine, epinephrine is not commercially available as a premixed ready-to-use solution.

- **Phenylephrine** is a pure α_1-agonist and increases BP primarily through vasoconstriction. It improves MAP by increasing SVR and stroke index through enhanced venous return to the heart. Given the presence of cardiac α_1-receptors, phenylephrine may also increase contractility and CO. Tachydysrhythmias are infrequent, particularly when phenylephrine is used as a single agent or at higher doses because it exerts little activity on β_1-adrenergic receptors. Phenylephrine may be a useful alternative in patients who cannot tolerate tachycardia or tachydysrhythmias from norepinephrine or epinephrine and in patients who are refractory to those agents. Phenylephrine is also an attractive agent for vasodilatory/distributive shock because of its selective α-agonism with primarily vascular effects. As with other vasopressors, the doses required

to achieve therapeutic goals are significantly higher than those traditionally recommended. Phenylephrine 0.5–9 mcg/kg/min, used alone or in combination with dobutamine or low dopamine doses, improves BP and myocardial performance in fluid-resuscitated patients with vasodilatory/distributive shock. In septic shock, phenylephrine does not significantly impair the cardiac index, pulmonary artery occlusion pressure (PAOP), or peripheral perfusion. Like norepinephrine and epinephrine, phenylephrine is not commercially available as a premixed ready-to-use solution.

- **Dopamine** has been described as having dose-related receptor activity at D_1-, D_2-, β_1-, and α_1-receptors, but this dose-response relationship has not been confirmed in critically ill patients. In patients with shock, great overlap of hemodynamic effects occurs, even at doses as low as 3 mcg/kg/min. Clinical trials and a meta-analysis indicate that low-dose dopamine does not enhance renal function or survival in critically ill patients. Dopamine is a natural precursor to norepinephrine and epinephrine but is generally not as effective for achieving goal MAP in patients with shock. Doses of 5–10 mcg/kg/min increase CO by improving contractility and heart rate, primarily from β_1 effects. At higher doses (>10 mcg/kg/min) it increases MAP as a result 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 shock is limited because large doses are frequently necessary to maintain CO and MAP. At doses >20 mcg/kg/min, further improvement in cardiac performance and regional hemodynamics is limited. In addition, its clinical use is often hampered by tachycardia and tachydysrhythmias, which may lead to myocardial ischemia. For these reasons, dopamine is no longer considered a first-line therapy for shock. Dopamine is commercially available as premixed ready-to-use solution of various concentrations.

- **Dobutamine** is primarily a selective β_1-agonist with mild β_2- and vascular α_1-activity, resulting in strong positive inotropic activity without concomitant vasoconstriction. Compared to dopamine, dobutamine produces a larger increase in CO and is less arrhythmogenic. β_2-induced vasodilation and increased myocardial contractility with subsequent reflex reduction in sympathetic tone lead to decreased SVR. Optimal uses of dobutamine in shock are for patients with low CO and high filling pressures (eg, left ventricular dysfunction on echocardiography) or ongoing signs of global or regional hypoperfusion despite adequate resuscitation; however, vasopressors may be needed to counteract arterial vasodilation. Dobutamine is an inotrope with vasodilatory properties (an “inodilator”). It is used for treatment of septic and cardiogenic shock to increase CO, typically by 25%–50%. Dobutamine increases stroke volume, left ventricular stroke work index, and thus cardiac index and Do_2 without increasing PAOP. Because dobutamine increases myocardial oxygen demand, it should be used cautiously in patients with cardiogenic shock. The combination of dobutamine and norepinephrine results in a lower increase in heart rate than use of epinephrine alone. Dobutamine is commercially available as a premixed ready-to-use solution.

- **Vasopressin** causes rapid and sustained vasoconstriction that increases SVR and BP, which allows for reductions in the dosage requirements of catecholamines and adrenergic agents in vasodilatory/distributive shock. These effects occur with doses up to 0.04 units/min. Doses >0.04 units/min may be associated with negative changes in CO and mesenteric mucosal perfusion. Cardiac ischemia occurs rarely with low doses; use of higher doses in septic shock patients with cardiac dysfunction warrants extreme caution. Vasopressin decreases heart rate after initiation because of reflex bradycardia from increased SVR. Unlike adrenergic agonists, the vasoconstrictive effects are preserved during hypoxemia and severe acidemia, and pulmonary arterial pressures do not increase. After treatment initiation, organ-specific vasodilation may preserve cardiac and renal function. Whereas V_2 stimulation promotes water retention from the distal kidney tubules and collecting ducts, V_1-receptors constrict efferent arterioles and dilate afferent arterioles to increase glomerular perfusion pressure and filtration rate, enhancing urine production. Vasopressin is not available as a premixed ready-to-use solution.

