Vasoactive Agent Use in Septic Shock: Beyond First-Line Recommendations

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Septic shock is a life-threatening disorder associated with high mortality rates requiring rapid identification and intervention. Vasoactive agents are often required to maintain goal hemodynamics and preserve tissue perfusion. However, guidance regarding the proper administration of adjunct agents for the management of septic shock is limited in patients who are refractory to norepinephrine. This review summarizes vasopressor agents and describes the nuanced application of these agents in patients with septic shock, specifically focusing on clinical scenarios with limited guidance including patients who are nonresponsive to first-line agents and individuals with mixed shock states, tachyarrhythmias, obesity, valvular abnormalities, or other comorbid conditions.

KEY WORDS sepsis, septic shock, vasoactive agents, norepinephrine, vasopressin, epinephrine, phenylephrine, angiotensin II.


Sepsis is a common source of morbidity and mortality in the intensive care unit (ICU), with mortality rates of ~25% and nearing 40% in patients who progress to septic shock.1–3 Although mortality rates have declined over the years due to advances in medical practice and diagnosis, the incidence of septic shock continues to rise.2 Patients presenting with sepsis are often critically ill and may progress rapidly to septic shock if not quickly identified and treated. Therefore, early and appropriate therapeutic interventions are imperative to survival. Following administration of appropriate antimicrobial therapy, administration of intravenous fluids is recommended to improve perfusion, commonly measured by mean arterial pressure (MAP).4 Other interventions are considered concomitantly to achieve and maintain MAP. At this juncture, vasoactive therapy is critical to optimizing organ perfusion. Most vasoactive agents are derivatives of endogenous catecholamines normally released in response to stress and activation of the sympathetic nervous system, often termed the fight-or-flight response. Catecholamine release results in adrenergic stimulation and a resultant increase in blood pressure and heart rate. In addition to catecholamine-derived vasoactive agents (norepinephrine [NE], epinephrine, phenylephrine, and dopamine), there are also noncatecholamine-derived vaspressors (vasopressin and angiotensin II). Mimicking endogenous catecholamines, catecholamine-derived vasoactive agents act at the adrenergic α, β, and dopamine receptors, whereas the noncatecholamine-derived agents primarily cause vasoconstriction via alternate pathways.5

The Surviving Sepsis Campaign (SSC) guidelines recommend NE as the first-line vasoactive agent in patients presenting with septic shock.6 However, in spite of the breadth of literature on this topic, a gap exists in how to apply broad guideline recommendations to design an appropriate individualized vasoactive regimen for patients with septic shock. Due to the heterogeneous etiology and presentation of sepsis from...
patient to patient, response to therapy may be improved with a more precise approach. Additionally, there may be patient scenarios in which choosing a certain vasoactive agent may cause undue harm and alternatives should be considered (e.g., using high-dose vasopressin in a patient with a mixed septic and cardiogenic shock state when epinephrine or dobutamine may be more appropriate). Although the SSC guidelines provide recommendations for treating the population as a whole, an individualized approach may be necessary in many situations, and understanding the pharmacology, receptor targets, and pharmacodynamic actions and interactions of each agent is imperative to designing an individualized vasoactive regimen. This review summarizes the various vasoactive agents available and focuses on providing an approach to tailoring vasoactive therapy for patients with septic shock, specifically focusing on common clinical scenarios often encountered in this population.

Catecholamine-Derived Vasoactive Agents

Due to the vasodilatory mechanisms of sepsis, it is critical to restore intravascular volume with aggressive fluid resuscitation in an attempt to optimize fluid status and tissue perfusion. Although current guidelines recommend administering a crystalloid volume of at least 30 ml/kg, the optimal volume for initial resuscitation is currently unclear. Patients still demonstrating signs of hypotension and hypoperfusion despite fluid resuscitation require the administration of vasoactive agents. The SSC guidelines recommend NE as the first-line vasoactive agent in patients presenting with septic shock. Historically, both NE and dopamine were recommended. However, dopamine was associated with increased mortality and increased tachyarrhythmias when compared with NE. As such, NE is now recommended as first-line therapy with a strong recommendation by the SSC guidelines, in spite of only moderate evidence to support this statement. In fact, only a few large well-designed multicenter randomized controlled trials have evaluated the most effective initial vasoactive agent in patients with septic shock. Meta-analyses in 2015 and 2016 consistently reported no difference in clinical outcomes, including mortality, when comparing NE with epinephrine, phenylephrine, and vasopressin. Notably few studies have evaluated the initial vasoactive agent selection for managing septic shock, and many patients included in these studies were already receiving NE at randomization. Despite the absence of strong evidence supporting the use of NE as first-line therapy for septic shock, compelling data are also lacking to suggest any agent other than NE should be used first line. Thus NE remains the standard of care for patients presenting with septic shock. After NE is initiated, patients should be monitored for hemodynamic response (i.e., achievement of goal MAP and stabilization of NE dose requirements to maintain goal MAP). If patients do not respond to the initiation of NE and require increasing doses or have continued markers of malperfusion (i.e., hyperlactatemia), second-line adjunctive agents should be considered. It is important to take all patient-specific factors, as well as pharmacodynamic effects of the vasoactive agents, into account when choosing adjunctive agents to initiate.

