Vasopressor and inotropic support in septic shock: An evidence-based review

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Objective: **In 2003, critical care and infectious disease experts representing 11 international organizations developed management guidelines for vasopressor and inotropic support in septic shock that would be of practical use for the bedside clinician, under the auspices of the Surviving Sepsis Campaign, an international effort to increase awareness and to improve outcome in severe sepsis.**

Design: **The process included a modified Delphi method, a consensus conference, several subsequent smaller meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee.**

Methods: **The modified Delphi methodology used for grading recommendations built on a 2001 publication sponsored by the International Sepsis Forum. We undertook a systematic review of the literature graded along five levels to create recommendation grades from A to E, with A being the highest grade. Pediatric considerations to contrast adult and pediatric management are in the article by Parker et al. on p. S591.**

Conclusion: **An arterial catheter should be placed as soon as possible in patients with septic shock. Vasopressors are indicated to maintain mean arterial pressure of <65 mm Hg, both during and following adequate fluid resuscitation. Norepinephrine or dopamine are the vasopressors of choice in the treatment of septic shock. Norepinephrine may be combined with dobutamine when cardiac output is being measured. Epinephrine, phenylephrine, and vasopressin are not recommended as first-line agents in the treatment of septic shock. Vasopressin may be considered for salvage therapy. Low-dose dopamine is not recommended for the purpose of renal protection. Dobutamine is recommended as the agent of choice to increase cardiac output but should not be used for the purpose of increasing cardiac output above physiologic levels. (Crit Care Med 2004; 32[Suppl.]:S455–S465)**

Shock may be defined as an impairment of the normal relationship between oxygen demand and oxygen supply. As a consequence, there are detrimental alterations in tissue perfusion, resulting in a reduction in the delivery of oxygen and other nutrients to tissue beds and causing cellular and then organ dysfunction. In hypovolemic, cardiogenic, and obstructive forms of shock, the primary defect is a fall in cardiac output, leading to hypoperfusion, hypotension, and anaerobic metabolism. In septic shock, however, there is a complex interaction between pathologic vasodilatation, relative and absolute hypovolemia, direct myocardial depression, and altered blood flow distribution, which occur as a consequence of the inflammatory response to infection. Even after the restoration of circulating volume, maldistribution of a normal or increased cardiac output typically persists as a consequence of microvascular abnormalities. In addition, cellular and organ injury also occur as direct consequences of the inflammatory response in sepsis and as a consequence of hypoperfusion.

Making recommendations about the choice of individual vasopressor agents in septic shock is made difficult by the paucity of controlled trials and by the clinical reality that agents are frequently used in combination. In modern practice, norepinephrine and dopamine are the vasopressors used most frequently, although dopamine has more marked inotropic effects. The relatively small inotropic effect of norepinephrine, and concerns about regional blood flow, mean that it is frequently used in combination with dobutamine. Epinephrine may also be used as an alternative and, again, combines vasopressor and inotropic effects. Phenylephrine, which has virtually only vasopressor actions, is also sometimes used. Dopamine and epinephrine in particular have important metabolic and endocrine effects that may complicate their use and be potentially detrimental. This review of the literature enables recommendations to be established and graded according to the strength of the available evidence.

End Points of Resuscitation and Monitoring in Septic Shock

The complexity of the pathophysiology and the limitations of routinely used hemodynamic monitoring techniques have made defining the end points of hemodynamic management of sepsis difficult. Nevertheless, the available literature does provide important guidance as to a basic approach to the use of vasopressors and inotropes in sepsis, although this will undoubtedly change as our understanding improves further. Septic shock is characterized by hypotension, which in adults generally refers to a mean arterial pressure below 65–70 mm Hg, and altered tissue perfusion. Poor tissue perfusion may be manifest clinically by reduced capillary refill, oliguria, and altered sensorium. Some caution is necessary in interpreting these signs, however, because signs of peripheral vasoconstriction may be absent in some patients who may seem

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deceptively well in the early phases of severe sepsis.

Other global markers of tissue perfusion that are used clinically include the acid-base status (base excess and blood lactate) and the mixed venous or central venous oxygen saturations. The adequacy of regional perfusion is usually assessed by evaluating indices of specific organ function, although none of these alone has been validated as a reliable indicator of adequate resuscitation. These include coagulation abnormalities (disseminated intravascular coagulation); altered renal function with increased blood urea nitrogen and creatinine; altered liver parenchymal function with increased serum levels of transaminases, lactate dehydrogenase, and bilirubin; and altered gut perfusion, manifest by ileus and malabsorption. A number of approaches may be employed to monitor the hemodynamic and perfusion status of patients with septic shock. The variables measured provide potential end points for the resuscitation process and information about the progress of the patient in response to treatment.

