Vasopressor and Inotropic Management Of Patients With Septic Shock

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ABSTRACT

Numerous studies have evaluated the role of vasopressors and inotropes in the management of septic shock. This review assesses available evidence for the use of specific vasopressors in the management of septic shock. Use of adjunctive vasopressor therapy is also evaluated, examining the potential value of individual agents. Lastly, inotropic agents are evaluated for use in patients with myocardial dysfunction.

INTRODUCTION

Septic shock is a consequence of a systemic infection that is characterized by hypotension unresponsive to fluid resuscitation. It is a major health care problem that afflicts millions of people annually around the world.[1] Initial management of patients with septic shock is to maintain mean arterial pressure (MAP) and cardiac output while addressing the infection with antimicrobial therapy and source control (when applicable). Patients who fail to respond to aggressive fluid resuscitation are candidates for vasopressor or inotropic therapy in order to maintain hemodynamic parameters. Numerous studies and review articles have evaluated the role of vasopressors (norepinephrine, dopamine, epinephrine, vasopressin, phenylephrine) and inotropes (dobutamine, milrinone) in the management of septic shock. Recently the Surviving Sepsis Campaign (SSC) issued revised recommendations in its third iteration of guidelines for treating severe sepsis and septic shock. This review is a critical assessment of existing literature on use of vasopressors and inotropes in the management of septic shock.

VASOPRESSOR AGENTS

Norepinephrine and Dopamine

The goal of vasoactive agents in septic shock is to improve arterial pressure while avoiding unwanted adverse effects. Traditionally, dopamine and norepinephrine have been the most commonly used agents in clinical practice.[2] The pharmacology and clinical effects of these drugs are similar in patients with septic shock. Both agents stimulate α-adrenergic and β-adrenergic receptors but to different extents, increasing vasoconstriction, cardiac contractility, and heart rate, respectively, to varying degrees (Table 1).[2,3] Dopamine also stimulates dopaminergic receptors, resulting in increased splanchnic and renal perfusion.[4] However, this effect has not been shown to prevent organ failure in critically ill patients.[5]

The vasopressor response to norepinephrine is stronger and more consistent than the response to dopamine.[6–8] The result is a more reliable improvement in hemodynamic parameters, most notably MAP and urine output, when norepinephrine is administered compared to dopamine for patients with septic shock.[6–8] Despite this, the use of norepinephrine or dopamine as the first-line vasopressor agent for the treatment of septic shock was, until recently, the subject of ongoing debate. As a result of its potency, norepinephrine was historically thought to be deleterious due to concerns about excessive vasoconstriction that potentiated end-organ hypoperfusion and contributed to increased mortality.[9–11] Over time, this assumption was challenged because several observational studies suggested that use of norepinephrine might be associated with lower mortality rates than use of dopamine.[2,12–13]

In 2004, a Cochrane meta-analysis of three studies comparing norepinephrine (n = 31) to dopamine (n = 31) for septic-shock treatment highlighted this controversy by acknowledging that available data were inadequate to determine whether one agent was superior to the other for mortality outcomes (relative risk [RR], 0.88; 95% confidence interval [CI], 0.57–1.36).[14] Subsequently, experts recommended either norepinephrine or dopamine as first-line vasoactive agents for patients with septic shock in the first SSC guidelines and their subsequent iteration.[15,16] Meanwhile, in clinical practice, norepinephrine use became more prevalent as emerging studies began to demonstrate improved outcomes and fewer adverse events with its use compared to dopamine.[2,14,17–18]

The largest of these studies was a multicenter, randomized trial performed by the Sepsis Occurrence in Acutely Ill Patients II (SOAP II) investigators.[18] Patients with shock (septic, cardiogenic, or hypovolemic) were randomized to receive either dopamine or norepinephrine to restore and maintain blood pressure. The primary endpoint was rate of death from any cause at 28 days after randomization. Secondary endpoints included the occurrence of adverse events, most notably arrhythmia. At randomization, patients received dopamine or norepinephrine titrated up to the predetermined maximum dose (20 mcg/kg per minute for dopamine and 0.19 mcg/kg per minute for norepinephrine—doses shown to have similar effects on MAP).[19,20] Open-label norepinephrine was added if the desired blood pressure was not achieved after the maximum dose of study drug was reached. Use of epinephrine or vasopressin was permitted as rescue therapy.

A total of 1,679 patients with shock were included in the study (dopamine, n = 858; norepinephrine, n = 821). Sepsis was the cause of shock for 1,044 patients (62.2%); 502 received norepinephrine and 542 received dopamine. Overall, there was no significant difference in mortality rates at 28 days between the treatment groups: 52.5% in the dopamine group versus 48.5% in the norepinephrine group ($P = 0.10$). However, there were more arrhythmic events, most notably atrial fibrillation,

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Table 1 Relative Receptor Potency[3]

Agent	Alpha-1	Beta-1	Beta-2	Dopamine	Vasopressin-1
Dobutamine	+	+++++	+++	0	0
Dopamine	+++	++++	++	+++++	0
Epinephrine	+++++	++++	+++	0	0
Milrinone	0	0	0	0	0
Norepinephrine	+++++	+++	++	0	0
Phenylephrine	+++++	0	0	0	0
Vasopressin	0	0	0	0	+++++

0 = no significant receptor affinity; + through +++++ = minimal to maximal receptor affinity

among patients who received dopamine (24.1%) compared with those who received norepinephrine (12.4%), $P < 0.001$.

