1. Apply Vasopressors (for Hypotension That Does Not Respond to Initial Fluid Resuscitation) to Maintain a Mean Arterial Pressure (MAP) $\geq 65$ mm Hg

**Background**
Adequate fluid resuscitation is a prerequisite for the successful and appropriate use of vasopressors in patients with septic shock. In general, the end points of fluid resuscitation are the same as those for the use of pharmacologic hemodynamic support (i.e., MAP $\geq 65$ mm Hg). Sometimes, fluid resuscitation alone may suffice.

When an appropriate fluid challenge fails to restore an adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be started. Vasopressor therapy may also be required transiently to sustain life and maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not been resolved or when a fluid challenge is in progress.

**Cautions**
Although all the vasopressor agents generally result in an increase in blood pressure, concerns remain in clinical practice about their potentially inappropriate or detrimental use.

- The most obvious of these relates to the inadequately volume-resuscitated patient, in whom vasopressor use may worsen already inadequate organ perfusion.

- Even when volume resuscitation has been performed, discussion continues as to whether vasopressor agents may raise blood pressure at the expense of the perfusion of vulnerable organs, most particularly the kidneys and the gut.

- A further concern relates to the possibility that overenthusiastic use, especially if an unnecessarily high blood pressure is targeted, may increase left ventricular work to an unsustainable degree and so worsen cardiac output and end-organ perfusion. This may be especially harmful in patients with pre-existing heart disease.
Monitoring

Because hypotension is a primary feature of septic shock and improving blood pressure is a therapeutic goal, accurate and continuous measurement of blood pressure is essential. It is therefore customary to use an arterial catheter to enable continuous invasive blood pressure monitoring. The radial artery is the site most frequently chosen, but the femoral artery is also often used. It is important to note that there may be marked differences in the blood pressure recordings at the two sites, especially in patients who are in shock, receiving vasopressors, and still hypovolemic.

Choice of Vasopressors

Norepinephrine (through a central venous catheter as soon as placement is possible) is the first choice vasopressor agent to correct hypotension in septic shock (Grade 1B).

Epinephrine (added to and potentially substituted for norepinephrine) may be used when an additional agent is needed to maintain adequate blood pressure (Grade 2B).[1-3]

Phenylephrine should not be used as a first-line vasopressor as part of the treatment of septic shock. Phenylephrine was reported to reduce splanchnic blood flow and oxygen delivery in septic shock patients.[4]

Vasopressin use may be considered in patients with refractory shock despite adequate fluid resuscitation and high-dose conventional vasopressors. Pending the outcome of ongoing trials, it is not recommended as a replacement for norepinephrine or dopamine as a first-line agent.

Dopamine

Dopamine may be used as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., a patient with low risk of tachyarrhythmias and absolute or relative bradycardia). Dopamine increases mean arterial pressure primarily by increasing cardiac index with minimal effects on systemic vascular resistance. The increase in cardiac index is due to an increase in stroke volume and, to a lesser extent, to increased heart rate.[5,6]

Splanchnic perfusion and the integrity of the gut mucosa may play an important role in the pathogenesis of multiple organ failure. The effect of dopamine on gastric tonometric and splanchnic variables has been evaluated with mixed results. At low doses, dopamine increases splanchnic oxygen delivery by 65 percent but splanchnic oxygen consumption by only 16 percent. Despite this, dopamine may decrease pH, perhaps by a direct effect on the gastric mucosal cell. The effects of dopamine on cellular oxygen supply in the gut remain incompletely defined.

Studies have shown that dopamine may alter the inflammatory response in septic shock by decreasing the release of a number of hormones, including prolactin.[7] Other potentially harmful endocrine effects have been demonstrated in trauma patients.[8-11] In a study of 12 stable mechanically ventilated patients, Dive et al. used intestinal manometry to demonstrate that dopamine resulted in impaired gastroduodenal motility.[12] Concerns remain that these and other poorly understood biological effects of dopamine might potentially have harmful effects in patients with septic shock.
Norepinephrine

Norepinephrine is a potent α-adrenergic agonist with some β-adrenergic agonist effects. Norepinephrine therapy usually causes a statistically and clinically significant increase in mean arterial pressure due to the vasoconstrictive effects, with little change in heart rate or cardiac output, leading to increased systemic vascular resistance.[13-15]

In open-label trials, norepinephrine has been shown to increase mean arterial pressure in patients with hypotension resistant to fluid resuscitation and dopamine. In the past, there was concern that norepinephrine may have negative effects on blood flow in the splanchnic and renal vascular beds, with resultant regional ischemia. This meant that in the past norepinephrine was commonly reserved for use as a last resort, with predictably poor results. However, recent experience with the use of norepinephrine in patients with septic shock suggests that it can successfully increase blood pressure without causing the feared deterioration in organ function. Norepinephrine seems to be more effective than dopamine at reversing hypotension in septic shock patients.[16]

Concern is frequently expressed with regard to the effect of norepinephrine on the kidney. In patients with hypotension and hypovolemia during hemorrhagic shock, for example, norepinephrine and other vasoconstrictor agents may have severe detrimental effects on renal hemodynamics. Despite the improvement in blood pressure, renal blood flow does not increase, and renal vascular resistance continues to rise.[17] However, in hyperdynamic septic shock, during which urine flow is believed to decrease mainly because of lowered renal glomerular perfusion pressure, the situation is different.[18] Norepinephrine markedly improves mean arterial pressure and glomerular filtration. This is particularly true in the high-output, low-resistance state of many septic shock patients. After restoration of systemic hemodynamics, urine flow reappears in most patients and renal function improves. This fact supports the hypothesis that the renal ischemia observed during hyperdynamic septic shock is not worsened by norepinephrine infusion and even suggests that this drug may be effective in improving renal blood flow and renal vascular resistance.[19-22]