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

Intravascular Volume Status. Adequate fluid resuscitation is a fundamental aspect of the hemodynamic management of patients with septic shock. Ideally, this should be achieved before vasopressors and inotropes are used, although it is frequently necessary to employ vasopressors early as an emergency measure in patients with severe shock. In fluid-responsive hearts, in which the Frank-Starling mechanism is intact, fluid administration increases preload and therefore stroke volume and cardiac output. Depending on the degree of vasodilatation, there may also be an increase in blood pressure. There are a number of approaches to monitoring intravascular filling that are employed currently. These include the use of traditional cardiac filling pressures (central venous pressure and pulmonary artery occlusion pressure), which are limited by errors in routine measurement, the confounding effects of mechanical ventilation, and uncertainties about the compliance of the left ventricle. Alternatives employed with increasing frequency in modern practice include central blood volume measurements using the transpulmonary indicator dilution technique and analysis of patterns of dynamic changes in the arterial waveform in response to mechanical ventilation (systolic pressure variation, stroke volume variation) as a predictor of volume responsiveness. This issue is addressed in more detail in the section on fluid resuscitation.

Cardiac Output. Cardiac output is frequently measured in patients with septic shock, both as a guide to the adequacy of resuscitation and to allow calculation of oxygen transport variables. It is also useful diagnostically in confirming the typical hyperdynamic picture of septic shock, although this is not always present, especially if the patient is still hypovolemic or has co-existing cardiac disease.

Mixed Venous Oxygen Saturation and Central Venous Oxygen Saturation. Mixed venous oxygen saturation ($S\bar{V}O_2$) can be measured in patients with a pulmonary artery catheter in place. $S\bar{V}O_2$ is dependent on cardiac output, oxygen demand, hemoglobin, and arterial oxygen saturation. The normal $S\bar{V}O_2$ value is 70–75% in critically ill patients but can be elevated in septic patients due to maldistribution of blood flow. Frequently, however, it may be low or even normal, and the value must be interpreted carefully in the context of the wider hemodynamic picture. Nevertheless, it is useful to measure $S\bar{V}O_2$ because if cardiac output becomes inadequate, $S\bar{V}O_2$ decreases. Moreover, if $S\bar{V}O_2$ remains low even though other end points of resuscitation have been corrected, this suggests increased oxygen extraction and therefore potentially incomplete resuscitation. Ronco et al. (1) studied terminally ill patients in whom treatment was withdrawn; $S\bar{V}O_2$ decreased dramatically before oxygen consumption started to fall, indicating that oxygen extraction capabilities are not necessarily profoundly altered even in patients in the final stage of the disease process. Hence, $S\bar{V}O_2$, if normal or high, does not necessarily indicate adequate resuscitation, whereas a low $S\bar{V}O_2$ should prompt rapid intervention to increase oxygen delivery to the tissues. The advent of continuous $S\bar{V}O_2$ monitoring using fiberoptic pulmonary artery catheters has greatly increased the value of this variable as a real-time monitor, so long as the systems are recalibrated appropriately.

Central venous oxygen saturation is becoming increasingly popular as an alternative to $S\bar{V}O_2$ because the measurement provides a clinically useful approximation to $S\bar{V}O_2$ and can be obtained from a central venous catheter without the need for pulmonary artery catheterization. In a recent study in patients with severe sepsis presenting to the emergency department, Rivers et al. (2) randomized 263 patients with severe sepsis or septic shock to receive either standard resuscitation or early goal-directed therapy for the first 6 hrs after admission. Central venous oxygen saturation was used as an intrinsic part of the early goal-directed therapy protocol, targeting a value of 70%. The mortality in the early goal-directed therapy group was 30.5% compared with 46.5% in the standard care group ($p = .009$).

Blood Lactate Levels. Hyperlactatemia (>2 mEq/L) is typically present in patients with septic shock and may be secondary to anaerobic metabolism due to hypoperfusion. However, the interpretation of blood lactate levels in septic patients is not always straightforward. Experimental studies have not always been able to show a reduction in high-energy phosphate levels in animal models of sepsis (3). The differences between studies may be related to the severity of the septic model, with more severe sepsis being associated with depletion of adenosine triphosphate, despite maintenance of systemic oxygen delivery and tissue oxygenation. Also, measurements of tissue Po_2 in septic patients have not demonstrated tissue hypoxia in the presence of lactic acidosis (4). However, if inhomogeneity in blood flow distribution is a real phenomenon, it is likely that cell hypoperfusion also exists with ischemia/reperfusion. A number of studies have suggested that elevated lactate levels may result from cellular metabolic failure rather than from global hypoperfusion in sepsis. Some organs may produce more lactate than others, in particular, the lungs in acute lung injury or acute respiratory distress syndrome (5, 6). Elevated lactate levels can also result from decreased clearance by the liver, and patients with septic shock may have a more severe liver injury than conventional liver function

tests may suggest (7). Nonetheless, the prognostic value of raised blood lactate levels has been well established in septic shock patients (8), particularly if the high levels persist (9, 10). It is also of interest to note that blood lactate levels are of greater prognostic value than oxygen-derived variables (11).