Epinephrine is similar to NE but with greater β1-adrenergic receptor activity in the cardiac myocardium, exerting greater chronotropic and inotropic effects (Table 1). Pharmacologically, because of its added β1-adrenergic effects at low doses, the use of epinephrine should be targeted for patients with septic shock who exhibit signs of tissue hypoperfusion and a reduced cardiac output or decreased central or mixed venous oxygen saturation. As with all vasoactive agents, epinephrine is not without its risks including splanchic hypoperfusion, digital ischemia, and tachyarrhythmias due to its β1-receptor effects. In patients in whom tachycardia or a malignant tachyarrhythmia prohibits further increases in NE dose, epinephrine is not an optimal agent because it may worsen tachycardia.

Additionally, the administration of epinephrine was associated with hyperlactatemia during the first 24 hours of therapy. As a result, lactate clearance may be an insufficient clinical indicator of patient response during the initial day of epinephrine therapy. The administration of epinephrine may confound the clinical picture in patients with unresolving lactate, and alternative therapies may be considered. One prospective trial randomized patients with septic shock to either NE (with dobutamine, as needed, to increase cardiac output) or epinephrine. Overall, no difference in mortality was observed between patient groups. Similarly, both a meta-analysis and Cochrane Review failed to detect differences in outcomes between NE and epinephrine. Because of these clinical factors, epinephrine is commonly used as a second-
line adjunctive agent in septic shock and for patients with a mixed cardiogenic component to their shock state.

Phenylephrine is a pure \(\alpha\)-adrenergic agonist. Pharmacodynamically, because phenylephrine causes \(\alpha_1\)-mediated vasoconstriction and primarily increases afterload, an indirect decrease in heart rate and cardiac output may occur. However, this effect was not demonstrated in clinical studies, likely because of stimulation of \(\alpha_1\) receptors in the myocardium causing positive inotropy (without chronotropy). This effect may offset the theoretical decrease in heart rate and cardiac output. In fact, small studies showed similar effects on cardiac output, heart rate, and stroke volume when comparing phenylephrine with NE in patients with septic shock. Therefore, until further studies are conducted, caution is warranted when initiating phenylephrine in patients with bradycardia or mixed cardiogenic and septic shock.

The 2012 SSC guidelines recommended phenylephrine for patients with tachyarrhythmias associated with NE, those with optimal cardiac output and low blood pressure, or as salvage therapy after suboptimal response to other vasoactive agents.\(^{29}\) However, the limited data comparing the use of phenylephrine and NE in septic shock demonstrated no difference in clinical outcomes.\(^{27,28}\) A 2017 multicenter cohort study evaluated clinical outcomes of patients with septic shock during a period of NE shortage.\(^{30}\) During this time, NE use decreased by more than 20% and mortality increased (absolute risk increase 3.7%; 95% confidence interval [CI] 1.5–6.0%, \(p=0.03\)). Importantly, during the NE shortage time frame, the use of other vasopressors, specifically phenylephrine, increased by almost 20%. Because of the lack of available data evaluating phenylephrine use in septic shock, the updated 2016 SSC guidelines recommend its use be limited until further research is conducted.\(^6\) Despite the lack of certainty with the use of phenylephrine, it plays a role in some niche populations. Phenylephrine is an appropriate vasoactive agent in patients who develop tachyarrhythmias from vasoactive agents with \(\beta\)-adrenergic activity including NE and epinephrine. Additionally, phenylephrine may be considered in patients with aortic stenosis (AS) and in patients with left ventricular outflow tract (LVOT) obstructions due to systolic anterior motion of the mitral valve, both of which are further detailed later.

