Septic Shock Treatment & Management

Updated: Jan 11, 2019
Author: Andre Kalil, MD, MPH; Chief Editor: Michael R Pinsky, MD, CM, Dr(HC), FCCP, FAPS, MCCM more...

TREATMENT

Vasopressor Therapy

If the patient does not respond to resuscitation with several liters (usually ≥4 L) of isotonic crystalloid solution or if evidence of volume overload is present, the depressed cardiovascular system can be stimulated by means of vasopressor therapy.

Vasopressor administration is required for persistent hypotension once adequate intravascular volume expansion has been achieved. Persistent hypotension is typically defined as systolic blood pressure lower than 90 mm Hg or MAP lower than 65 mm Hg with altered tissue perfusion. The mean blood pressure required for adequate splanchnic and renal perfusion (MAP, 60 or 65 mm Hg) is based on clinical indices of organ function.

The goal of vasopressor therapy is to reverse the pathologic vasodilation and altered blood flow distribution that occur as a result of the activation of adenosine triphosphate (ATP)-dependent potassium channels in vascular smooth muscle cells and the synthesis of the vasodilator nitric oxide (NO).

First-line agents: Norepinephrine vs dopamine

The recommended first-line agent for septic shock is norepinephrine, preferably administered through a central catheter. [11, 60] Norepinephrine has predominant alpha-receptor agonist effects and results in potent peripheral arterial vasoconstriction without significantly increasing heart rate or cardiac output. The dosage range for norepinephrine is 5-20 µg/min, and it is not based on the weight of the patient.

Norepinephrine is preferred to dopamine for managing septic shock because dopamine is known to cause unfavorable flow distribution (more arrhythmias). In this setting, norepinephrine has been shown to be both significantly safer and somewhat more effective.

In a systematic review of randomized controlled trials, norepinephrine was significantly superior to dopamine in improving both in-hospital and 28-day mortality in septic shock patients. [88] In a meta-analysis that evaluated these 2 agents in the setting of septic shock, the investigators determined that in comparison with dopamine, epinephrine was associated with a decreased risk of death and a lower incidence of arrhythmic events. [89]

In theory, norepinephrine is the ideal vasopressor in the setting of warm shock, wherein peripheral vasodilation exists in association with normal or increased cardiac output. The typical patient with warm shock has warm extremities but exhibits systemic hypotension and tachycardia, the results of decreased systemic vascular resistance.

Dopamine should be used only in certain highly specific situations, such as when there is a low risk of tachyarrhythmias and in the presence of coexistent bradycardia. Treatment usually begins at 5-10 µg/kg/min IV, and the infusion is adjusted according to the blood pressure and other hemodynamic parameters. Often, patients may require high dosages of dopamine (up to 20 µg/kg/min). Low-dose dopamine is not recommended for renal protection. [11, 60]

Second-line agents

Second-line vasopressors appropriate for patients who have persistent hypotension despite maximal doses of norepinephrine or dopamine include sythenthetic human angiotensin II, epinephrine, phenylephrine, and vasopressin.

In December 2017, synthetic human angiotensin II (Giapreza) was approved by the FDA for adults with septic or other distributive shock. Approval was based on the ATHOS-3 clinical trial (n = 321) in patients with vasodilatory shock and critically low blood pressure. Eligible patients had vasodilatory shock despite intravenous volume resuscitation with at least 25 mL/kg over the previous 24 hours and the administration of high-dose vasopressors. Significantly more patients responded to treatment with the angiotensin II injection added to conventional therapy compared with those on conventional therapy plus placebo. At 48 hours, the mean improvement in the cardiovascular Sequential Organ Failure Assessment (SOFA) score (scores range from 0 to 4, with higher scores indicating more severe dysfunction) was greater in the angiotensin II group than in the placebo group ($P = .01$). [71]

Epinephrine clearly increases MAP in patients unresponsive to other vasopressors, mainly by virtue of its potent inotropic effects on the heart; thus, it should probably be the first alternative agent considered in patients with septic shock who show a poor clinical response to norepinephrine or dopamine. [11, 60] Adverse effects include tachyarrhythmias, myocardial and splanchnic ischemia, and increased systemic lactate concentrations.

