CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Vasopressor Support in Septic Shock*

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When fluid administration fails to restore an adequate arterial pressure and organ perfusion in patients with septic shock, therapy with vasopressor agents should be initiated. The ultimate goals of such therapy in patients with shock are to restore effective tissue perfusion and to normalize cellular metabolism. Although arterial pressure is the end point of vasopressor therapy, and the restoration of adequate pressure is the criterion of effectiveness, BP does not always equate to blood flow; so, the precise BP goal to target is not necessarily the same in all patients. There has been longstanding debate about whether one catecholamine vasopressor agent is superior to another, but different agents have different effects on pressure and flow. The argument about which catecholamine is best in a given situation is best transformed into a discussion about which agent is best suited to implement the therapeutic strategy chosen. Despite the complex pathophysiology of sepsis, an underlying approach to its hemodynamic support can be formulated that takes both pressure and perfusion into account when choosing therapeutic interventions. The efficacy of hemodynamic therapy in sepsis should be assessed by monitoring a combination of clinical and hemodynamic parameters. How to optimize regional blood and microcirculatory blood flow remains uncertain. Thus, specific end points for therapy are debatable and are likely to evolve. Nonetheless, the idea that clinicians should define specific goals and end points, titrate therapies to those end points, and evaluate the results of their interventions on an ongoing basis remains a fundamental principle. ***(CHEST 2007; 132:1678–1687)***

Key words: dopamine; epinephrine; norepinephrine; phenylephrine; sepsis; septic shock; vasopressin; vasopressor

Abbreviations: ACCCM = American College of Critical Care Medicine; pHi = intracellular pH

Septic shock results when infectious agents or infection-induced mediators in the bloodstream produce hemodynamic decompensation. Its pathogenesis involves a complex interaction among pathologic vasodilation, relative and absolute hypovolemia, myocardial dysfunction, and altered blood flow distribution due to the inflammatory response to infection; even after the restoration of intravascular volume, microcirculatory abnormalities may persist and lead to the maldistribution of cardiac output.[1,2] About half of the patients who succumb to septic shock die of multiple organ system failure, and most other nonsurvivors have progressive hypotension with low systemic vascular resistance that is refractory to therapy with vasopressor agents.[1] Although myocardial dysfunction is not uncommon, death from myocardial failure is rare.[3]

The initial priority in managing septic shock is to maintain a reasonable mean arterial pressure and cardiac output to keep the patient alive while the source of infection is identified and addressed. Another therapeutic goal is to interrupt the pathogenic sequence leading to septic shock. While these latter goals are being pursued, adequate organ system perfusion and function must be maintained, guided by cardiovascular monitoring.

This review will focus on vasopressor support for patients with septic shock. Hemodynamic therapy for sepsis can be conceptualized in three broad

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categories: fluid resuscitation, vasopressor therapy, and inotropic therapy. Although many vasoactive agents have both vasopressor and inotropic actions, the distinction is made on the basis of the intended goals of therapy; vasopressor actions raise BP, while inotropic actions raise cardiac output. This is not to minimize the importance of assessing the effects of vasoactive agents on perfusion, as should be made clear from the discussion below.

General Approach

Septic shock requires early, vigorous resuscitation. An integrated approach directed at rapidly restoring systemic oxygen delivery and improving tissue oxygenation has been demonstrated[4] to improve survival significantly in patients with septic shock. While the specific approach that is utilized may vary, there are critical elements that should be incorporated into any resuscitative effort. Therapy should be guided by parameters that reflect the adequacy of tissue and organ perfusion. Fluid infusion should be vigorous and titrated to clinical end points of volume repletion. Systemic oxygen delivery should be supported by ensuring arterial oxygen saturation, maintaining adequate levels of hemoglobin, and using vasoactive agents that are directed to physiologic and clinical end points.