### Table 1. Receptor Activity and Drug Targets of Vasoactive Agents

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha_1)</td>
<td>Vascular smooth muscle</td>
<td>Vascular smooth muscle: vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Myocardial tissue(^{15})</td>
<td>Myocardial tissue: positive inotropy</td>
</tr>
<tr>
<td>(\beta_1)</td>
<td>Myocardial tissue</td>
<td>Positive inotropy and chronotropy</td>
</tr>
<tr>
<td>(\beta_2)</td>
<td>Vascular smooth muscle</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Dopamine (DA) 1 and 2</td>
<td>Renal, mesenteric, and coronary vascular beds</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Vasopressin 1 (V(_1))</td>
<td>Vascular smooth muscle</td>
<td>Vasocostriction</td>
</tr>
<tr>
<td>Vasopressin 2 (V(_2))(^{16})</td>
<td>Renal collecting ducts and some vascular smooth muscle</td>
<td>Renal collecting ducts: antidiuretic effect/water retention</td>
</tr>
<tr>
<td>Angiotensin receptors</td>
<td>Angiotensin I and II: Kidney, heart, adrenal glands, and skeletal muscle</td>
<td>Vascular smooth muscle: Vasodilation Angiotensin I: Vasocostriction, stimulation of norepinephrine and vasopressin release Angiotensin II: Vasodilation</td>
</tr>
<tr>
<td>Drug</td>
<td>Receptor targets</td>
<td>Action</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>(\alpha_1) (predominantly) and (\beta_1) receptors</td>
<td>High doses: (\alpha_1) predominates (\beta) receptors</td>
</tr>
<tr>
<td>Epinephrine(^{17})</td>
<td>Low doses (&lt; 4 (\mu g/min)): (\beta) receptors ((\beta_1) predominates)</td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>(\alpha_1) receptors</td>
<td>Moderate doses: (\beta) receptors ((\beta_1) predominates) High doses: (\alpha_1) predominates (\beta) receptors</td>
</tr>
<tr>
<td>Dopamine(^3,(^{18})</td>
<td>Low doses: DA receptors</td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>V(_1) and V(_2) receptors</td>
<td></td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Angiotensin I receptors</td>
<td></td>
</tr>
</tbody>
</table>

*Note:* The receptor locations and mediated actions detailed here are not all-inclusive and focus on those that have a clinically significant hemodynamic effect in patients with septic shock.
Dopamine has dose-dependent effects and primarily acts at dopamine receptors at low doses and adrenergic receptors at moderate (predominantly β receptors) and high doses (predominantly α receptors) (Table 1). In addition to its tachyarrhythmic potential, dopamine exerts endocrinologic effects by decreasing prolactin, growth hormone, luteinizing hormone, thyrotrophic-releasing hormone, and thyroid-stimulating hormone. Because of its overall adverse effect profile (particularly tachyarrhythmias), dopamine is only recommended for patients with a low risk of tachyarrhythmias or for those with symptomatic bradycardia. However, it is difficult to identify proactively which patients can be classified as having a low risk of tachyarrhythmias. Because of this, dopamine use in patients with septic shock should be limited to individuals with symptomatic bradycardia. Alternative vasopressors with higher levels of recommendation (i.e., NE, epinephrine, and vasopressin) should be used before dopamine in all other patients.

Adverse Drug Effect Mitigation with Catecholamine-Derived Vasoactive Agents

Despite the prioritization of catecholamines in septic shock, interest is increasing in limiting the use of these agents to prevent the development of adverse events associated with catecholamine administration. Higher catecholamine doses were independently associated with mortality rates as high as 90% in patients receiving NE doses greater than 1 μg/kg/minute. Although it is difficult to distinguish between association and causality, higher catecholamine doses may be a marker of the severity of septic shock and may contribute to the development of organ failure. Until more research is completed, catecholamine doses should be optimized to maintain perfusion and goal MAP, and limited to the lowest effective dose, to mitigate the risks associated with catecholamine use (e.g., tachyarrhythmias and vasoconstriction-induced hypoperfusion).