The doses of dopamine and norepinephrine were similar in the two groups throughout the trial. However, more patients in the dopamine group (26%) than in the norepinephrine group (20%) required open-label norepinephrine ($P < 0.001$), primarily due to an early termination of dopamine and switch to open-label norepinephrine to address uncontrolled arrhythmias. These differences were minor and unlikely to influence outcomes or limit the ability to determine differences between the two study drugs. The use of open-label epinephrine ($P = 0.10$) and vasopressin ($P = 0.67$) was similar in the two groups.

The publication of these new data prompted De Backer et al. to perform a meta-analysis of all studies providing outcomes data for septic-shock patients who were given norepinephrine compared with dopamine.[21] There were 11 published studies: five observational (1,360 patients) and six randomized (1,408 patients) totaling 2,768 patients. In the observational studies, there was significant heterogeneity ($P < 0.001$) and no observed difference in mortality ($P = 0.72$). However, after exclusion of the trial responsible for the heterogeneity[22] (n = 458), dopamine use was associated with an increased risk of death compared to norepinephrine use ($P < 0.01$). In the randomized trials, no heterogeneity was detected and dopamine use was associated with an increased risk of death ($P < 0.035$). Outcomes data for arrhythmic events was reported in two of the randomized trials (1,296 patients) but none of the observational studies. In both trials, dopamine use was associated with an increased risk of various types of arrhythmic events ($P = 0.001$). There are several limitations to the analysis; most notably, the studies that were reviewed reported various primary endpoints (mortality versus hemodynamic variables), times at which outcomes were measured, times of exposure to study drugs, and adverse events. Despite requiring adjustments to overcome these limitations, the systemic review provides a comprehensive and thorough analysis of the available data and convincingly demonstrates that dopamine use in patients with septic shock is associated with greater mortality and arrhythmic events compared to norepinephrine use.

Consequently, experts now recommend norepinephrine as the first-choice vasoactive agent for patients with septic shock and suggest dopamine as an alternative to norepinephrine for select patients with low risk of tachyarrhythmias and/or bradycardia.[1] To our knowledge, the suggestion that dopamine may be used for this patient population is based on the pharmacology of the drug rather than any specific evidence from clinical trials. Therefore, more than two decades after the question was first investigated, there is convincing data to suggest that norepinephrine is preferred to dopamine for use in patients with septic shock.

Additional studies are needed to evaluate the use of norepinephrine compared to vasopressor agents other than dopamine.

Epinephrine

Epinephrine is a catecholamine with potent activity at α-adrenergic and β-adrenergic receptors. Epinephrine increases MAP by increasing cardiac output and vascular tone;[23] it has been shown to adversely affect splanchnic blood flow and increase lactate levels.[24,25] However, according to the SSC guidelines, studies have not shown worse outcomes with epinephrine, and thus it is considered the first alternative to norepinephrine.[1] Four studies evaluated in the SSC guidelines showed no difference in the risk of dying (RR, 0.96; 95% CI, 0.77–1.21) between norepinephrine and epinephrine.[25–28] In fact, only one of the four studies was a comparison between norepinephrine and epinephrine;[28] the others were a comparison between epinephrine and a combination of norepinephrine and dobutamine.

Myburgh et al. conducted a randomized, double-blind study comparing norepinephrine with epinephrine in patients who required vasopressor support for any reason.[28] The study included 277 patients, 158 of whom had severe sepsis (epinephrine, n = 76; norepinephrine, n = 82). Within the severe sepsis subgroup, there was no significant difference between the cohorts with respect to median time to achieve MAP goal, number of vasopressor-free days, and 28-day or 90-day mortality. There was no difference between the cohorts with respect to use of other vasopressors or inotropes. During the entire study, significantly more patients in the epinephrine cohort were withdrawn by treating clinicians (18 epinephrine patients versus four norepinephrine patients). Reasons for withdrawal in the epinephrine cohort included lactic acidosis (seven patients), tachycardia (four patients), and failure to achieve prescribed parameters (five patients).

Three studies cited by the SSC guidelines as a comparison between epinephrine and norepinephrine reveal a significant proportion of patients who received dobutamine in the norepinephrine groups.[25–27] A total of 155 out of 195 patients (79.5%) received dobutamine. In the Annane study,[26] dobutamine was used if needed (129 of 169 patients), whereas it was used at the outset in the remaining two studies (26 of 26 patients). Annane et al. conducted a multicenter, randomized, double-blind study in 330 patients (norepinephrine/dobutamine, n = 169; epinephrine, n = 161) with septic shock. The primary outcome was 28-day all-cause mortality. At day 28, there were no mortality differences between the two cohorts (epinephrine, 64 deaths [40%] versus norepinephrine/dobutamine, 58 deaths [34%];

$P = 0.31$). There were no differences between the cohorts with respect to severe adverse events (arrhythmias, cerebrovascular or myocardial events, or other catecholamine-related events). Evaluation of arterial pH and lactate showed epinephrine to be associated with significantly lower pH through day 3 of therapy and higher lactate concentrations on day 1.[26] These metabolic effects are presumed to be secondary to aerobic glycolysis within skeletal muscles, rather than decreased organ perfusion.[29] The pH and lactate effects of epinephrine did not have any impact on organ recovery or survival. These studies suggest that epinephrine would be a suitable alternative to the combined therapy of norepinephrine and dobutamine.