Phenylephrine exerts a pure alpha-receptor agonist effect, which results in potent vasoconstriction, albeit at the expense of depressed myocardial contractility and heart rate. Phenylephrine may be considered a first-line agent in patients with extreme tachycardia; its pure alpha-receptor activity will not result in increased chronotropy. [90]

Vasopressin, or antidiuretic hormone (ADH), has been proposed for use in septic shock because it is an endogenous peptide with potent vasoactive effects and its circulating levels are depressed in septic shock. According to the 2012 Surviving Sepsis Campaign

guidelines, vasopressin should not be the single initial vasopressor but should be reserved for salvage therapy. [11] After first-line treatment, 0.03 U/min of vasopressin may be added to norepinephrine, with an anticipated effect equivalent to that of norepinephrine alone. [11, 60]

Characteristics of the vasopressors

Norepinephrine

Norepinephrine is a potent alpha-adrenergic agonist with minimal beta-adrenergic agonist effects. It can increase blood pressure successfully in patients with sepsis who remain hypotensive after fluid resuscitation and dopamine. The dosage may range from 0.2 to 1.5 µg/kg/min, and dosages as high as 3.3 µg/kg/min have been used because of the alpha-receptor downregulation in sepsis.

In patients with sepsis, indices of regional perfusion (eg, urine flow) and lactate concentration have improved after norepinephrine infusion. Several studies have found that a significantly greater percentage of patients treated with norepinephrine were resuscitated successfully, in comparison with patients treated with dopamine. [88, 89] Therefore, norepinephrine should be used early and should not be withheld as a last resort in patients with sepsis who are in shock.

Concerns about compromising splanchnic tissue oxygenation have not been borne out by the data; the studies have confirmed no deleterious effects on splanchnic oxygen consumption and hepatic glucose production, provided that adequate cardiac output is maintained.

Synthetic human angiotensin II

Angiotensin II, the major bioactive component of the renin-angiotensin-aldosterone system (RAAS), serves as one of the body's central regulators of blood pressure. It raises blood pressure by vasoconstriction and increased aldosterone release; direct action of angiotensin II on the vessel wall is mediated by binding to the G-protein–coupled angiotensin II receptor type 1 on vascular smooth muscle cells, which stimulates Ca2+/calmodulin-dependent phosphorylation of myosin and causes smooth muscle contraction. It is indicated for adults with septic or other distributive shock.

It is initiated at 20 ng/kg/min IV by continuous infusion. Monitor blood pressure response every 5 minutes and titrate by increments of up to 15 ng/kg/min as needed to achieve or maintain target blood pressure, not exceeding 80 ng/kg/min during the first 3 hours of treatment. Maintenance ranges from 1.25 ng/kg/min and should not exceed 40 ng/kg/minute.

Thromboembolism was observed in clinical trials. It should be administered with concurrent venous thromboembolic prophylaxis.

Dopamine

A precursor of norepinephrine and epinephrine, dopamine has varying effects, according to the doses infused. At lower doses, it has a much greater effect on beta receptors; at higher doses, it has more alpha-receptor effects and increases peripheral vasoconstriction.

Dosages range from 2 to 20 µg/kg/min. A dosage lower than 5 µg/kg/min results in vasodilation of renal, mesenteric, and coronary beds. [11] At a dosage of 5-10 µg/kg/min, $beta_1$ -adrenergic effects induce an increase in cardiac contractility and heart rate. At dosages of about 10 µg/kg/min, alpha-adrenergic effects lead to arterial vasoconstriction and elevation in blood pressure. [11]

Dopamine is often effective for restoring mean arterial pressure in patients with septic shock who remain hypotensive after volume resuscitation. The blood pressure increases primarily as a result of the drug's inotropic effect, which is useful in patients who have concomitant reductions in cardiac function. However, as mentioned above, in a comparison of norepinephrine to dopamine for the management of arterial pressure in septic shock, failure of dopamine to reach mean arterial pressure targets occurred in 30% of the treatment arm, necessitating adding norepinephrine.