Catecholamine-derived agents with β1-receptor activity can cause malignant tachyarrhythmias. Dopamine was most commonly associated with arrhythmia development, with tachyarrhythmias as high as 38%. However, rates of arrhythmias with NE and epinephrine have ranged as high as 12%. Notably, there appears to be a dose-dependent effect between catecholamines and the development of tachyarrhythmias. In two studies evaluating goal MAP in patients with septic shock, higher NE doses were associated with a higher incidence of arrhythmias. The noncatecholamine-derived agent vasopressin does not exert action on α- or β-myocardial receptors, making it a suitable alternative to catecholamines in patients who develop tachyarrhythmias.

Raising MAP with vasoactive agents in patients with septic shock ultimately improves global tissue and organ perfusion. However, these vasoconstriction-mediated effects can be detrimental at higher doses, compromising perfusion and causing side effects such as splanchnic hypoperfusion and tissue necrosis. Splanchnic vasoconstriction and hypoperfusion can be detrimental if not identified early, resulting in mucosal and cellular damage that can progress to intestinal ischemia. Although all vasoactive agents may theoretically cause splanchnic hypoperfusion by nature of their mechanism, existing literature shows conflicting data on the effect of catecholamines on splanchnic perfusion. Ultimately, the true effect of vasoactive agents on splanchnic perfusion is still in question and rarely documented in clinical practice. Additionally, it is difficult to attribute specifically splanchnic hypoperfusion to catecholamines. It may be prudent to limit high-dose catecholamines (NE more than 1 μg/kg/min) to minimize the risk of all potential adverse drug effects associated with excessive catecholamine doses.

Noncatecholamine-Derived Vasoactive Agents

In addition to direct vasoconstrictive effects, the administration of exogenous vasopressin is hypothesized to improve MAP by supplementing endogenous vasopressin stores in the setting of a relative deficiency in septic shock. Vasopressin primarily acts on the V1 receptor leading to pronounced vasoconstriction and blood pressure augmentation (Table 1). Clinical trials evaluating vasopressin in septic shock have been mixed. Vasopressin administration has consistently demonstrated a NE-sparing effect, whereby NE dose requirements decreased significantly following the administration of vasopressin. However, randomized controlled trials of vasopressin in septic shock failed to demonstrate a survival benefit with the adjunctive use of vasopressin with NE compared with NE monotherapy. Vasopressin may also have a positive effect on kidney function by reducing the risk of
progression of acute kidney injury and the need for renal replacement therapy (RRT).54, 56 The potential positive effects of vasopressin on kidney function should be interpreted cautiously because they have not been corroborated in large clinical trials and may be attributed to the lower serum creatinine values and increased urine output seen after the initiation of vasopressin, thus impacting the clinician’s decision to start RRT.54, 56 A potential positive interaction with vasopressin and corticosteroids was reported, showing that corticosteroids may result in increased V1-receptor expression (Figure 1).57, 58 Secondary analysis of a clinical trial evaluating vasopressin versus NE found that corticosteroids and vasopressin resulted in improved survival.59 However, this positive interaction and resultant improvement in clinical outcomes were not replicated in studies in 2014 and 2016.54, 57

The package insert for vasopressin recommends starting at a dose of 0.01 units/minute and titrating to response, up to a maximum dose of 0.07 units/minute.60 However, in practice, unlike most vasoactive agents, vasopressin is not commonly titrated to response, but rather it is recommended to be administered at a fixed nontitrated dose of 0.03 units/minute for the treatment of septic shock.6 Clinical trials evaluating the dosing of vasopressin evaluated vasopressin dosing up to 0.03 units/minute53 and 0.06 units/minute.54 Higher doses of vasopressin may be beneficial in patients requiring high-dose NE. A study of 50 patients with vasodilatory shock receiving high-dose NE (more than 0.6 μg/kg/min) randomized patients to two dosing regimens of vasopressin (0.033 units/min and 0.067 units/min).61 Both groups achieved goal MAP values with no significant differences in clinical outcomes. However, patients assigned to 0.067 units/minute had lower NE dose requirements at 1, 12, 24, and 48 hours compared with those receiving 0.033 units/minute. Given the uncertainty regarding the most effective dose, vasopressin doses above 0.03 units/minute should be used cautiously and reserved for patients with refractory shock who are nonresponsive to high catecholamine doses.