In shock states, the estimation of BP using a cuff may be inaccurate, and the use of an arterial cannula provides a more appropriate and reproducible measurement of arterial pressure.[5,6] These catheters also allow beat-to-beat analysis so that decisions regarding therapy can be based on immediate and reproducible BP information, facilitating the administration of large quantities of fluids and potent vasopressor and inotropic agents to critically ill patients.[1]

Although patients with shock and mild hypovolemia may be treated successfully with rapid fluid replacement alone, hemodynamic monitoring may be useful in providing a diagnostic hemodynamic assessment in patients with moderate or severe shock. In addition, because hemodynamics can change rapidly in patients with sepsis, and because noninvasive evaluation is frequently incorrect in estimating filling pressures and cardiac output, hemodynamic monitoring is often useful for monitoring the response to therapy.

Goals and Monitoring of Vasopressor Therapy

When fluid administration fails to restore an adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be initiated.[6] The ultimate goals of hemodynamic therapy in patients with shock are to restore effective tissue perfusion and to normalize cellular metabolism. In patients with septic shock, tissue hypoperfusion results not only from decreased perfusion pressure attributable to hypotension but also from abnormal shunting of a normal or increased cardiac output.[1] Cellular alterations may also occur. Hemodynamic support of sepsis thus requires the consideration of both global and regional perfusion.

Arterial pressure is the end point of vasopressor therapy, and the restoration of adequate pressure is the criterion of effectiveness. BP, however, does not always equate to blood flow, and the precise level of mean arterial BP to aim for is not necessarily the same in all patients. Animal studies[7,8] have suggested that below a mean arterial BP of 60 mm Hg, autoregulation in the coronary, renal, and CNS vascular beds is compromised, and flow may become linearly dependent on BP. Loss of autoregulation can occur at different levels in different organs, however, and the degree to which septic patients retain intact autoregulation is uncertain. Some patients (especially those with preexisting hypertension) may require higher BPs to maintain adequate perfusion.

The precise BP goal to target in patients with septic shock remains uncertain. Most experts agree, largely on the basis of the animal studies cited above and on physiologic reasoning, that in septic patients with evidence of hypoperfusion, the mean arterial pressure should be maintained at $>$ 60 mm Hg[6] or 65 mm Hg.[9] There are no data from randomized clinical trials demonstrating that failure to maintain BP at this level worsens outcome, but it seems unlikely that such a clinical trial will be conducted soon. It should be recognized that individual patients may have BPs that are somewhat lower than these thresholds without hypoperfusion; it is the scenario of hypotension with shock that merits vasopressor support.

Some investigators, however, have argued that higher BP targets are warranted. The renal circulation may be especially sensitive to perfusion pressure, and vasopressor therapy to augment renal perfusion pressure has been shown to increase urine output and/or creatinine clearance in a number of open-label clinical series[10–17]; the targeted mean BP varied, but was as high as 75 mm Hg. Improvements in renal function with increased perfusion pressure, however, have not been demonstrated in prospective, randomized studies. Randomized trials[18,19] comparing norepinephrine titrated to either 65 or 85 mm Hg in patients with septic shock have found no significant differences in metabolic variables or renal function.

It is important to supplement end points such as BP with an assessment of regional and global perfusion. Bedside clinical assessment provides a good

indication of global perfusion. Indications of decreased perfusion include oliguria, clouded sensorium, delayed capillary refill, and cool skin. Some caution is necessary in interpreting these signs in septic patients, however, since organ dysfunction can occur in the absence of global hypoperfusion.