Gut Tonometry. The measurement of regional perfusion as a means of detecting inadequate tissue oxygenation has focused on the splanchnic circulation, as the hepatosplanchnic circulation is particularly sensitive to changes in blood flow and oxygenation for several reasons. First, under normal conditions, the gut mucosa receives the majority of total intestinal blood flow. However, in sepsis, there is a redistribution of flow away from the mucosa toward the serosa and muscularis (12), resulting in mucosal hypoxia. Any further reduction in splanchnic flow has a correspondingly greater effect on gut hypoxia. Second, the gut may have a higher critical oxygen delivery threshold than other organs (13). Third, the tip of the villus is supplied by a central arteriole and drained by venules passing away from the tip. A countercurrent exchange mechanism operates in the villus, whereby a base-to-tip Po_2 gradient exists, making the tip particularly sensitive to changes in regional flow and oxygenation. Fourth, constriction of the villus arteriole occurs during sepsis (14), rendering the villus even more sensitive to reductions in blood flow. Fifth, the capillary density at the villus tip is reduced during sepsis (15), impeding the transfer of oxygen. Finally, gut ischemia increases intestinal permeability, which may increase translocation of bacteria or cytokines. This mechanism is frequently suggested as a possible trigger or "motor" of the sepsis response and multiple organ failure, and recent work has suggested that the lymphatic drainage of the gut may be an important route by which inflammatory mediators released by injured gut reach the systemic circulation (16).

Gastric tonometry has been proposed as a method to assess regional perfusion in the gut by measuring intragastric ΔPco_2. Originally, the Pco_2 value was used, together with the arterial bicarbonate, to calculate gastric intramucosal pH (pHi), but arterial bicarbonate represents global conditions, is nonspecific, and is measured only intermittently. Consequently, pHi measurement has become obsolete, and the change in the Pco_2 signal itself is considered more representative of conditions in the gut. Gastric mucosal Pco_2 is influenced directly by systemic arterial Pco_2, and some clinicians have proposed using the gastric-arterial Pco_2 difference as the primary tonometric variable of interest (17). Even this measure is not a simple measure of gastric mucosal hypoxia because either anaerobic metabolism, decreased gastric blood flow in the absence of anaerobic metabolism, or a combination of the two can increase gastric mucosal Pco_2 (17). An early trial suggested that tonometry-derived variables might be useful in guiding therapy (18), but these findings were not confirmed recently (19), and many investigators have emphasized the limited sensitivity and specificity of these measurements. Various vasoactive agents have been shown to have divergent effects on gastric Pco_2 and pHi that are neither consistent nor predictable (20). Perhaps most problematic, tonometric Pco_2 measurement is confounded by enteral feeding, which is often started relatively early in modern intensive care practice. Taken together, these limitations make gastric tonometry of interest largely as a research tool rather than as a useful clinical monitor for routine use.

Sublingual Capnometry. Sublingual capnometry is a new technique just beginning the process of clinical evaluation. It is based on the principle that reduced perfusion leading to an increase in tissue Pco_2 occurs in areas of the gastrointestinal tract other than just the stomach, including the readily accessible sublingual mucosa (21). The device itself uses a Pco_2-sensitive optode placed under the tongue to detect changes in the local CO_2 tension. Recently, in an observational study of 54 unstable critically ill patients, of whom 21 had either severe sepsis or septic shock and 27 died, Marik and Bankov (22) demonstrated that the initial sublingual Pco_2–Pco_2 gap was the best predictor of outcome ($p = .0004$), followed by the initial sublingual Pco_2 reading itself ($p = .004$). The area under the receiver operating characteristic curve for the sublingual Pco_2–Pco_2 gap was 0.75, and the best threshold for discriminating between survivors and nonsurvivors was a gap of <25 mm Hg. Data were obtained at admission (after insertion of a pulmonary artery catheter), at 4 hrs, and at 8 hrs, and there were no differences between either blood lactate or $S\bar{V}o_2$ between survivors and nonsurvivors during this period. Clearly, although initial reports are encouraging, much more experience is required to establish whether this technique will have a role as a routine clinical monitor in the future.

Question: Is it recommended to monitor arterial blood pressure continuously in septic shock by using an arterial catheter?

Yes; Grade E

Recommendations: All patients with septic shock requiring vasopressors should have an arterial catheter placed as soon as practical if resources are available.

Grade E

Rationale: In shock states, measurement of blood pressure using a cuff is commonly inaccurate, whereas use of an arterial catheter provides a more accurate and reproducible measurement of arterial pressure. Monitoring using these catheters also allows beat-to-beat analysis so that decisions regarding therapy can be based on immediate blood pressure information (23). Placement of an arterial catheter in the emergency department is typically not possible or practical. It is important to appreciate the complications of arterial catheter placement, which include hemorrhage and damage to arterial vessels.