While the SSC guidelines advocate the addition of epinephrine to norepinephrine when needed, few data have evaluated combination therapy of these agents. A recent prospective, randomized, double-blind study compared the addition of epinephrine or dobutamine to norepinephrine in the management of septic shock.[30] Patients were initiated on norepinephrine and, if the MAP was less than 70 mm Hg after reaching a dose of 0.1 mcg/kg per minute, then epinephrine or dobutamine was started. Results showed that the use of epinephrine was associated with significant improvements in hemodynamic parameters (heart rate, MAP, cardiac index), oxygen delivery, and urine output, while arterial pH and serum lactate were significantly worse. There was no difference in mortality between the two groups. The investigators commented that while epinephrine and dobutamine have inotropic ($\beta 1$) effects, epinephrine has vasoconstrictor (α) effects to augment hemodynamic response, whereas dobutamine has vasodilation ($\beta 2$) effects, thus reducing its benefits.

The addition of one catecholamine in a patient already receiving a different catecholamine highlights the importance of dose initiation and titration. At what point is it reasonable or necessary to add a second agent? Seguin et al. noted that in evaluating studies comparing epinephrine versus the combination of norepinephrine and dobutamine, the dose of catecholamines administered is just as important as the choice of catecholamines.[27] Mahmoud et al.[30] commented on the significant increase in systemic vascular resistance (SVR) in patients who were in the norepinephrine-epinephrine cohort and noted that this may have been a consequence of titration of epinephrine up to 0.3 mcg/kg per minute, whereas another study saw no change in SVR at an epinephrine dose of 0.1 mcg/kg per minute.[31] Martin et al. successfully used norepinephrine monotherapy in 15 of 16 patients who received a mean dose of 1.5 mcg/kg per minute.[32] Thus, it has been suggested that a dose of norepinephrine should be determined at which a second agent should be added.[33] However, despite the variation in norepinephrine dosing strategies in the literature, the SSC states that it is unrealistic to define a maximal dose of norepinephrine that could be used for all patients; instead, the decision to add a second agent should be made on clinical grounds (i.e., treatment failure or intolerability).[34] Nevertheless, as discussed below, excessive catecholamine exposure may be detrimental to the patient, and it seems reasonable that careful attention to doses used and associated outcomes may reveal a norepinephrine dose at which a second vasopressor may be added.

Epinephrine's evolution in the management of septic shock to being the first alternative to norepinephrine highlights its efficacy as both an inotrope and vasopressor. Data support the use of epinephrine as an alternative to the combination of norepinephrine and dobutamine. Early concerns about lactic acidosis appear to be unfounded. Additional studies evaluating the combination of epinephrine with norepinephrine will aid in determining the relative benefit of this combination compared with the combination of norepinephrine and dobutamine.

Vasopressin

Vasopressin (antidiuretic hormone) is a neurohypophyseal hormone with various actions. Receptor-mediated actions of vasopressin include vasoconstriction (arginine-vasopressin-receptor 1a [AVPR1a]), adrenocorticotropin hormone release (AVPR1b), and water retention (AVPR2).[35] Vasopressin also stimulates oxytocin receptors, leading to vasodilation.[35] Levels of vasopressin increase rapidly in patients with septic shock; however, they decline sharply to low levels seven days after the onset of shock.[36,37] Depressed levels of vasopressin are presumed to be secondary to impaired synthesis. Vasopressin deficiency may be exacerbated in patients who are also receiving corticosteroids, which are known to inhibit vasopressin secretion.[35] At low levels (less than 10 pmol/L), the antidiuretic actions of vasopressin predominate, with increasing levels leading to progressive predominance of vasoconstrictor effects.[35]

Several small studies have documented the potential benefits of vasopressin therapy in septic shock.[38–41] Vasopressin infusions are associated with decreases in norepinephrine dosing requirements as well as increases in creatinine clearance and urine output. These studies supported the notion that vasopressin might provide a significant benefit in the management of septic shock, but they were not powered to determine a mortality benefit.