- **Angiotensin II** increases SVR and may be used for vasodilatory/distributive shock. BP rapidly increases after initiation in patients with low SVR. The starting dose is 10–20 ng/kg/min with rapid titration (as quickly as every 5 minutes) to MAP goal. In the first 3 hours of treatment, the dose may be increased up to 80 ng/kg/min; thereafter, the dose 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, it may have a deleterious effect on regional tissue perfusion because its risk of lactic acidosis and delirium are higher. Angiotensin II has only been evaluated in patients without depressed CO so it should 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. Heart rate increases significantly after initiation, so it should be used cautiously in vulnerable patients (eg, older patients with coronary artery disease). Because it increases the risk of thromboembolic events, concurrent thromboembolism prophylaxis should be employed. Patients receiving angiotensin II have a higher risk for secondary infection. It has been associated with bronchospasm and should be avoided in patients with asthma or current bronchospasm.

TABLE 12-1

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
Angiotensin II (5000–10,000 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 (500–4000 mcg/mL D_5W or NS)	Tachycardia, dysrhythmias, hypotension						
2–10 mcg/kg/min	+	0	++++	++	0	0	0
>10–20 mcg/kg/min	++	0	++++	+++	0	0	0
Dopamine (800–3200 mcg/mL D_5W or NS)	Tachycardia, dysrhythmias, decreased PaO_2, mesenteric hypoperfusion, gastrointestinal motility inhibition, T-cell inhibition						
1–3 mcg/kg/min	0	0	+	0	++++	0	0
3–10 mcg/kg/min	0/+	0	++++	+	++++	0	0
>10–20 mcg/kg/min	+++	0	++++	+	0	0	0
Epinephrine (8–16 mcg/mL D_5W or NS)	Tachycardia, dysrhythmias, decreased PaO_2, mesenteric hypoperfusion, increased lactate, hyperglycemia, immunomodulation						
0.01–0.05 mcg/kg/min	++	++	++++	+++	0	0	0
0.05–3 mcg/kg/min	++++	++++	+++	+	0	0	0
Norepinephrine (16–64 mcg/mL D_5W)	Mixed effects on myocardial performance and mesenteric perfusion, peripheral ischemia						
0.02–3 mcg/kg/min	+++	+++	+++	+/++	0	0	0
Phenylephrine (100–400 mcg/mL D_5W or NS)	Mixed effects on myocardial performance, peripheral ischemia						
0.5–9 mcg/kg/min	+++	+	+	0	0	0	0
Vasopressin (0.2–1 units/mL D_5W or NS)	Mixed effects on myocardial performance, mesenteric hypoperfusion, peripheral ischemia, hyponatremia, thrombocytopenia, hyperbilirubinemia						
0.01–0.1 units/min	0	0	0	0	0	+++	+++

AT, angiotensin; D, dopamine; D_5W, dextrose 5% in water; NS, normal saline; PaO_2, partial pressure of arterial oxygen; V, vasopressin.

[a]Activity ranges from no activity (0) to maximal (++++) activity. Angiotensin II has ++++ activity at AT-1 and AT-2 receptors but no activity at other receptors.

Use of Vasopressors and Inotropes in Distributive (Septic) Shock

- Norepinephrine should be started when a MAP ≥65 mm Hg and/or adequate tissue perfusion are not achieved with fluid resuscitation. Infusions are initiated at 0.05–0.1 mcg/kg/min and rapidly titrated to preset BP goals (usually MAP ≥65 mm Hg) and/or improvement in global and regional peripheral perfusion (eg, decrease blood lactate or restore urine production).
- Epinephrine is second-line or adjunctive therapy to norepinephrine because it is associated with tachydysrhythmias, lactate elevation, and variable pH values.
- Phenylephrine improves myocardial performance in hyperdynamic, normotensive patients with sepsis but worsens myocardial performance in patients with cardiogenic shock because of decreased CO and increased SVR. Therefore, phenylephrine use warrants caution, and it should not be used as an initial vasopressor in shock patients with impaired myocardial performance.
- Dopamine is no longer recommended as a first-line vasopressor because of the limitations described previously.
- Current guidelines recommend a trial of dobutamine for patients with septic shock in the presence of myocardial dysfunction. 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. Dobutamine should be started at doses ranging from 2.5 to 5 mcg/kg/min up to a maximum of 20 mcg/kg/min. Doses >20 mcg/kg/min are limited by tachycardia, myocardial ischemia, hypertension, and tachydysrhythmias. Like other inotropes, dobutamine is usually given until improvement in myocardial function with resolution of the underlying etiology or dose-limiting side effects are observed.
- Vasopressin may be considered as add-on therapy to catecholamine adrenergic agents rather than as first-line therapy. Adjunctive use may obviate the need for dose escalation of adrenergic agents, decrease norepinephrine dosage, and increase MAP. In patients with septic shock, doses are generally fixed at 0.03–0.04 units/min, with higher doses reserved for salvage therapy. 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.
- The role of angiotensin II is currently unclear, but it will most likely be used as an adjunctive therapy to catecholamines and vasopressin.
- Corticosteroid therapy in septic shock improves hemodynamic variables and allows lower catecholamine vasopressor dosages with minimal adverse effects on patient safety. Corticosteroids should be considered when fluids and moderate- to high-dose vasopressors are unable to restore hemodynamic stability, or when weaning of vasopressor therapy proves futile. 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. Adverse events are few because corticosteroids are administered for a short period, usually 7 days. Studies suggest that short-term, low-dose corticosteroids do not increase rates of gastrointestinal bleeding and superinfections but do increase the risk for hypernatremia, hyperglycemia, and perhaps neuromuscular weakness. Acutely elevated serum BUN and WBC count may also occur.