Although the effect of vasopressin on cardiac output was not shown to be clinically relevant in clinical trials,55, 61, 62 vasopressin should be reserved for patients with adequate cardiac function. Caution is warranted when considering vasopressin in patients with mixed septic and cardiogenic shock due to its potent V1-mediated vasoconstrictive effects increasing afterload with no chronotropic or inotropic effects, thereby reducing cardiac output.63 Additionally, because of its V1 nitric oxide–mediated pulmonary vasodilatory effects, vasopressin may be useful in patients with right ventricular failure and pulmonary hypertension.64

Figure 1. Vasoactive agents in septic shock. AT1 = angiotensin 1; V1 = vasopressin 1. Depiction of the dynamic interplay of the vasoactive agents norepinephrine, epinephrine, phenylephrine, dopamine, vasopressin, and angiotensin II as well as corticosteroids used in septic shock.
Following initiation of vasopressin, patients should be monitored for a positive response to therapy. At the bedside, this can be determined by trending MAP and concomitant vasoactive doses. One study reported that 45% of patients receiving vasopressin for septic shock in combination with NE had a positive hemodynamic response (defined as a MAP higher than 65 mm Hg and a decrease in catecholamine dose requirements 6 hrs after vasopressin initiation). These patients had significant improvements in clinical outcomes including ICU mortality (50% vs 68%, p<0.01), ICU-free days (2.3 days vs 1.6 days), and catecholamine-free days (6.3 days vs 3.9 days) in responders versus nonresponders, respectively. Hemodynamic response to vasopressin was associated with a reduced odds of ICU mortality (odds ratio 0.51, 95% CI 0.35–0.76, p=0.001). Additionally, markers of severity of illness (lactate, sequential organ failure assessment score, and baseline catecholamine dose) were associated with increased ICU mortality, and lactate was independently associated with a reduced odds of hemodynamic response, indicating that higher severity of tissue malperfusion may decrease the odds of both ICU survival and a positive response to vasopressin. In practice, after 6 hrs of vasopressin administration, hemodynamics should be reevaluated to determine if the patient has responded to vasopressin therapy (i.e., MAP goal achieved and concomitant vasopressor doses decreasing). Alternative approaches should be considered if the patient has not responded to vasopressin.

Angiotensin II was recently approved by the U.S. Food and Drug Administration for the treatment of severe hypotension. Angiotensin II is an endogenous hormone in the renin-angiotensin-aldosterone system, with potent vasoconstricting properties. The administration of exogenous angiotensin II results in a multitude of physiologic effects, primarily vasoconstriction via the angiotensin-1 receptor and release of aldosterone, endogenous NE, and vasopressin (Figure 1). To date, only one large randomized controlled trial has evaluated the use of angiotensin II in vasodilatory shock. The Angiotensin II for the Treatment of High-Output Shock trial (ATHOS-3) compared the use of angiotensin II (20–200 ng/kg/min) to placebo in 321 patients with preserved cardiac function (cardiac index higher than 2.3 L) requiring more than 0.2 μg/kg/minute of NE. In this trial, more patients randomized to angiotensin II had a positive MAP response at 3 hrs (MAP 75 mm Hg or higher increase of 10 mm Hg with no further increase in background vasopressors) compared with placebo. In addition, patients in the angiotensin II arm had a significant, albeit small, decrease in NE requirements at 3 hrs (–0.03 μg/kg/min with angiotensin II vs 0.03 μg/kg/min with placebo; p<0.001). No significant differences in 7- or 28-day all-cause mortality were detected. Although the role of angiotensin II in patients with septic shock is unclear, it should be noted that 70% of patients in the study just mentioned were receiving NE and vasopressin at the time of randomization. Therefore, at this time, angiotensin II may be best reserved for patients with preserved cardiac function whose MAP goal is not achieved despite use of NE and vasopressin until further data are available regarding its use as a second-line and/or adjunctive agent. Additionally, further safety data on angiotensin II is warranted. In one meta-analysis, the drug appeared to be well tolerated with minimal adverse effects (albeit this study did not include data from the ATHOS-3 study). However, the U.S. product labeling for angiotensin II warns of increased thrombotic events (rates of 12.9% with angiotensin II vs 5.1% with placebo in the ATHOS-3 trial), thrombocytopenia, and infection risk, among others. As with vasopressin use, if and when angiotensin II is administered, hemodynamic response should be monitored, and if a positive hemodynamic response does not occur after the initiation of angiotensin II, alternative therapies should be considered.