The Vasopressin and Septic Shock Trial (VASST)[37] was a randomized, double-blind trial comparing vasopressin with norepinephrine in the management of septic shock. The primary outcome was all-cause mortality at 28 days. Patients receiving at least 5 mcg per minute of norepinephrine were randomized to receive low-dose vasopressin (0.01–0.03 units per minute) or norepinephrine (5–15 mcg per minute). Open-label vasopressor therapy was allowed when the study drugs reached the maximum protocol dose. A total of 778 patients were included in the study (vasopressin, n = 396; norepinephrine, n = 382). The 28-day mortality rates were 35.4% and 39.3% for the norepinephrine and vasopressin cohorts, respectively ($P = 0.26$). In the *a priori* identified subgroup of less-severe septic shock (norepinephrine dose less than 15 mcg per minute), the vasopressin group had lower mortality than the norepinephrine group at 28 days (26.5% versus 35.7%, $P = 0.05$). However, the test for heterogeneity by severity of shock subgroups was not significant ($P = 0.10$). Thus, the potential benefit seen in the less-severe septic-shock cohort can only be viewed as hypothesis-generating. The incidence of serious adverse events was similar between the two groups (vasopressin, 10.3%; norepinephrine, 10.5%). Digital ischemia occurred in 2% of the vasopressin patients compared with 0.5% of the norepinephrine patients ($P = 0.11$).[37]

VASST was designed to detect a 10% difference in mortality assuming a 60% mortality rate in the norepinephrine cohort.

The lower mortality rate of 39.3% seen in the norepinephrine cohort made the study underpowered to detect a smaller but clinically significant difference in mortality. To realize a statistically significant 4% difference in mortality (39% versus 35%), a sample size of 2,286 patients per group would have been required. It has been noted that the mean duration of time that elapsed from meeting the study inclusion criteria to drug infusion was 12 hours.[35] For patients who received vasopressin within 12 hours of randomization, there was a trend toward decreased mortality compared with the norepinephrine group (32.2% versus 40.5%, $P = 0.12$).

Post-hoc analyses of VASST showed an interesting vasopressin-corticosteroid interaction.[42] For patients who received corticosteroids, use of vasopressin was associated with a significant decrease in mortality compared with norepinephrine plus corticosteroids (35.9% versus 44.7%, $P = 0.03$). Conversely, for groups that did not receive corticosteroids, vasopressin was associated with a trend toward increased mortality (33.7% versus 21.3%, $P = 0.06$). In patients who received corticosteroids and vasopressin, serum vasopressin concentrations were significantly increased at six hours (by 33%) and 24 hours (by 67%) compared with those who did not receive corticosteroids. The investigators theorized that one of the potential benefits of corticosteroids could be the increase in vasopressin concentrations. A recent study examined the interaction of vasopressin and hydrocortisone in 61 patients with septic shock.[43] Unlike the VASST trial, addition of hydrocortisone to vasopressin infusions did not lead to an increase in vasopressin concentrations. Important differences between the findings in VASST and the findings by Gordon et al. are: 1) VASST measured vasopressin concentrations in 107 patients compared with 61 in the Gordon study; 2) VASST limited vasopressin infusions to 0.03 units per minute while Gordon et al. used titrated doses up to 0.06 units per minute; 3) APACHE II scores were likely lower in Gordon et al. (steroid cohort median, 19) compared to VASST (all steroid patients' mean, 27.4); and 4) baseline vasopressin levels were much higher in Gordon et al. (steroid cohort mean, 302 pmol/L) compared with VASST (steroid cohort median, less than 10 pmol/L). Thus, patient differences at baseline between the studies may have accounted for variations in the effects of steroids on vasopressin serum concentrations.

Data from VASST showed that vasopressin serum concentrations were lower as body mass index (BMI) increased (although mortality was decreased as BMI increased).[44] Indeed, data are emerging that suggest the vasopressin dose in VASST was too low.[45,46] In comparing two vasopressin dosing regimens (0.033 units per minute versus 0.067 units per minute), it was shown that the higher dose restored cardiovascular function more effectively in patients with vasodilatory shock.[46] Another study showed a decreased response to vasopressin in patients who received lower doses on a per-kilogram basis.[45] The SSC guidelines recommend a maximum vasopressin dose of 0.03 units per minute. However, data suggesting that higher doses may be beneficial have led to a recommendation that a large, randomized trial be pursued to explore high-dose vasopressin in managing septic shock.[35]

The use of vasopressin monotherapy in the management of septic shock has undergone preliminary investigation. One retrospective study compared vasopressin monotherapy to norepinephrine in the management of 130 adult patients (65 in each treatment arm) with septic shock.[47] The primary endpoint of the study was achievement of goal MAP after six hours of therapy. Results showed no difference between the two agents in the proportion of patients reaching goal MAP (vasopressin, 63%; norepinephrine, 67.7%; $P = 0.69$). The previously discussed study by Gordon et al. demonstrated in an open-label, prospective fashion that use of vasopressin monotherapy could be studied in a randomized, double-blind format, a study that is currently under way (http://www.controlled-trials.com/ISRCTN20759191).

The SSC guidelines do not recommend vasopressin as a single agent for the management of septic shock and instead suggest that it can be added to norepinephrine monotherapy with the intent of either increasing MAP or decreasing norepinephrine dose.[1] In addition, the guidelines state that combined data from seven trials comparing norepinephrine with vasopressin (or terlipressin) do not support the routine use of vasopressin (RR of mortality, 1.12; 95% CI, 0.96–1.3; fixed effects; $I^2 = 0\%$). A recent meta-analysis evaluated nine comparative trials involving vasopressin or terlipressin in the management of vasodilatory shock.[48] The use of vasopressin was associated with a decrease in mortality for patients with septic shock (42.5% versus 49.2%; RR, 0.87; 95% CI, 0.75–1.0; $P = 0.05$). The authors found the number needed to treat was one to 15. Vasopressin was also associated with a significant decrease in norepinephrine dosing requirements and heart rate while not decreasing cardiac output. The mean dose of vasopressin used in the trials was 0.055 ± 0.027 units per minute. There were no differences in adverse events between the treatment groups (RR, 0.98; $P = 0.92$). The investigators concluded that vasopressin is safe, is useful in weaning patients off catecholamines, and is associated with decreased mortality.