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

- In contrast to other forms of shock, medications are a distant alternative to fluid resuscitation, which is the primary therapy for hypovolemic shock. 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. Few studies have compared the various agents, but norepinephrine is considered the first-line vasopressor of choice.

EVALUATION OF THERAPEUTIC OUTCOMES

- The initial goals of therapy are to restore effective tissue and organ perfusion. Place priority on the ABCs of life support (ie, airway, breathing, and

circulation), assessing vital signs and mental status, and determining tissue perfusion (eg, urine production after catheterization).

- Evaluate the underlying cause of tissue hypoperfusion to identify the correct treatment approach.
- For patients with sepsis, measure blood lactate concentration and administer 30 mL/kg of crystalloid for hypotension within 3 hours of presentation and obtain MAP ≥65 mm Hg with vasopressors, reassess volume status, and remeasure serum lactate if the initial concentration was elevated within 6 hours of presentation. Usual care must include rapid (ie, within 1 hour of recognition) antibiotic administration and aggressive fluid resuscitation.
- Initial fluid resuscitation should include crystalloids if the patient is fluid responsive, vasopressors to achieve MAP at least 65 mm Hg (or SBP 80–90 mm Hg in trauma patients), and frequent clinical assessments to meet perfusion goals (eg, additional fluid challenge or inotropic therapy to achieve lactate clearance ≥20%, $SCVO_2$ ≥70% (0.70), or urine production ≥0.5 mL/kg/hr).
- Initiate vasopressors/inotropes if tissue perfusion is not responding to fluid challenges. Titration and monitoring should be guided by the "best clinical response" and lactate clearance. Although doses required for efficacy may be much higher than recommended by most references, use the lowest effective dosage while minimizing evidence of global hypoperfusion (lactate, $SCVO_2$) and regional hypoperfusion such as myocardial (eg, tachydysrhythmias, 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 (cold extremities) ischemia. Continue vasopressors/inotropes until myocardial depression and/or BP improve, usually measured in hours to days.
- Monitor patients frequently for their response to therapy. If perfusion is not restored with the initial treatment approach, perform echocardiography with additional treatment options implemented based on the findings.
- Consider hemodynamic monitoring with a pulmonary artery (Swan-Ganz) catheter in complex patients (eg, mixed shock states) or when the validity of measurements from other monitoring devices is in question. The catheter provides multiple cardiovascular parameters, including CVP, pulmonary artery pressure, PAOP (wedge pressure), CO, SVR, and SVO_2. However, the pulmonary artery catheter should not be used routinely for patients with shock because it is more invasive (leading to a higher risk of complications) than a central venous catheter and is not associated with improved clinical outcomes.
- Laboratory tests for monitoring of shock include serum electrolytes, BUN, serum creatinine, and complete blood count to identify possible infection (WBC count), oxygen-carrying capacity of the blood (hemoglobin, hematocrit), and ongoing bleeding (hemoglobin, hematocrit, platelet count). Hepatic transaminases may be acutely elevated when blood flow to the liver is reduced because of sustained hypotension ("shock liver"), although the concentrations should decrease over time with recovery.
- In bleeding patients, monitor coagulation function via PT/INR, platelets, and perhaps viscoelastic tests (eg, thromboelastography) with initiation of appropriate support measures as indicated.
- Observe for an increasing blood lactate concentration and arterial base deficit or a decreasing bicarbonate concentration, which indicate inadequate perfusion leading to anaerobic metabolism.
- In patients responding to initial therapy, the goal is to discontinue vasopressors and inotropes as soon as the patient is hemodynamically stable. However, taper vasopressor/inotrope therapy slowly, and monitor the patient carefully to avoid worsening hemodynamics. Reevaluate fluid responsiveness frequently so the patient can be weaned from the vasopressor as soon as possible. Titrate doses downward approximately every 10 minutes to determine if the patient can tolerate gradual withdrawal and eventual discontinuation. Shock requiring vasopressor and/or inotropic support usually resolves within several days to 1 week.

See Chapter 41, Shock Syndromes, authored by Seth R. Bauer, Robert MacLaren, and Brian L. Erstad, for a more detailed discussion of this topic.