Corticosteroids exert pleiotropic effects. Noticeably, corticosteroids have been reported to improve blood pressure and perfusion in patients with septic shock. Therefore, it may be prudent to consider corticosteroids as a shock therapy. Although the mechanism of corticosteroids in septic shock is multifaceted, the supplementation of corticosteroids in this population is thought to result in hemodynamic improvements. However, the use of corticosteroids in septic shock remains controversial, and numerous studies reported contradictory results. Studies implied that starting corticosteroids late after shock onset (1–3 days) and in patients who are not severely ill does not improve overall patient outcomes. The potential benefit of corticosteroids appears to lie with early initiation (within the first 12 hrs of shock onset) in patients with refractory septic shock. Additionally, several meta-analyses and a Cochrane Review evaluated the use of
corticosteroids in septic shock with contradictory results, albeit significant heterogeneity among the included studies make generalizations difficult.\textsuperscript{74–77} The most recent meta-analysis of all landmark trials showed that corticosteroid use in sepsis may result in a small nonsignificant reduction in mortality (risk ratio [RR] 0.93, 95% CI 0.84\textendash1.03) and significant improvements in shock reversal rates at day 7 (RR 1.26, 95% CI 1.12\textendash1.42).\textsuperscript{77} Overall, the question of whether or not to use corticosteroids in patients with septic shock remains unanswered. In clinical practice, corticosteroids are commonly used in patients who are unresponsive to fluid administration and require increasing vasoactive doses, a guideline-supported practice, albeit with weak recommendations due to low quality of evidence.\textsuperscript{6, 78} Regardless, the best supporting data with corticosteroid use in patients with septic shock are for those with early refractory shock, and other uses remain controversial.

Vasoactive Agents in Refractory Septic Shock

As previously discussed, aggressive fluid resuscitation with crystalloids should be initiated as soon as possible in all patients with septic shock. In patients refractory to fluids, vasoactive agents are warranted. Choosing and designing a vasoactive regimen for patients with septic shock is not a one-size-fits-all approach. Each agent should be carefully selected and titrated to the specific needs of the individual patient. Hemodynamic response should be targeted and monitored in all patients, and alternative agents should be trialed in patients who are refractory to the current regimen (i.e., lactate and vasoactive doses increasing and no achievement of MAP goal) (Figure 2). Norepinephrine remains the first-line vasoactive agent, and patients who are refractory to NE should be evaluated for cardiac function. It may be prudent to start at a “medium” dose of NE (e.g., 10 μg/min) and titrate every 5 minutes in either direction to achieve the desired MAP goal. If cardiac function is compromised, epinephrine or dobutamine are necessary for their inotropic effects and should be monitored for response (i.e., improvement in cardiac output or central or mixed venous oxygen saturation and lactate) following initiation. If cardiac function is preserved, vasopressin should be administered. Patients who do not promptly demonstrate an improvement in hemodynamics with vasopressin 0.03 units/minute within 1 hour should have intravenous hydrocortisone 50 mg every 6 hours initiated, and alternative vasoactive therapies should be further discussed. These include increasing vasopressin dose to 0.04 units/minute or higher, adding angiotensin II, or continuing to titrate up NE doses (taking care to monitor for adverse effects with excessive catecholamine doses). In patients truly refractory to these escalating approaches, requiring high catecholamine doses on multiple agents without the achievement of goal MAP, addition of epinephrine (if not already added and if heart rate allows) may be warranted in an attempt to restore organ perfusion. This algorithmic approach should be tailored to patient presentation, response, and updated goals of care following discussion with the patient and family.

Vasoactive Agents in Common Clinical Scenarios

Tachyarrhythmias

Alternative agents should be considered for patients who develop severe tachyarrhythmias, especially while receiving catecholamine-derived vasoactive agents. A recent meta-analysis compared vasopressin plus NE to NE alone in patients with vasodilatory shock (including both septic and postcardiac surgical patients) and found that administration of vasopressin plus NE was associated with a lower risk of atrial fibrillation development.\textsuperscript{79} Phenylephrine may also be considered for its lack of β-receptor activity and would be a suitable alternative to NE or epinephrine in patients who are already receiving vasopressin and develop tachyarrhythmias. In a proactive manner, catecholamines should be limited in patients at high risk of developing tachyarrhythmia based on presenting factors. In patients presenting with significant tachycardia (heart rate higher than 140 bpm) or with a baseline tachyarrhythmia, phenylephrine and vasopressin should be prioritized to not precipitate a tachyarrhythmia. Similarly, limiting catecholamine-derived agents in patients with pronounced heart rate variability from baseline after initiation of catecholamines (i.e., significant increase in heart rate after the initiation of NE but no tachyarrhythmia development at present) would be advised.