Potential benefits associated with use of vasopressin include decreasing heart rate without decreasing cardiac output, thus possibly preventing myocardial dysfunction or tachycardia-induced cardiomyopathy.[49] Further, reduction in catecholamine requirements may mitigate adverse effects on immune function, coagulation, metabolic efficiency, and stimulation of bacterial growth.[50] In addition, evaluation of kidney injury in the VASST trial showed that for patients in the risk category under the RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria, vasopressin was associated with a trend toward a lower rate of progression to renal failure or loss (20.8% versus 39.6%, $P = 0.03$) and a lower rate of renal replacement therapy (17.0% versus 37.7%, $P = 0.02$).[51]

While VASST was unable to demonstrate a clear benefit for the addition of vasopressin to norepinephrine, emerging data suggest that vasopressin may be a reasonable second-line agent in patients deemed to have an insufficient response to norepinephrine.

Phenylephrine

Phenylephrine is an α-1 receptor agonist with principal activity at large arterioles and little effect at terminal arterioles.[52] With no cardiac effects, phenylephrine is unlikely to cause tachycardia. However, due to the potential for decreasing stroke volume, the SSC guidelines do not recommend phenylephrine

for the treatment of septic shock unless patients experience serious arrhythmias with norepinephrine, have high cardiac output, or require salvage therapy.[1]

A study in 32 patients with septic shock evaluated 12-hour systemic and regional hemodynamic effects of phenylephrine compared to norepinephrine.[52] Results showed that each drug was associated with significant increases in systemic vascular resistance index and left ventricular stroke work index, with associated significant decreases in heart rate. Pulmonary vascular resistance index increased only with phenylephrine (293 ± 253 dyne•s/cm^5/m^2 versus 348 ± 296 dyne•s/cm^5/m^2, $P < 0.05$). There were no significant differences between the two groups with respect to global oxygen transport variables or acid base balance. Goal MAP (65–75 mm Hg) was reached in all patients; however, MAP was significantly higher in the norepinephrine group ($P = 0.011$) despite the use of significantly greater doses of phenylephrine compared with norepinephrine ($P < 0.001$). The investigators noted that while phenylephrine had systemic hemodynamic effects comparable to norepinephrine, phenylephrine was less effective at correcting arterial hypotension.

No comparative outcomes trials have evaluated the efficacy of phenylephrine. Thus, it is reasonable that use of phenylephrine be relegated to situations in which norepinephrine is not tolerated. Its role as salvage therapy is more difficult to justify. As a pure α-agonist, it is unlikely to provide additional benefit to an existing infusion of norepinephrine. The need for additional vasopressor response in a patient who is receiving combined inotrope, norepinephrine, and vasopressin therapy would suggest continuing to increase the norepinephrine dose (doses up to 3.3 mcg/kg per minute have been studied)[53] or possibly increasing the dose of vasopressin.

INOTROPIC AGENTS

Cardiac depression with impaired left ventricular function is a well-recognized manifestation of septic shock, reported in up to 60% of patients.[54] Elevated catecholamine levels in response to reduced venous return in early sepsis facilitate an adrenergic response to augment cardiac contractility and heart rate. As sepsis progresses, mitochondrial dysfunction and tissue hypoxia lead to reduced adenosine triphosphate formation. The mismatch between myocardial oxygen supply and demand results in the death of cardiac myocytes.[55,56] The presentation of cardiac dysfunction in septic shock can manifest as an elevated troponin level, decreased contractility, an impaired ventricular response to fluid, or ventricular dilation.[56] Regardless of the manifestation, it is important to recognize that sepsis-induced myocardial dysfunction is associated with increased mortality in comparison to patients without cardiovascular impairment.[57]

The most recent SSC guidelines recommend that a trial of dobutamine infusion (up to 20 mcg/kg per minute) be administered or added to pre-existing vasopressor therapy in the presence of myocardial dysfunction, defined as elevated cardiac filling pressures and low cardiac output. Inotropic therapy with dobutamine is also recommended for patients with ongoing signs of hypoperfusion despite achievement of adequate intravascular volume and MAP.[1] These guideline recommendations, however, are based upon a paucity of outcomes data from randomized controlled trials.