Clinical assessments can be supplemented by other measures, such as serum lactate levels and mixed venous oxygen saturation. Elevated lactate levels in patients with sepsis may result from global hypoperfusion or from cellular metabolic alterations, which may or may not represent tissue hypoxia,[20] but its prognostic value, particularly of the trend in lactate concentrations, has been well established in septic shock patients.[21–23] Mixed venous oxyhemoglobin saturation reflects the balance between oxygen delivery and consumption, and can be elevated in septic patients due to the maldistribution of blood flow, so values must be interpreted in the context of the wider hemodynamic picture. Low values, however, suggest increased oxygen extraction and therefore potentially incomplete resuscitation. A 2001 study[4] showed that the monitoring of central venous oxygen saturation can be a valuable guide to early resuscitation. The correlation between central venous oxygen saturation and mixed venous oxyhemoglobin saturation is reasonable,[24] but may not always be reliable.[25]

The adequacy of regional perfusion is usually assessed clinically.[1] Methods for measuring regional perfusion more directly have been under investigation, with a focus on the splanchnic circulation, which is especially susceptible to ischemia and may drive organ failure.[26] Measurements of oxygen saturation in the hepatic vein have revealed oxygen desaturation in a subset of septic patients, suggesting that the hepatosplanchnic oxygen supply may be inadequate in some patients, even when more global parameters appear to be adequate.[27] Direct visualization of the sublingual circulation[28] or sublingual capnometry[29] may be useful to monitor the restoration of microvascular perfusion in patients with sepsis.

Adrenergic Agents

There has been longstanding debate about whether one catecholamine vasopressor agent is superior to another. While these discussions are enlightening in that they tend to highlight differences in pharmacology among the agents, sometimes the arguments tend to focus on the agents themselves when actually it is the therapeutic strategy that differs. Different catecholamine agents have different effects on α-adrenergic and β-adrenergic receptors, as shown in Figure 1. The hemodynamic actions

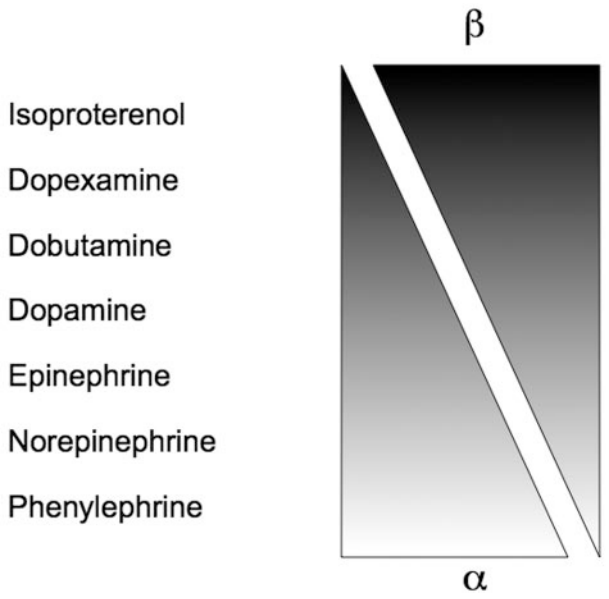

Figure 1. α-adrenergic and β-adrenergic effects of vasoactive catecholamines.

of these receptors are well known, with α-adrenergic receptors promoting vasoconstriction, β_1-adrenergic receptors increasing heart rate and myocardial contractility, and β_2-adrenergic receptors causing peripheral vasodilation.

The result of these differential effects on adrenergic receptors is that the different agents have different effects on pressure and flow, as shown in Figure 2. Conceived in these terms, the argument about which catecholamine is best to use in a given situation is transformed into a discussion about which agent is best suited to implement the therapeutic strategy chosen. This may or may not make the choice easier, but it does emphasize the need to define the goals and end points of therapy, and to identify how those end points will be monitored.

Individual Vasopressor Agents

Dopamine

Dopamine, the natural precursor of norepinephrine and epinephrine, has distinct dose-dependent pharmacologic effects. At doses of < 5 μg/kg/min, dopaminergic receptors are activated, leading to vasodilation in the renal and mesenteric beds.[30] At doses of 5 to 10 μg/kg/min, β_1-adrenergic effects predominate, increasing cardiac contractility and heart rate. At doses of > 10 μg/kg/min, α_1-adrenergic effects predominate, leading to arterial vasoconstriction and an increase in BP. There is a great deal of overlap in these effects, particularly in critically ill patients.