Valvular Abnormalities

The presence of valvular abnormalities has significant implications in the treatment of septic shock. Abnormalities of interest are AS and
Figure 2. Vasoactive treatment algorithm. AVP = arginine vasopressin; CO = cardiac output; MAP = mean arterial pressure; NE = norepinephrine. aConsider phenylephrine in patients with unacceptably high heart rate or malignant tachyarrhythmias. It is considered the vasoactive agent of choice in patients with aortic stenosis or in those with left ventricular outflow track obstruction due to systolic anterior motion of the mitral valve. bIf heart rate is acceptable and tachyarrhythmias are not present.
patients who present with or develop a LVOT obstruction due to systolic anterior motion (SAM) of the mitral valve. In patients presenting with AS and septic shock requiring vasoactive agent support to maintain MAP, phenylephrine is considered the vasoactive agent of choice due to its pure α agonism and lack of β-adrenergic effects on the myocardium, thereby reducing oxygen demand. It is important to note that effects on the myocardium, thereby reducing SAM. Patients with SAM commonly express epinephrine is preferred in patients with LVOT due to its theorized benefit. Additionally, phenylephrine is preferred in patients with LVOT due to SAM. Patients with SAM commonly express reduced cardiac output due to LVOT obstruction. Vasoactive agents with β-adrenergic properties will increase heart rate (decreasing filling time) and increase cardiac contractility that worsens the LVOT obstruction. The α-mediated effects of phenylephrine were not shown to impact heart rate or cardiac contractility significantly. Thus in patients with LVOT obstruction from SAM, phenylephrine could be considered as the vasopressor of choice for sustained hypotension following fluid administration. In both scenarios, patients with AS and LVOT obstruction from SAM, it may be reasonable to consider administering alternative non-adrenergic vasoactive agents, such as vasopressin, in an attempt to reduce heart rate.

Obesity

Unfortunately, no specific data guide clinicians on the superiority of specific vasoactive agents in obese patients. Additionally, there is little pharmacokinetic data detailing the effect of obesity on each agent. One study showed that increasing body weight significantly increases the clearance of epinephrine in patients with septic shock, an effect that was not seen in a pharmacokinetic study of dobutamine. At this time, it is difficult to apply these data to clinical practice, and more data are needed to determine the potential effect of obesity on the pharmacokinetics of the various vasoactive agents. Regardless, common clinical debates still held in this regard include whether vasoactive doses should be based on body weight and whether obesity impacts the clinical effects of vasoppressors.

Critically ill obese patients were shown to have differences in inflammatory markers, infectious etiologies, and clinical outcomes. Additionally, critically ill obese patients receive less fluids (on ml/kg basis) and lower vasopressor doses (on µg/kg/min basis) than nonobese patients. However, when evaluating weight-based dosing of NE versus non-weight-based dosing in obese patients, no significant difference between goal MAP achievement was detected between dosing strategies. Despite the fact that initial doses will differ in obese patients, the ultimate result and clinical outcomes should be similar, regardless of the dosing strategy, because NE is titrated to goal MAP.

With regard to vasopressin, a medication that is not commonly titrated and is typically administered at a fixed dose, one study showed lower serum vasopressin levels in obese patients 24 and 72 hours after its initiation. However, several studies reported no impact with weight or obesity on the hemodynamic effects of vasopressin. At this time, evidence is insufficient to alter vasoactive therapies in obese patients, and dosing and utilization should be optimized and titrated to hemodynamic effect and response.