Care bundles incorporated into the most recent SSC guidelines recommend measurement of central venous oxygen saturation ($S_{cv}O_2$) within the first six hours in patients with persistent arterial hypotension despite adequate fluid resuscitation or initial serum lactate greater than 4 mmol/L.[1] $S_{cv}O_2$ values less than 70% in the setting of adequate blood volume are indicative of impaired oxygen delivery, warranting inotropic therapy in cases of low cardiac output to achieve adequate perfusion.[58]

Currently available inotropes for sepsis-induced cardiac dysfunction include dobutamine and milrinone. Dobutamine achieves increases in cardiac output through β-adrenergic-mediated stimulation of adenylate cyclase, resulting in increased levels of cyclic adenylate monophosphate (cAMP), which augments the release of calcium from the sarcoplasmic reticulum and enhances the force of cardiac contraction. Milrinone increases cardiac output by preventing the breakdown of cAMP through selective inhibition of the enzyme phosphodiesterase 3.[59]

Several factors should be incorporated into clinical decision-making when selecting an inotropic agent. Despite varying mechanisms, dobutamine and milrinone have similar efficacy with regard to increasing cardiac output and decreasing cardiac filling pressures. Milrinone, however, causes more significant vasodilation, leading to greater reductions in blood pressure and SVR when compared with dobutamine. Because dobutamine provides direct stimulation of the β-1 adrenergic receptors, it is recognized as more problematic with regard to tachycardia and arrhythmia. Dobutamine increases myocardial oxygen demand to a greater extent than milrinone, which can be problematic in cases of new or recent myocardial ischemia. Renal impairment significantly increases the half-life of milrinone, warranting adjustment in this population to prevent drug accumulation and cardiac adverse effects. It is important to recognize that since milrinone exerts its pharmacodynamic activity outside of the β-1 receptor, the drug maintains inotropic activity in the setting of recent or concurrent β-blockade.[59] No comparative trials have evaluated dobutamine and milrinone in patients with septic shock. Milrinone tends to be indicated less in patients with hypotension or renal impairment compared with dobutamine, both of which are prevalent in patients with septic shock.

Dobutamine is the inotrope endorsed by the sepsis guidelines based largely on the trial comparing early goal-directed therapy (EGDT) versus standard care in sepsis.[1] Rivers et al. demonstrated that a protocolized approach to early resuscitation could significantly reduce 28-day mortality in patients presenting with severe sepsis or septic shock. After optimization of central venous pressure, MAP, and hematocrit, dobutamine was added for patients with a persistently low $S_{cv}O_2$. In the EGDT trial, dobutamine therapy was initiated at 2.5 mcg/kg per minute and increased by 2.5 mcg/kg per minute every 30 minutes if $S_{cv}O_2$ was 70% or less to a maximum dose of 20 mcg/kg per minute. In the event of hypotension (MAP less than 65 mm Hg) or tachycardia (heart rate greater than 120 beats per minute), the dose of dobutamine was discontinued or decreased. At the conclusion of the six-hour resuscitation period, 13.7% of the EGDT patients required treatment with dobutamine compared with 0.8% of patients receiving standard therapy ($P < 0.001$).[60]

The results of the EGDT trial have recently been challenged

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by the ProCESS trial (Protocolized Care for Early Septic Shock), which was designed to evaluate whether all components of EGDT are still warranted in the contemporary era of sepsis management. The standard-therapy protocol arm required administration of fluids and vasoactive agents to reach goals for systolic blood pressure and shock index, which were compared to patients managed by the EGDT protocol or usual care. Inotropes were not included in the standard-therapy protocol arm. No differences in mortality at 60 days, 90 days, or one year were noted among groups. The incidence of acute renal failure requiring initiation of renal replacement therapy, however, was higher in the standard-therapy arm compared with the other two groups ($P = 0.04$) even though those patients received significantly more fluid resuscitation ($P < 0.001$). The results of this study should be applied with caution, as patients in the EGDT trial had higher rates of pre-existing cardiac disease and higher serum lactate levels at presentation.[61] Furthermore, the ARISE (Australasian Resuscitation in Sepsis Evaluation) trial is another recent study challenging the impact of EGDT that was conducted in a manner similar to ProCESS. Patients receiving EGDT were more likely to receive dobutamine (15.2% versus 2.6%, $P < 0.001$) compared with patients in the usual-care arm. Despite higher MAP in the EGDT group at the end of the six-hour intervention period ($P = 0.04$), no difference in mortality at 90 days was noted between groups ($P = 0.90$).[62]

Clinicians may question whether a role for inotropes continues to exist in patients with septic shock in light of these recent challenges to EGDT. Although the role of inotropes during the initial resuscitation phase of septic-shock patients may be diminished, a recent consensus statement on circulatory shock and hemodynamic monitoring published by the European Society of Intensive Care Medicine suggests initiation of inotropes when altered cardiac function is accompanied by inadequate cardiac output and signs of tissue hypoperfusion that persist following optimization of preload.[63]

Unanswered questions remain regarding inotrope therapy in the setting of septic shock. Is there an appropriate objective trigger to initiate therapy? Studies have varied widely, initiating therapy based upon cardiac index, $S_{cv}O_2$ monitoring, and vasopressor requirements. The roles of noninvasive monitoring and initiation of inotropic therapy should be further explored. How should adverse effects be handled for patients on inotropic therapy? Management of patients who develop adverse effects while receiving inotropic agents is poorly defined. Patients in the EGDT trial had their dobutamine doses reduced or discontinued if hypotension or tachycardia developed. For patients who develop hypotension upon dobutamine initiation, the role of epinephrine should be further investigated. Is there a role for milrinone in patients with septic shock? A pilot study of patients with systemic inflammatory response syndrome or sepsis on various combinations of vasopressors and inotropes noted that initiation of milrinone 0.5 mcg/kg per minute without an initial bolus improved cardiac index and left ventricular stroke work index. Even after omission of the milrinone bolus, a substantial decrease in systemic vascular resistance index was noted.[64] Further investigation is needed to determine if the drug is beneficial to patients with sepsis, perhaps as an alternative therapy for patients failing dobutamine due to tachyarrhythmia.