Question: Does vasopressor support improve outcome from septic shock?

Yes; Grade E

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

Grade E

Rationale: Adequate fluid resuscitation is a prerequisite for the successful and appropriate use of either vasopressors or inotropes in patients with septic shock, and in general, the end points of fluid resuscitation are the same as those for the use of pharmacologic hemodynamic support. Sometimes, fluid resuscitation alone may suffice. The choice of fluid remains a matter of debate, but patients with septic shock can be successfully resuscitated with either crystalloid or colloid, or a combination of both. It is also

necessary to maintain a minimum hemoglobin concentration to ensure adequate blood oxygen carriage and oxygen dispatch to the tissues. These aspects of the management of the patient with septic shock are discussed in detail elsewhere.

Four agents with vasopressor activity are commonly used in the treatment of patients with septic shock. These are dopamine, norepinephrine, epinephrine, and phenylephrine. More recently, there has been an increasing trend to use low-dose hydrocortisone as an adjunct to vasopressor therapy, especially in patients who exhibit a poor response to the primary vasopressor agent. The other recent change in practice is the increasing interest in the possible role of vasopressin as an alternative vasopressor agent in patients with septic shock.

Although all the vasopressor agents mentioned generally result in an increase in blood pressure, concerns remain in clinical practice about their potentially inappropriate or detrimental use. The most obvious of these relates to the inadequately volume-resuscitated patient, in whom vasopressor use may worsen already inadequate organ perfusion. Even when volume resuscitation has been performed, discussion continues as to whether vasopressor agents may raise blood pressure at the expense of the perfusion of vulnerable organs, most particularly, the kidneys and the gut. A further concern relates to the possibility that overenthusiastic use, especially if an unnecessarily high blood pressure is targeted, may increase left ventricular work to an unsustainable degree and so worsen cardiac output and end-organ perfusion. Although this is much more likely to occur in patients with cardiogenic shock, cardiac depression is a feature of severe sepsis, and a number of patients presenting with septic shock may already have significant underlying cardiac disease.

The precise level of mean arterial pressure to aim for is not certain and is likely to vary between individual patients. In animal studies, a mean arterial pressure of <60 mm Hg is associated with compromised autoregulation in the coronary, renal, and central nervous system vascular beds, and blood flow may be reduced. Some patients, however, especially the elderly, may require higher blood pressures to maintain adequate organ perfusion. To address this question specifically, LeDoux et al. (24) studied ten patients with septic shock who had been fluid resuscitated to a pulmonary artery occlusion pressure of ≥12 mm Hg and were requiring vasopressors to maintain mean arterial pressures of ≥60 mm Hg. Norepinephrine infusions were used to raise the blood pressure incrementally from 65 to 75 mm Hg and then to 85 mm Hg, with detailed global and regional hemodynamic and metabolic measurements being taken at each stage. Cardiac index increased from 4.7 ± 0.5 L·min^{-1}·m^{-2} to 5.5 ± 0.5 L·min^{-1}·m^{-2} ($p = .07$), and left ventricular stroke work index increased accordingly ($p = .01$). There were no significant changes in urine output, blood lactate, tonometric Pco_2 gap, skin capillary blood flow, or red blood cell velocity and, thus, no suggestion of either harm or benefit from the maneuver. Although fascinating, the wider applicability of these results is limited by the small number of patients and the short-term nature of the norepinephrine infusion. Nevertheless, it further reinforces the need to assess perfusion in patients on an individualized basis by a combination of the methods outlined previously.

Question: Is the combination of norepinephrine and dobutamine superior to dopamine in the treatment of septic shock?

Uncertain; Grade D

Recommendations: Either norepinephrine or dopamine (through a central catheter as soon as possible) is the first-choice vasopressor agent to correct hypotension in septic shock.

Grade D

Rationale: The effects of dopamine on cellular oxygen supply in the gut remain incompletely defined, and the effects of norepinephrine alone on splanchnic circulation may be difficult to predict. The combination of norepinephrine and dobutamine seems to be more predictable and more appropriate to the goals of septic shock therapy than norepinephrine alone. Dopamine is the natural precursor of norepinephrine and epinephrine, and it possesses several dose-dependent pharmacologic effects. Generally, at doses of <5 μg·kg^{-1}·min^{-1}, dopamine stimulates dopaminergic DA1 receptors in the renal, mesenteric, and coronary beds, resulting in vasodilation. Infusion of low doses of dopamine causes an increase in glomerular filtration rate, renal blood flow, and sodium excretion. At doses of 5–10 μg·kg^{-1}·min^{-1}, β-adrenergic effects become predominant, resulting in an increase in cardiac contractility and heart rate. Dopamine also causes the release of norepinephrine from nerve terminals, contributing to its cardiac effects. At higher doses (>10 μg·kg^{-1}·min^{-1}), α-adrenergic effects predominate, leading to arterial vasoconstriction and an increase in blood pressure.