Other Comorbidities and Medication Use

Globally, it is not known what true clinical effect, if any, other preexisting comorbidities (such as diabetes, immune suppression, chronic kidney disease, oncologic and hematologic disorders, etc.), home medication use, and genetic factors have on the pathophysiology of septic shock and the subsequent effect on and response to vasoactive agent initiation. It is theorized that chronic antihypertensive agent use may have an effect on outcomes in patients with septic shock. Patients taking β-antagonists before admission for septic shock may demonstrate an upregulation in β receptors due to chronic therapy. Therefore, it would be reasonable to presume that patients with home β-blocker therapy before admission may require increased vasoactive doses to achieve goal hemodynamics. Additionally, patients with an upregulation and augmentation of β1-receptors may be at greater risk of tachyarrhythmia development when β-blocker therapy is withdrawn, although the clinical implications are largely unknown. However, contradictory to this, one study found that patients with septic shock who were chronically receiving β-blockers had lower mortality rates than those not on chronic β-blockers. Ultimately, further data are needed to determine the
true implications of chronic β-blocker therapy on septic shock treatment and outcomes.

Chronic use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may also have noteworthy implications in septic shock. One evaluation of patients with septic shock and use of chronic β-blockers and ACEIs before hospital admission found that the shortest time on vasopressors occurred in patients with home ACEIs compared with patients on home β-blockers, both agents, or neither agent (19 hrs vs 24 hrs vs 30 hrs vs 30 hrs, respectively; \( p = 0.031 \)).91 However, no differences in clinical outcomes were detected between groups, and patient numbers were small in the cohorts evaluated.91 At this time, it is difficult to apply these data to clinical practice when patients present with a history of chronic β-blocker and ACEI use. The question of chronic antihypertensive use and effect on clinical outcomes in patients with septic shock warrants further investigation and is currently being studied in a multicenter observational evaluation (ClinicalTrials.gov identifier NCT03190408).92 Chronic ACEI and ARB use may also have significant effects in patients with sepsis who receive angiotensin II. Due to potential upregulation of angiotensin I receptors in patients receiving chronic ACEIs, an exaggerated increase in MAP may occur when giving angiotensin II.69 However, downregulation of angiotensin I receptors in patients receiving ARBs may result in a diminished response to angiotensin II initiation, an effect shown in a small subgroup analysis of the ATHOS-3 trial.67 Unfortunately, there is a need for further published data evaluating these scenarios to determine the true clinical effects of chronic ACEIs and ARBs in patients who receive angiotensin II.

Whether to continue chronic antihypertensive therapies during shock treatment is unknown, and it would seem contradictory to administer antihypertensive therapy in the setting of vasopressor agents. However, a 2013 study examined whether the administration of esmolol to normalize heart rate in the setting of septic shock would improve outcomes.93 The investigators reported improvements in hemodynamic parameters (heart rate, cardiac index, stroke volume, and MAP) in the cohort of patients treated with esmolol. This raises the question of whether β-blocker therapy is beneficial in septic shock and whether β-blocker therapy should be continued in patients with a history of receiving therapy before admission.

Pharmacogenomics/Genetics

The promise of pharmacogenomic therapy was recently demonstrated for the treatment of various cancers. Similarly, pharmacogenomic therapy holds unrealized potential for the treatment of septic shock at the present time. The future of septic shock treatment may include a broad genomic profile of patients on admission to determine optimal vasopressor treatments, corticosteroid response, and predilection to adverse effects. One example of the potential uses of this field is with the detection of genetic variations on the leucyl-cystinyl aminopeptidase (LNPEP) enzyme that is primarily responsible for the clearance of endogenous and exogenous vasopressin. One study found that patients with a homozygous (TT) genotype of the LNPEP rs4869317 single nucleotide polymorphism had increased vasopressin clearance (\( p = 0.028 \)) and increased 28-day mortality compared with other genotypes (51% vs 36.4%; adjusted hazard ratio 1.58, 95% CI, 1.21–2.06, \( p = 0.0007 \)).94 These findings have potential implications for all patients with septic shock, regardless of whether they receive exogenous vasopressin. However, at the current time, we are only at the gestational phases of research and understanding in this area.

Conclusions

Septic shock is a life-threatening disorder with mortality rates ~40%. Therapeutic interventions, including vasoactive agents to maintain goal hemodynamics, are imperative to patient care and survival. Norepinephrine is the first-line vasoactive agent of choice, but alternative and adjunctive agents such as epinephrine, vasopressin, angiotensin II, and phenylephrine may be warranted in specific scenarios and if patients do not have an appropriate hemodynamic response to the initiation of NE. Ultimately, more data are needed to elucidate how to best individualize care for patients with septic shock, and future research is needed to determine the effects of comorbidities, chronic medication use, and genetics on the pathophysiology of septic shock and subsequent implications for treatment.

References