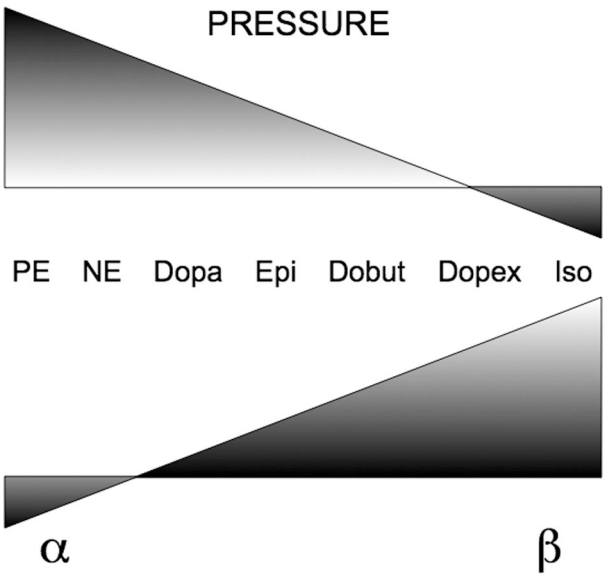

FIGURE 2. Effects of vasoactive catecholamines on pressure and blood flow. PE = phenylephrine; NE = norepinephrine; Dopa = dopamine; Epi = epinephrine; Dobut = dobutamine; Dopex = dopexamine; Iso = isoproterenol.

Dopamine increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume, and to a lesser extent to an increase in heart rate.[31–41] In open-label trials,[31–41] dopamine (median dose, 15 μg/kg/min) increased mean arterial pressure by 24% in septic patients who remained hypotensive after receiving optimal fluid resuscitation. Dopamine has been shown to increase oxygen delivery, but its effects on calculated or measured oxygen consumption have been mixed, suggesting that tissue oxygenation may not always be improved, perhaps due to a failure to improve microcirculatory flow.[32,33,42,43] The effect of dopamine on splanchnic perfusion has also been mixed. Increases in splanchnic blood flow have been reported,[31,32,34,44–46] but have not always been associated with increases in splanchnic oxygen consumption, beneficial effects on gastric intramucosal pH, or improvement in hepatosplanchnic energy balance.

Low doses of dopamine increase renal blood flow and glomerular filtration rate in laboratory animals and healthy volunteers, supporting the idea that dopamine can reduce the risk of renal failure in critically ill patients by increasing renal blood flow. This notion has now been put to rest by a definitive clinical trial[47] that randomized 328 critically ill patients with early renal dysfunction to low-dose ("renal") dopamine (2 μg/kg/min) or placebo. No difference was found in either the primary outcome (peak serum creatinine level), other renal outcomes (increase in creatinine level, need for renal replacement, and urine output), or secondary outcomes (survival to either ICU or hospital discharge, ICU or hospital stay, or arrhythmias).[47]

Dopamine use was associated with increased mortality in patients with shock in an observational cohort study[48] of 198 European ICUs and remained a significant predictor after multivariate analysis. Given the limitations of observational studies, this finding will need to be confirmed by prospective studies. A large prospective randomized clinical trial comparing dopamine to norepinephrine in patients with septic shock is ongoing.

Dopamine effectively increases mean arterial pressure in patients who remain hypotensive after optimal volume expansion, largely as a result of increasing cardiac index, so it may be chosen in patients with compromised cardiac function or cardiac reserve. Its major side effects are tachycardia and arrhythmogenesis, both of which are more prominent than with other vasopressor agents. There is also concern about the potential for decreased prolactin release, lymphocyte apoptosis, and consequent immunosuppression.[49,50]

Norepinephrine

Norepinephrine is a potent α-adrenergic agonist with less pronounced β-adrenergic agonist effects. Norepinephrine increases mean arterial pressure by vasoconstriction, with a small increase (10 to 15%) in cardiac output and stroke volume.[10–12,16,51,52] Filling pressures are either unchanged[10–12,16,53] or modestly increased (1 to 3 mm Hg).[15,17,32,34,36]

Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in septic shock patients. In open-label trials,[11,12,16,17,34,52–55] norepinephrine administration at doses ranging from 0.01 to 3.3 μg/kg/min has been shown to increase mean arterial pressure in patients who remained hypotensive after fluid resuscitation and dopamine. The large doses of the drug required in some patients may be due to α-receptor downregulation in sepsis.[56]

In the only randomized trial[36] comparing vasopressor agents, 32 volume-resuscitated septic patients were given either dopamine or norepinephrine to achieve and maintain normal hemodynamic and oxygen transport parameters for at least 6 h. Dopamine administration was successful in only 31% of patients, whereas norepinephrine administration (mean [± SD] dose, 1.5 ± 1.2 μg/kg/min) was successful in 93% ($p < 0.001$). Of the 11 patients who did not respond to dopamine, 10 responded when norepinephrine was added to therapy. Serum lactate levels were decreased as well, suggesting that norepinephrine therapy improved tissue oxygenation.[36]

The vasoconstrictive effects of norepinephrine can have detrimental effects on renal hemodynamics in patients with hypotension and hypovolemia, with a potential for renal ischemia.[57–59] The situation may differ in adequately resuscitated patients with hyperdynamic septic shock.[15] Norepinephrine has a greater effect on efferent than afferent renal arteriolar resistance and increases the filtration fraction. Several studies[10,13,15,17,32,36,37,53,60] have shown increases in urine output and renal function in patients with septic shock treated with norepinephrine alone or with norepinephrine added to dobutamine.

The results of studies of the effects of norepinephrine on splanchnic blood flow in patients with septic shock have been mixed. The effects of norepinephrine on both splanchnic blood flow and oxygen consumption have been unpredictable both among patients and within groups.[31,34] Comparisons between norepinephrine and other vasoactive agents have also been variable. One pilot study[32] found that gastric mucosal intracellular pH (pHi) was significantly increased during 3 h of treatment with norepinephrine but significantly decreased during treatment with dopamine. A more recent study[61] compared the effects of norepinephrine, epinephrine, and dopamine in 20 patients with septic shock. In the 10 patients with moderate shock, no differences in splanchnic blood flow or gastric-arterial P_{CO_2} difference were observed. In the 10 patients with severe shock, the effects of norepinephrine and dopamine were similar. Epinephrine increased cardiac index more than norepinephrine, but splanchnic blood flow was lower despite this higher cardiac index.[61]

Norepinephrine can increase BP in patients with septic shock without causing a deterioration in cardiac index and organ function. Although the effect of the drug on oxygen transport variables and splanchnic parameters has varied in different studies, other clinical parameters of peripheral perfusion, such as urine flow and lactate concentration, are significantly improved in most studies. In a multivariate analysis[62] including 97 septic shock patients, mortality was favorably influenced by the use of norepinephrine; the use of high-dose dopamine, epinephrine, or dobutamine had no significant effect. Controlled data comparing norepinephrine to other catecholaminergic agents are sparse, with only one randomized study.[36] Whether using norepinephrine in septic shock patients affects mortality compared to dopamine or epinephrine will hopefully be clarified by the ongoing prospective clinical trials.

Phenylephrine

Phenylephrine, a selective α_1-adrenergic agonist, increases BP by vasoconstriction. Its rapid onset, short duration, and primary vascular effects make it an attractive agent in the management of hypotension associated with sepsis, but there are concerns about its potential to reduce cardiac output in these patients.