The systemic hemodynamic effects of dopamine in patients with septic shock are well established. Dopamine increases mean arterial pressure primarily by increasing cardiac index with minimal effects on systemic vascular resistance. The increase in cardiac index is due to an increase in stroke volume and, to a lesser extent, to increased heart rate (25–36). Patients receiving dopamine at rates of >20 μg·kg^{-1}·min^{-1} show increases in right heart pressures and in heart rate, and therefore, doses should not usually exceed 20 μg·kg^{-1}·min^{-1}, at least not without adequate hemodynamic monitoring.

Splanchnic perfusion and the integrity of the gut mucosa may play an important role in the pathogenesis of multiple organ failure. The effect of dopamine on gastric tonometric and splanchnic variables has been evaluated with mixed results. At low doses, dopamine increases splanchnic oxygen delivery by 65% but splanchnic oxygen consumption by only 16%. Despite this, dopamine may decrease pHi, perhaps by a direct effect on the gastric mucosal cell. The effects of dopamine on cellular oxygen supply in the gut remain incompletely defined. Ruokonen et al. (33) and Meier-Hellmann et al. (36) have documented that dopamine increases splanchnic blood flow. Neviere et al. (37) reported that dopamine is associated with a reduction in gastric mucosal blood flow; there were changes in gastric Pco_2, gastric-arterial Pco_2 difference, and calculated pHi. They (37) concluded that they could not determine whether the reduction in gastric mucosal blood flow was critical because there were no changes in the acid-base variables of the patients. More recently, Jakob et al. (38) demonstrated that dopamine increased splanchnic blood flow in septic patients but that this did not correlate with changes in monoethylglycinexylidide formation (the cytochrome P450–dependent conversion of lidocaine to monoethylglycinexylidide in the liver). The same group also demonstrated that the dopamine infusion resulted in a decrease in splanchnic oxygen consumption, despite the increase in blood flow. They then performed a *post hoc* compar-

ison with septic patients receiving dobutamine infusions, in whom splanchnic blood flow also increased, but without any change in splanchnic oxygen consumption, leading the authors to conclude that dopamine resulted in an impairment of hepatosplanchnic metabolism that may be detrimental (39).

In contrast, De Backer et al. (40) compared the effects of dopamine, norepinephrine, and epinephrine on measures of splanchnic perfusion in ten patients with a moderate degree of septic shock. The gradient between mixed-venous and hepatic-venous oxygen saturations was lower with dopamine, although there were no other significant differences, leading to the authors to conclude that overall effects of all three drugs were similar in the small study group, although, if anything, dopamine had the most beneficial profile of effects on splanchnic circulation.

Recent studies have shown that dopamine may alter the inflammatory response in septic shock by decreasing the release of a number of hormones, including prolactin (41). Other potentially harmful endocrine effects have been demonstrated in trauma patients (42–45). In a study of 12 stable mechanically ventilated patients, Dive et al. (46) used intestinal manometry to demonstrate that dopamine infused at 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ resulted in impaired gastroduodenal motility. Concerns remain that these and other poorly understood biological effects of dopamine might potentially have harmful effects in patients with septic shock.

Norepinephrine is a potent α-adrenergic agonist with some β-adrenergic agonist effects. The effects of norepinephrine have been examined in a number of studies on patients with septic shock. In open-label trials, norepinephrine has been shown to increase mean arterial pressure in patients with hypotension resistant to fluid resuscitation and dopamine, although the potential that norepinephrine may have negative effects on blood flow in the splanchnic and renal vascular beds, with resultant regional ischemia, has meant that in the past norepinephrine was commonly reserved for use as a last resort, with predictably poor results. However, recent experience with the use of norepinephrine in patients with septic shock suggests that it can successfully increase blood pressure without causing the feared deterioration in organ function. Many studies have given septic patients fluid to correct hypovolemia before starting dopamine, with or without dobutamine, titrated to doses of 7–25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to achieve the target blood pressure. Only if this regime failed was norepinephrine added (33, 47–53). In older studies, norepinephrine was added after the use of metaraminol, methoxamine, or isoproterenol (25, 54). A few studies have used norepinephrine as the only adrenergic agent to correct sepsis-induced hemodynamic abnormalities (32, 33, 35, 55, 56). In most studies, the mean dose of norepinephrine was 0.2–1.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$, although the initial dose can be as low as 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (48), and the highest reported norepinephrine dose was up to 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (57). Thus, large doses of the drug can be required in some patients with septic shock, which may be due to adrenergic receptor "down-regulation" in sepsis (58).