Dopamine may be particularly useful in the setting of cold shock, where peripheral vasoconstriction exists (cold extremities) and cardiac output is too low to maintain tissue perfusion. Undesirable effects include tachycardia, increased pulmonary shunting, the potential to decrease splanchnic perfusion, and an increase in pulmonary arterial wedge pressure (PAWP).

Low-dose (renal-dose) dopamine has been studied. Dopamine at a dosage of 2-3 µg/kg/min is known to initiate diuresis by increasing renal blood flow in healthy animals and volunteers; however, several well-designed clinical trials have not found such regimens to have any beneficial effects on renal blood flow and function in the setting of circulatory shock of any etiology.

Multiple studies also have not shown prophylactic or therapeutic low-dose dopamine administration to have any beneficial effect in patients with sepsis who are critically ill. In view of the real side effects of dopamine infusion, the use of renal-dose dopamine should be abandoned.

Epinephrine

Epinephrine can increase MAP by increasing cardiac index and stroke volume, as well as by increasing systemic vascular resistance and heart rate. This agent may increase oxygen delivery and oxygen consumption. The use of epinephrine is recommended only in patients who are unresponsive to traditional agents. The undesirable effects of epinephrine include the following:

- An increase in systemic and regional lactate concentrations
- The potential to produce myocardial ischemia and promote development of arrhythmias
- Reduced splanchnic flow

Phenylephrine

Phenylephrine is a selective $alpha_1$ -adrenergic receptor agonist that is used primarily in anesthesia to increase blood pressure. Although the data are limited, studies have found

phenylephrine to increase MAP in patients who were septic and hypotensive with increased oxygen consumption. However, concern remains about this agent's potential to reduce cardiac output and lower heart rate in patients with sepsis. Phenylephrine may be a good choice when tachyarrhythmias limit therapy with other agents.

Vasopressin

Vasopressin is synthesized in the hypothalamus and excreted by the posterior pituitary. In contrast to endogenous catecholamines (eg, norepinephrine), whose serum levels are universally high in septic shock, vasopressin stores are limited and its levels are low. [91] Furthermore, catecholamine effectiveness on vascular smooth muscle cells is inhibited by the activation of ATP-dependent potassium channels and NO.

Exogenous administration of vasopressin results in vasoconstriction via activation of V1 receptors on vascular smooth muscle cells that have the effect of inhibiting ATP-dependent potassium channels and, in theory, restoring the effectiveness of catecholamines. Vasopressin is also thought to inhibit NO synthase and therefore counteract the vasodilatory effect of NO. In addition, vasopressin increases renal perfusion by causing vasodilation of afferent renal arterioles, in contrast to the renal vasoconstriction caused by catecholamines.

Several small clinical trials have shown that low-dose vasopressin increases MAP and decreases the requirement for catecholamines while maintaining mesenteric and renal perfusion. [91] However, a large, randomized trial (the Vasopressin and Septic Shock Trial [VASST]) did not find mortality to be significantly lower in patients who received vasopressin in addition to norepinephrine than in those who received norepinephrine alone, even though vasopressin reduced the requirement for norepinephrine. [92]

Overall, the major adverse effects attributed to vasopressin (myocardial ischemia, cardiac arrest, mesenteric, and digital ischemia) were not significantly increased in the trial; however, patients with known coronary artery disease or congestive heart failure were excluded from the study. [92] The incidence of digital ischemia was higher with vasopressin use. Because the mean time to receiving the drug in VASST was 12 hours, this study does not address the use of vasopressin in early sepsis resuscitation.