Few studies have evaluated the use of phenylephrine in patients with hyperdynamic sepsis. As such, guidelines on its clinical use are limited. Phenylephrine has been shown to increase BP when administered to normotensive hyperdynamic septic patients at doses of 0.5 to 8 μg/kg/min, with little change in cardiac output or stroke volume.[63,64]

Only one small study[65] of 13 patients has evaluated the effects of phenylephrine on treating patients with hypotension associated with sepsis. Phenylephrine added to either low-dose dopamine or dobutamine increased mean arterial pressure and cardiac index without a change in heart rate. A significant increase in urine output without a change in serum creatinine level was observed during phenylephrine therapy.[65]

The limited information available on phenylephrine therapy suggests that this drug can increase BP modestly in fluid-resuscitated septic shock patients without impairing cardiac or renal function. Phenylephrine is a second-line agent but may be a good therapeutic option when tachyarrhythmias limit therapy with other vasopressors.[6]

Epinephrine

Epinephrine is a potent α-adrenergic and β-adrenergic agent that increases mean arterial pressure by increasing both cardiac index and peripheral vascular tone.[14,66–68] Epinephrine increases oxygen delivery, but oxygen consumption may be increased as well.[66–70] Lactate levels can be increased after the use of epinephrine in sepsis patients, although whether this results from excess vasoconstriction and compromised perfusion or increased lactate production remains uncertain.[54,66,70]

The chief concern with the use of epinephrine in patients with sepsis is the potential to decrease regional blood flow, particularly in the splanchnic circulation.[54,71–73] In a study[61] of patients with severe septic shock, epinephrine administration increased global oxygen delivery and consumption, but caused lower absolute and fractional splanchnic blood flow and lower indocyanine green clearance, thus validating the adverse effects of therapy with epinephrine alone on the splanchnic circulation. Another group has reported[74] improved gastric mucosal perfusion with epinephrine compared to a norepinephrine/dobutamine combination, but subsequently the same group reported superiority of a therapy with a norepinephrine/dopexamine combination over therapy with epinephrine.[75] A fairly large (n = 330) random-

ized clinical trial[76] comparing therapy with epinephrine to that with norepinephrine with or without dobutamine has been completed, and preliminary results were reported at the European Society of Intensive Care Medicine meeting; no significant difference was found in the rates of 28-day mortality, ICU mortality, or hospital mortality.

Epinephrine administration can increase BP in patients who are unresponsive to traditional agents. It increases heart rate, and has the potential to induce tachyarrhythmias, ischemia, and hypoglycemia. Because of its effects on gastric blood flow and its propensity to increase lactate concentrations, epinephrine has been considered a second-line agent, the use of which should be considered in patients failing to respond to traditional therapies.[6]

Vasopressin

Vasopressin is a peptide hormone that is synthesized in the hypothalamus and is then transported to and stored in the pituitary gland. Released in response to decreases in blood volume, decreased intravascular volume, and increased plasma osmolality, vasopressin constricts vascular smooth muscle directly via V1 receptors and also increases responsiveness of the vasculature to catecholamines.[77,78] Vasopressin may also increase BP by the inhibition of vascular smooth muscle nitric oxide production[79] and K^+-ATP channels.[78,80]

Normal levels of vasopressin have little effect on BP in physiologic conditions,[77] but vasopressin helps to maintain BP during hypovolemia,[81] and seems to restore impaired hemodynamic mechanisms and also to inhibit pathologic vascular responses in patients with shock.[78] Increased levels of vasopressin have been documented in patients with hemorrhagic shock,[82] but a growing body of evidence indicates that this response is abnormal or blunted in those with septic shock. One study[83] found markedly increased levels of circulating vasopressin in 12 patients with cardiogenic shock, but much lower levels in 19 patients with septic shock, which were hypothesized to be inappropriately low. One potential mechanism for this relative vasopressin deficiency would be the depletion of pituitary stores, possibly in conjunction with impaired synthesis. The depletion of vasopressin stores in the neurohypophysis evaluated by MRI has in fact been described in a small group of septic shock patients.[84] A 2003 prospective cohort study[85] of patients with septic shock found that vasopressin levels were almost always elevated in the initial hours of septic shock and decreased afterward; relative vasopressin deficiency, as defined by the investigators, developed in one third of patients.