Norepinephrine therapy usually causes a statistically and clinically significant increase in mean arterial pressure due to the vasoconstrictive effects, with little change in heart rate or cardiac output, leading to increased systemic vascular resistance. Several studies have demonstrated increases in cardiac output ranging from 10% to 20% and increases in stroke volume index of 10% to 15% (25, 35, 50), which may have been due either to β-receptor agonist effects or to improved cardiac performance as a result of a better coronary perfusion pressure. Other studies, however, have observed no significant changes in either cardiac output or stroke volume index after the use of norepinephrine in the presence of a significant increase in vascular resistance, suggesting that norepinephrine is exerting predominantly α_1-receptor agonist effects (47–49, 53, 59, 60). Obviously, because cardiac index is either increased or unchanged and mean arterial pressure is consistently increased, left ventricular stroke work index is always statistically increased with norepinephrine. With regard to pulmonary artery occlusion pressure, no clinically significant changes are reported.

Norepinephrine should be used only to restore adequate values of mean arterial blood pressure, which might be regarded as values sufficient to restore urine output (being cognizant of the premorbid blood pressure) or toward the lower part of the normal range. Higher values should be avoided during norepinephrine therapy because elevated cardiac afterload may be deleterious, especially in cases of severe underlying cardiac dysfunction. Mean arterial pressure is a better target for the titration of therapy than systemic vascular resistance due to the methodologic problems of the use of systemic vascular resistance as the sole measurement of peripheral resistance.

Norepinephrine seems to be more effective than dopamine at reversing hypotension in septic shock patients. Martin et al. (32) carried out a study with the most striking findings. They prospectively randomized 32 volume-resuscitated patients with hyperdynamic sepsis syndrome to receive either dopamine (2.5–25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or norepinephrine (0.5–5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to achieve and maintain normal hemodynamic and oxygen transport variables for at least 6 hrs. If the goals were not achieved with one agent, the other was added. The groups were similar at baseline. Dopamine administration (10–25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was successful in only 31% of patients (5 of 16), whereas norepinephrine (0.5–1.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) resulted in success in 93% of patients (15 of 16; $p < .001$). Of the 11 patients who did not respond to dopamine, ten responded when norepinephrine was added. In contrast, the one patient who did not respond to norepinephrine failed to respond to dopamine. The survival rate differed between the two groups (59% for norepinephrine vs. 17% for dopamine), although the study was not statistically designed to examine this issue. In a recent larger study from the same group, 97 patients with septic shock were entered into an observational study, in which they were treated in a standardized fashion. After antibiotic treatment, respiratory support, and fluid resuscitation, dopamine (5–15 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was used to support the blood pressure, and dobutamine (5–25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was added if the $S\bar{V}o_2$ was <70%. If hypotension, oliguria, or lactic acidosis persisted, patients then received either high-dose dopamine (16–25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or norepinephrine (0.5–5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$), although this choice was left to the discretion of the individual clinician and was not randomized. If the patients remained in shock, epinephrine could then be added. The results were analyzed statistically with the aim of establishing which aspects of therapy were associated with outcome. Four factors were significantly associated with a poor outcome (pneumonia as the cause of septic shock, organ

system failure index of ≤3, low urine output at study entry, and admission blood lactate level of >4 mmol/L). The only factor that was associated with a favorable outcome was the use of norepinephrine as part of the hemodynamic support of the patient, with these 57 patients having a significantly lower hospital mortality (62% vs. 82%; $p < .001$; relative risk, 0.68; 95% confidence interval, 0.54–0.87) than the 40 patients who received support with high-dose dopamine or epinephrine, or both.

Concern is frequently expressed with regard to the effect of norepinephrine on the kidney. In patients with hypotension and hypovolemia during hemorrhagic shock, for example, norepinephrine and other vasoconstrictor agents may have severe detrimental effects on renal hemodynamics. Despite the improvement in blood pressure, renal blood flow does not increase, and renal vascular resistance continues to rise (61). However, in hyperdynamic septic shock, during which urine flow is believed to decrease mainly as a result of lowered renal glomerular perfusion pressure, the situation is different. In an elegant study in a dog model, Bellomo et al. (62) were able to demonstrate that during endotoxic shock, norepinephrine infused at 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ resulted in an increase in renal blood flow. Under baseline conditions, however, the effect of norepinephrine was to reduce renal blood flow.