Combination Therapies

The effects of dopamine on cellular oxygen supply in the gut remain incompletely defined, and the effects of norepinephrine alone on splanchnic circulation may be difficult to predict.[23-25] The combination of norepinephrine and dobutamine seems to be more predictable and more appropriate to the goals of septic shock therapy than norepinephrine with dopamine or dopamine alone.[26, 27]
Grading the Evidence

The Grade 1 recommendations below are based on strong evidence for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

- The 2012 Surviving Sepsis Campaign Guidelines recommend mean arterial pressure (MAP) be maintained $\geq 65$ mm Hg (Grade 1C).

  Vasopressor therapy is required to sustain life and maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not yet been resolved. Below a certain mean arterial pressure, autoregulation in various vascular beds can be lost, and perfusion can become linearly dependent on pressure. Thus, some patients may require vasopressor therapy to achieve a minimal perfusion pressure and maintain adequate flow.[28, 29] The titration of norepinephrine to as low as MAP of 65 mm Hg has been shown to preserve tissue perfusion.[29] In addition, pre-existing comorbidities should be considered as to most appropriate MAP target. For example, a MAP of 65 mm Hg might be too low in a patient with severe uncontrolled hypertension, and in a young previously normotensive patient, a lower MAP might be adequate. Supplementing end points such as blood pressure with assessment of regional and global perfusion, such as blood lactate concentrations and urine output, is important. Adequate fluid resuscitation is a fundamental aspect of the hemodynamic management of patients with septic shock, and should ideally be achieved before vasopressors and inotropes are used, but using vasopressors early as an emergency measure in patients with severe shock is frequently necessary. When that occurs great effort should be directed to weaning vasopressors with continuing fluid resuscitation.

- The Surviving Sepsis Campaign also recommends norepinephrine as the first choice vasopressor agent to correct hypotension in septic shock, administered through a central catheter as soon as one is available (Grade 1B).

The Grade 2 suggestions below are weaker recommendations for care based on a number of qualitative considerations. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence. “UG” level evidence is ungraded.

- The Surviving Sepsis Campaign suggests that epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (Grade 2C). Vasopressin 0.03 units/minute may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone (UG). The Surviving Sepsis Campaign suggests that epinephrine be the first chosen alternative agent in septic shock that is poorly responsive to norepinephrine (Grade 2B).

  There is no high-quality primary evidence to recommend one catecholamine over another. Much literature exists that contrasts the physiologic effects of choice of vasopressor and combined inotrope/vasopressors in septic shock. Human and animal studies suggest
some advantages of norepinephrine and dopamine over epinephrine (the latter with the potential for tachycardia as well as disadvantageous effects on splanchnic circulation and hyperlactemia) and phenylephrine (decrease in stroke volume). There is, however, no clinical evidence that epinephrine results in worse outcomes, and it should be the first chosen alternative to dopamine or norepinephrine. Phenylephrine is the adrenergic agent least likely to produce tachycardia, but as a pure vasopressor would be expected to decrease stroke volume. Dopamine increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases mean arterial pressure due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Either may be used as a first-line agent to correct hypotension in sepsis. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function, but causes more tachycardia and may be more arrhythmogenic.[30] It may also influence the endocrine response via the hypothalamic-pituitary axis and have immunosuppressive effects.

Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state.[31] Low doses of vasopressin may be effective in raising blood pressure in patients refractory to other vasopressors, and may have other potential physiologic benefits.[32-37] Terlipressin has similar effects but is long lasting.[38] Studies show that vasopressin concentrations are elevated in early septic shock, but with continued shock, concentration decreases to normal range in the majority of patients between 24 and 48 hours.[39] This has been called “relative vasopressin deficiency” because in the presence of hypotension, vasopressin would be expected to be elevated. The significance of this finding is unknown. The recent VASST trial, a randomized, controlled trial comparing norepinephrine alone to norepinephrine plus vasopressin at 0.03 units/minute showed no difference in outcome in the intent to treat population. An a priori defined subgroup analysis showed that the survival of patients receiving less than 15 µg/min norepinephrine at the time of randomization was better with vasopressin. It should be noted however that the pre-trial rationale for this stratification was based on exploring potential benefit in the 15 µg or greater norepinephrine requirement population. Higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischemia and should be reserved for situations where alternative vasopressors have failed.[40] Cardiac output measurement to allow maintenance of a normal or elevated flow is desirable when these pure vasopressors are instituted.
References


Content adapted extensively from:

**TIPS**

1. Include the use of vaspressors on a standardized protocol for the treatment of hypotension not responding to fluid administration.

2. Be sure that emergency department and intensive care nurses and staff are familiar with the appropriate dosing of dopamine, dobutamine, and norepinephrine.

3. Do not wait to start vasopressors until a fluid challenge or bolus of intravenous fluid is completed before using vasopressor agents if severe hypotension is present.

4. If you are unable to wean vasopressors, consider other diagnoses such as depressed cardiac function, adrenal insufficiency, tension pneumothorax, or cardiac tamponade, etc.