Given this theoretical rationale, observational studies[86–88] have demonstrated that the addition of a low dose of vasopressin (0.01 to 0.04 U/min) to a course of catecholamines can raise BP in patients with pressor-refractory septic shock. Two small randomized studies[89,90] comparing vasopressin to norepinephrine have demonstrated that the initiation of vasopressin decreases catecholamine requirements, and one of these[89] showed improved renal function. Similar data are available for terlipressin, a synthetic vasopressin analog.[91] There is concern, however, that vasopressin infusion in septic patients may either decrease splanchnic perfusion or redistribute blood flow away from the splanchnic mucosa.[92,93] Vasopressin should be thought of as replacement therapy for relative deficiency rather than as a vasopressor agent to be titrated to effect.

A large randomized clinical trial (Vasopressin vs Norepinephrine in Septic Shock Study)[94] has now been completed comparing vasopressin to norepinephrine therapy in 776 patients with pressor-dependent septic shock, and the preliminary results were presented at the European Society of Intensive Care Medicine meeting. Patients were randomized to receive vasopressin (0.03 U/min) or 15 μg/min norepinephrine in addition to their original vasopressor infusion; the primary end point was 28-day mortality rate; a prespecified subgroup analysis was performed in patients with less severe septic shock (norepinephrine, 5 to 14 μg/min) and more severe septic shock (norepinephrine, $>$ 15 μg/min). For the group as a whole, there was no difference in mortality, but vasopressin appeared to be better in the less severe subgroup.[94]

Vasopressin (0.03 U/min) added to norepinephrine appears to be as safe and effective as norepinephrine in fluid-resuscitated patients with septic shock. Vasopressin may be more effective in patients receiving lower doses of norepinephrine than when started as rescue therapy, although the answer to the question of what therapy to administer in patients with high vasopressor requirements despite vasopressin infusion remains uncertain.

Complications of Vasopressor Therapy

All of the catecholamine vasopressor agents can cause significant tachycardia, especially in patients who have received inadequate volume resuscitation. Tachyarrhythmias can occur as well. In patients with significant coronary atherosclerosis, vasopressor-induced coronary artery constriction may precipitate myocardial ischemia and infarction; this is of particular concern in patients treated with vasopressin. In the presence of myocardial dysfunction, excessive

Table 1 —*Consensus Recommendations for Vasopressor Support in Sepsis Patients**

Strength of Evidence	ACCM Practice Parameters	Strength of Recommendation	Strength of Evidence	Surviving Sepsis Campaign	Strength of Recommendation
	When fluid administration fails to restore an adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be initiated; vasopressor therapy may also be required transiently to maintain perfusion in the face of life-threatening hypotension, even when adequate cardiac filling pressures have not yet been attained	None (text)	I	When an appropriate fluid challenge fails to restore adequate BP 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 a fluid challenge is in progress and hypovolemia has not yet been corrected	E
	Arterial cannulation should be performed in patients with shock to provide a more accurate measurement of intraarterial pressure and to allow beat-to-beat analysis so that decisions regarding therapy can be based on immediate and reproducible BP information	None (basic principle)	IV	All patients requiring vasopressors should have an arterial catheter placed as soon as practical if resources are available	E
I	Dopamine and norepinephrine are both effective for increasing arterial BP; it is imperative to ensure that patients receive adequate fluid resuscitated; dopamine raises cardiac output more than norepinephrine, but its use may be limited by tachycardia; norepinephrine may be a more effective vasopressor in some patients	C	II	Either norepinephrine or dopamine (through a central catheter as soon as available) is the first-choice vasopressor agent to correct hypotension in septic shock patients	D
II	Phenylephrine is an alternative to increase BP, especially in the setting of tachyarrhythmias; epinephrine can be considered for therapy of refractory hypotension, although adverse effects are common, and epinephrine may potentially decrease mesenteric perfusion	D			
III	Administration of low doses of dopamine to maintain renal function is not recommended	B	III	Low-dose dopamine should not be used for renal protection as part of the treatment of severe sepsis	B
V	Low doses of vasopressin given after 24 h as hormone replacement may be effective in raising BP in patients refractory to other vasopressors, although no conclusive data are yet available regarding outcome	D	V	Vasopressin use may be considered in patients with refractory shock despite adequate fluid resuscitation and high-dose conventional vasopressor therapy; pending the outcome of ongoing trials, it is not recommended as a replacement for norepinephrine or dopamine as a first-line agent; if used in adults, it should be administered at an infusion rate of 0.01 to 0.04 U/min; it may decrease stroke volume	E