The effects of norepinephrine on renal function in patients with sepsis have been evaluated in four studies. Desjars et al. (59) studied 22 septic shock patients treated with norepinephrine (0.5–1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and dopamine (2–3 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Serum creatinine, blood urea nitrogen, free water clearance, and fractional excretion of sodium decreased significantly, whereas urine output, creatinine clearance, and osmolar clearance increased significantly. In this study (59), six of seven patients considered at risk for developing acute renal failure had improved renal function during norepinephrine treatment, and only one developed nonoliguric acute renal failure requiring dialysis. Martin et al. (56) studied 24 septic shock patients treated with norepinephrine (1.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) plus dobutamine (8–14 $\mu g \cdot kg^{-1} \cdot min^{-1}$) plus dopamine (6–17 $\mu g \cdot kg^{-1} \cdot min^{-1}$). No patient received low-dose dopamine or furosemide. Normalization of systemic hemodynamics was followed by reestablishment of urine flow, decrease in serum creatinine, and increase in creatinine clearance. Fukuoka et al. (55) studied 15 patients with septic shock treated with norepinephrine (0.05–0.24 $\mu g \cdot kg^{-1} \cdot min^{-1}$), dopamine (9 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and dobutamine (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Only patients with a normal serum lactate concentration had an increase in systemic vascular resistance and an increase in urine flow. Creatinine clearance was not affected (18.8 ± 5.5 mL/min before and 20.1 ± 6.6 mL/min after norepinephrine). Patients with elevated serum lactate concentrations had no change in vascular resistance, a decrease in creatinine clearance (32.6 ± 6.4 to 11.9 ± 4.9 mL/min), and required higher doses of furosemide. The authors concluded that the serum lactate concentration may predict which patients will experience potentially adverse renal effects with norepinephrine. However, this study included only a very limited number of patients and is at variance with the findings of other studies (25, 32, 35, 50, 52) in which vascular resistance and urine flow were increased in patients with elevated lactate concentrations (as high as 4.8 ± 1.6 mmol/L) (32). Redl-Wenzl et al. (50) studied 56 patients with septic shock treated with norepinephrine (0.1–2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and dopamine (2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). During norepinephrine infusion, creatinine clearance increased significantly from 75 ± 37 to 102 ± 43 mL/min after 48 hrs of treatment. The authors concluded that mean arterial pressure could be increased by norepinephrine with a positive effect on organ perfusion and oxygenation.

The effects of norepinephrine on serum lactate concentrations have been assessed in several studies. Four studies assessed changes in serum lactate concentrations over a relatively short period of time (i.e., 1–3 hrs). Hesselvik and Brodin (49) reported unchanged lactate levels during norepinephrine therapy, but the actual values were not given. In the other three studies (33, 35, 52), mean values of serum lactate concentrations did not change over the 1- to 3-hr study period. It should be noted that initial values were not very high (1.8–2.3 mmol/L). Because blood flow tended to improve significantly and lactic acid concentrations decreased (but not significantly) in one study, it is unclear whether sufficient time elapsed between measurements to see a significant norepinephrine-induced change in serum lactate concentrations. Martin et al. (32) infused norepinephrine into patients with septic shock in whom initial lactate concentrations were elevated (4.8 ± 1.6 mmol/L), and a statistically and clinically significant decrease in lactate levels was observed at the end of the 6-hr study period. Zhou et al. (63) infused dopamine into 16 patients with septic shock and then switched to norepinephrine, epinephrine, and a norepinephrine-dobutamine combination to maintain the same blood pressure in a random fashion. There was a trend toward a lower lactate level with norepinephrine compared with dopamine or epinephrine, and this difference became significant with the norepinephrine-dobutamine combination. Once again, however, the lactate values were already low (all were <2.6 ± 2.2 mmol/L), and the infusion of each drug was for only 120 mins. Norepinephrine thus does not worsen, and may even improve, tissue oxygenation, as assessed by serum lactate levels, in patients with septic shock. Very recently, De Backer et al. (40) compared norepinephrine, epinephrine, and dopamine in patients with moderate and severe septic shock and found no effect of norepinephrine on arterial lactate levels.

The effects of norepinephrine alone on the splanchnic circulation are difficult to predict. The combination of norepinephrine and dobutamine seems to be more predictable and more appropriate to the goals of septic shock therapy than the effects of epinephrine alone. Ruokonen et al. (33) measured splanchnic blood flow and splanchnic oxygen consumption in septic shock patients receiving either norepinephrine (0.07–0.23 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or dopamine (7.6–33.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to correct hypotension. With norepinephrine, no overall changes in splanchnic blood flow and splanchnic oxygen consumption or extraction were noted, and in individual patients, its effects on splanchnic blood flow were unpredictable (increased in three patients, decreased in two). Dopamine caused a consistent and statistically significant increase in splanchnic blood flow. Meier-Hellmann et al. (36) studied patients changed from dobutamine to norepinephrine. They observed a significant decrease in hepatic venous oxygen saturation. In another group of patients, they studied the effects of switching from dobutamine plus norepinephrine to the latter drug alone. They observed the previously reported changes in hepatic venous

oxygen saturation together with a decrease in splanchnic blood flow (indocyanine green dye dilution technique) and in cardiac output. Splanchnic oxygen consumption remained unchanged due to a regional increase in oxygen extraction. The decrease in splanchnic blood flow paralleled the decrease in cardiac output. The authors concluded that as long as cardiac output is maintained, treatment with norepinephrine alone has no negative effects on splanchnic tissue oxygenation. This finding was confirmed by Marik and Mohedin (35), who observed a significant increase in pHi (from 7.16 ± 0.07 to 7.23 ± 0.07) over 3 hrs of norepinephrine treatment. During treatment with dopamine, pHi decreased significantly (7.24 ± 0.04 to 7.18 ± 0.05).