CONCLUSION

There are convincing data to support norepinephrine as the preferred first-line vasopressor agent for patients with septic shock. Available data suggest that dopamine use may be associated with a higher incidence of mortality and arrhythmic events compared with norepinephrine administration; however, pharmacology and expert opinion suggest that it may be a useful alternative to norepinephrine for select patients with septic shock and low risk of tachyarrhythmias and/or bradycardia. Emerging data support vasopressin as a reasonable second-line agent in patients who are responding inadequately to norepinephrine. Phenylephrine should be reserved for patients unable to tolerate norepinephrine due to arrhythmia; its use as a salvage agent is difficult to justify using current literature. Additional studies are needed to further delineate the role of epinephrine and inotropes in patients with sepsis-induced cardiac dysfunction.

REFERENCES

1. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580–637.
2. Sakr Y, Reinhart K, Vincent JL, et al. Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study. *Crit Care Med* 2006;34:589–597.
3. Overgaard CB, Dzavik V. Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. *Circulation* 2008;118:1047–1056.
4. Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet* 2000;356:2139–2143.
5. Van den Berghe G, de Zegher F. Anterior pituitary function during critical illness and dopamine treatment. *Crit Care Med* 1996;24:1580–1590.
6. Martin C, Saux P, Albanese J, et al. A new look at norepinephrine to treat human hyperdynamic septic shock. *Anesthesiology* 1987;67:A648.
7. Desjars P, Pinaud M, Potel G, et al. A reappraisal of norepinephrine therapy in human septic shock. *Crit Care Med* 1987;15:134–137.
8. Meadows D, Edwards JD, Wilkins RG, Nightingale P. Reversal of intractable septic shock with norepinephrine therapy. *Crit Care Med* 1988;16:663–666.
9. Moyer JH, Skelton JM, Mills LC. Norepinephrine; effect in normal subjects; use in treatment of shock unresponsive to other measures. *Am J Med* 1953;15:330–343.
10. Smulyan H, Cuddy RP, Eich RH. Hemodynamic effects of pressor agents in septic and myocardial infarction shock. *JAMA* 1964;190:188–194.
11. Cohn JN, Luria MH. Studies in clinical shock and hypotension: II. Hemodynamic effects of norepinephrine and angiotensin. *J Clin Invest* 1965;44:1494–1504.
12. Martin C, Viviand X, Leone M, Thirion X. Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 2000;28:2758–2765.
13. Boulain T, Runge I, Bercault N, et al. Dopamine therapy in septic shock: detrimental effect on survival? *J Crit Care* 2009;24:575–582.
14. Mullner M, Urbanek B, Havel C, et al. Vasopressors for shock. *Cochrane Database Syst Rev* 2004;CD003709.
15. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32:858–873.
16. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;36:296–327.
17. Patel GP, Grahe JS, Sperry M, et al. Efficacy and safety of dopamine versus norepinephrine in the management of septic shock. *Shock* 2010;33:375–380.

18. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010;362:779–789.
19. Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *JAMA* 1994;272:1354–1357.
20. De Backer D, Creteur J, Silva E, et al. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? *Crit Care Med* 2003;31:1659–1667.
21. De Backer D, Aldecoa C, Njimi H, Vinvent JL. Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis. *Crit Care Med* 2012;40:725–730.
22. Povoa P, Carneiro A, Ribeiro O, et al. Influence of vasopressor agent in septic shock mortality. Results from the Portuguese Community-Acquired Sepsis Study (SACiUCI study). *Crit Care Med* 2009;37:410–416.
23. Hollenberg SM. Vasopressor support in septic shock. *Chest* 2007;132:1678–1687.
24. Meier-Hellmann A, Reinhart K, Bredle DL, et al. Epinephrine impairs splanchnic perfusion in septic shock. *Crit Care Med* 1997;25:399–404.
25. Levy B, Bollaert PE, Charpentier C, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. *Intensive Care Med* 1997;23:282–287.
26. Annane D, Vignon P, Renault A, et al. CATS Study Group: norepinephrine plus dobutamine versus epinephrine alone for management of septic shock. A randomised trial. *Lancet* 2007;370:676–684.
27. Seguin P, Bellissant E, Le Tulzo Y, et al. Effects of epinephrine compared with the combination of dobutamine and norepinephrine on gastric perfusion in septic shock. *Clin Pharmacol Ther* 2002;71:381–388.
28. Myburgh JA, Higgins A, Jovanovska A, et al. CAT Study investigators: a comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med* 2008;34:2226–2234.
29. Levy B, Gibot S, Franck P, et al. Relation between muscle Na+K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet* 2005;365:871–875.
30. Mahmoud KM, Ammar AS. Norepinephrine supplemented with dobutamine or epinephrine for the cardiovascular support of patients with septic shock. *Indian J Crit Care Med* 2012;16:75–80.
31. Le Tulzo Y, Seguin P, Guacouin A, et al. Effects of epinephrine on right ventricular function in patients with severe septic shock and right ventricular failure. *Intensive Care Med* 1997;23:664–670.
32. Martin C, Papazian L, Perin G, et al. Norepinephrine or dopamine for treatment of hyperdynamic septic shock? *Chest* 1993;103:1826–1831.
33. Alaniz C, Pollard S. Vasopressor dosing in septic shock. *Crit Care Med* 2013;12:e483–e484.
34. Annane D, Dellinger RP. Vasopressor dosing in septic shock (reply). *Crit Care Med* 2013;12:e484.
35. Russell JA. Bench to beside review: vasopressin in the management of septic shock. *Crit Care* 2011;15:226.
36. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 1997;95:1122–1125.
37. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008;358:877–887.
38. Landry DW, Levin HR, Gallant EM, et al. Vasopressin pressor hypersensitivity in vasodilatory septic shock. *Crit Care Med* 1997;25:1279–1282.
39. Luckner G, Dunser MW, Jochberger S, et al. Arginine vasopressin in 316 patients with advanced vasodilatory shock. *Crit Care Med* 2005;33:2659–2666.
40. Luckner G, Mayr VD, Jochberger S, et al. Comparison of two dose regimens of arginine vasopressin in advanced vasodilatory shock. *Crit Care Med* 2007;35:2280–2285.
41. Dunser MW, Mayr AJ, Ulmer H, et al. Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. *Circulation* 2003;107:2313–2319.
42. Russell JA, Walley KR, Gordon AC, et al. Interaction of vasopressin infusion, corticosteroid treatment, and mortality in septic shock. *Crit Care Med* 2009;37:811–818.
43. Gordon AC, Mason AJ, Perkins GD, et al. The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. *Crit Care Med* 2014;42:1325–1333.
44. Wacharasint P, Boyd JH, Russell JA, Walley KR. One size does not fit all in severe infection: Obesity alters outcome, susceptibility, treatment and inflammatory response. *Crit Care* 2013;17:R122.
45. Miller JT, Welage LS, Kraft MD, Alaniz C. Does body weight impact the efficacy of vasopressin therapy in the management of septic shock? *J Crit Care* 2012;27:289–293.
46. Torgersen C, Dunser MW, Wenzel V, et al. Comparing two different arginine vasopressin doses in advanced vasodilatory shock: a randomized, controlled, open-label trial. *Int Care Med* 2010;36:57–65.
47. Daley MJ, Lat I, Mieure KD, et al. A comparison of initial monotherapy with norepinephrine versus vasopressin for resuscitation in septic shock. *Ann Pharmacother* 2013;47:301–310.
48. Serpa Neto A, Nassar AP, Cardoso SO, et al. Vasopressin and terlipressin in adult vasodilatory shock: a systematic review and meta-analysis of nine randomized controlled trials. *Crit Care* 2010;16:R154.
49. Ricard C. Stress-related cardiomyopathies. *Ann Intensive Care* 2011;1:39–46.
50. Singer M, Mattay MA. Clinical review: thinking outside the box—an iconoclastic view of current practice. *Crit Care* 2011;15:225.
51. Gordon AC, Russell JA, Walley KR, et al. The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Med* 2010;36:83–91.
52. Morelli A, Ertman C, Rehberg S, et al. Phenylephrine versus norepinephrine for initial hemodynamic support of patients with septic shock: a randomized controlled trial. *Crit Care* 2008;12:R43.
53. Martin C, Saux P, Eon B, et al. Septic shock: a goal-directed therapy using volume loading, dobutamine and/or norepinephrine. *Acta Anaesthesiol Scand* 1990;34:413–417.
54. Vieillard-Baron A, Caille V, Charron C, et al. Actual incidence of global left ventricular hypokinesia in adult septic shock. *Crit Care Med* 2008;36:1701–1706.
55. Rudiger A. Beta-block the septic heart. *Crit Care Med* 2010;38:S608–S612.
56. Zanotti-Cavazzoni SL, Hollenberg SM. Cardiac dysfunction in severe sepsis and septic shock. *Curr Opin Crit Care* 2009;15:392–397.
57. Blanco J, Muriel-Bombin A, Sagredo V, et al. Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicentre study. *Crit Care* 2008;12:158.
58. Hollenberg SM, Ahrens TS, Annane D, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004. *Crit Care Med* 2004;32:1928–1948.
59. Parissis J, Farmakis D, Nieminen M. Classical inotropes and new cardiac enhancers. *Heart Fail Rev* 2007;12:149–156.
60. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–1377.
61. ProCESS Investigators, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. *New Engl J Med* 2014;370:1683–1693.
62. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, et al. Goal-directed resuscitation for patients with early septic shock. *New Engl J Med* 2014;371:1496–1506.
63. Cecconi M, DeBacker D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med* 2014;40:1795–1815.
64. Heinz G, Geppert A, Delle Karth G, et al. IV milrinone for cardiac output increase and maintenance: comparison in nonhyperdynamic SIRS/sepsis and congestive heart failure. *Intensive Care Med* 1999;25:620–624. ■