*Strength of evidence: level I, large, randomized trials with clear-cut results, low risk of false-positive (α) error or false-negative (β) error; level II, small, randomized trials with uncertain results, moderate to high risk of false-positive (α) error and/or false-negative (β) error; level III, nonrandomized, contemporaneous control subjects; level IV, nonrandomized, historical control subjects and expert opinion; level V, case series, uncontrolled studies, and expert opinion. Strength of recommendation: A, supported by at least two level I investigations; B, supported by only one level I investigation; C, supported by level II investigations only; D, supported by at least one level III investigation; E, supported by level IV or level V investigations only.

vasoconstriction can decrease stroke volume, cardiac output, and oxygen delivery. Should this occur, the dose of the vasopressor should be lowered or the addition of an inotropic agent such as dobutamine should be considered.[52] Excessive doses of vasopressors can also cause limb ischemia and necrosis.

The administration of vasopressors may potentially impair blood flow to the splanchnic system, and this can be manifested by stress ulceration, ileus, malabsorption, and even bowel infarction.[54,70] Gut mucosal integrity occupies a key position in the pathogenesis of multiple organ failure, and countercurrent flow in splanchnic microcirculation gives the gut a higher critical threshold for oxygen delivery than other organs. Thus, it makes sense to avoid episodes of intramucosal acidosis, which might be detected either by a fall in gastric mucosal pHi or an increase in gastric mucosal P_{CO_2}, if possible. Whether to monitor these parameters routinely is less certain, as pHi or gastric P_{CO_2}-directed care has not been shown to reduce mortality in patients with septic shock in prospective randomized controlled trials.

Consensus Recommendations

Consensus recommendations regarding vasopressor support in patients with septic shock have been put forth by the American College of Critical Care Medicine (ACCCM)[6,95] and the Surviving Sepsis campaign[9]; these recommendations differ more in wording than in substance, and are compiled in Table 1. The Surviving Sepsis campaign will likely amend the vasopressin section to take the Vasopressin vs Norepinephrine in Septic Shock Study trial results under consideration.

Conclusion

The ultimate goals of hemodynamic therapy in shock are to restore effective tissue perfusion and to normalize cellular metabolism. In patients with sepsis, both global and regional perfusion must be considered. In addition, mediators of sepsis can perturb cellular metabolism, leading to the inadequate utilization of oxygen and other nutrients despite adequate perfusion; one would not expect organ dysfunction mediated by such abnormalities to be corrected by hemodynamic therapy.

Despite the complex pathophysiology of sepsis, an underlying approach to its hemodynamic support can be formulated that is particularly pertinent with respect to vasoactive agents. Both arterial pressure and tissue perfusion must be taken into account when choosing therapeutic interventions, and the efficacy of hemodynamic therapy should be assessed by monitoring a combination of clinical and hemodynamic parameters. It is relatively easy to raise BP, but somewhat harder to raise cardiac output in septic patients. How to optimize regional blood and microcirculatory blood flow remains uncertain. Thus, specific end points for therapy are debatable and are likely to evolve. Nonetheless, the idea that clinicians should define specific goals and end points, titrate therapies to those end points, and evaluate the results of their interventions on an ongoing basis remains a fundamental principle. The ACCCM practice parameters[6,95] were intended to emphasize the importance of such an approach so as to provide a foundation for the rational choice of vasoactive agents in the context of evolving monitoring techniques and therapeutic approaches.

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