Reinelt et al. (64) tested the hypothesis that when dobutamine is added to norepinephrine to obtain a 20% increase in cardiac index in septic shock patients, splanchnic blood flow and oxygen consumption increases and hepatic metabolic activity (hepatic glucose production) improves. Splanchnic blood flow and cardiac index increased in parallel, but there was no effect on splanchnic oxygen consumption, and hepatic glucose production decreased. The conclusion of the authors was that splanchnic oxygen consumption was not dependent on delivery in septic shock patients well resuscitated with norepinephrine. Levy et al. (51) studied the effects of the combination of norepinephrine and dobutamine on gastric tonometric variables in 30 septic shock patients. pHi and gastric Pco_2 gap were normalized within 6 hrs, whereas in epinephrine-treated patients, pHi decreased and gastric Pco_2 gap increased. Changes in the epinephrine group were only transient and were corrected within 24 hrs but could potentially have caused splanchnic ischemia. The authors concluded that the combination of norepinephrine with dobutamine was more predictable than epinephrine. Zhou et al. (63) demonstrated that the combination of norepinephrine and dobutamine was associated with higher pHi values than epinephrine alone in septic patients.

Summarizing the results of studies of norepinephrine, it can be concluded that norepinephrine markedly improves mean arterial pressure and glomerular filtration. This is particularly true in the high-output–low-resistance state of many septic shock patients. After restoration of systemic hemodynamics, urine flow reappears in most patients and renal function improves without the use of low-dose dopamine or furosemide. This fact supports the hypothesis that the renal ischemia observed during hyperdynamic septic shock is not worsened by norepinephrine infusion and even suggests that this drug may be effective in improving renal blood flow and renal vascular resistance. Clinical experience with norepinephrine in septic shock patients suggests that this drug can successfully increase blood pressure without causing deterioration in cardiac index or organ function. Norepinephrine (at doses of 0.01–3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) consistently improves hemodynamic variables in the large majority of patients with septic shock. The effects of norepinephrine on oxygen transport variables remain undefined from the available data, but most studies find other clinical variables of peripheral perfusion to be significantly improved. There is some evidence that outcome may be better with norepinephrine than with high-dose dopamine. Unfortunately only one published study was controlled (32), and a prospective, randomized clinical trial is still required to assess whether the use of norepinephrine in septic shock patients affects mortality compared with other vasopressors.

Question: Should low-dose dopamine be routinely administered for renal protection?

No; Grade B

Recommendations: Low-dose dopamine should not be used for renal protection as part of the treatment of severe sepsis.

Grade B

Rationale: Although no prospective, randomized studies have demonstrated a significant improvement in renal function with vasopressors, a number of open-label clinical series support an increase in renal perfusion pressure (47–50, 55, 56, 59, 65, 66). Excessive doses of vasopressors may shift the renal autoregulation curve to the right, necessitating a greater perfusion pressure for a specified renal blood flow. The precise target mean blood pressure level depends on the premorbid blood pressure, but it can be as high as 75 mm Hg (47, 49, 50, 55, 56, 59, 65, 66). However, individual levels should be kept at the minimum needed to reestablish urine flow, and in some patients, this can be achieved with a mean arterial pressure of 60 or 65 mm Hg. Certain patients may remain oliguric, despite normalization of systemic hemodynamic variables (48, 50, 55, 56, 59). This may be due to the absence of an increase in renal blood flow, a decrease in glomerular perfusion pressure, or because renal failure has become established.

Although in nonseptic conditions combination therapy with the use of low-dose dopamine (1–4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in addition to norepinephrine in an anesthetized dog model and in healthy volunteers resulted in significantly higher renal blood flow and lower renal vascular resistance (67, 68), such effects have not been conclusively demonstrated in septic shock. The Australian and New Zealand Intensive Care Society Clinical Trials Group (69) recently performed the only large randomized, clinical trial of the effect of low-dose dopamine on the development of renal failure in a general intensive care unit population of patients with systemic inflammatory response syndrome and early renal dysfunction. A total of 328 patients, including patients with sepsis, were randomized either to receive dopamine at 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or placebo, but no protective effect on renal function or other outcomes was found.

Question: Should epinephrine or phenylephrine be administered as firstline vasopressors in septic shock?

No; Grade D

Recommendations: Epinephrine or phenylephrine should not be used as firstline vasopressors as part of the treatment of septic shock. Epinephrine decreases splanchnic blood flow, increases gastric mucosal Pco_2 production, and decreases pHi, suggesting that the drug alters oxygen supply in the splanchnic circulation. Phenylephrine was reported to reduce splanchnic blood flow and oxygen delivery in septic shock patients.

Grade D

Rationale: Epinephrine can increase arterial pressure in patients who fail to respond to fluid administration or other vasopressors, primarily by increasing cardiac index and stroke volume (66, 70–72). Moran et al. (72) reported a linear relationship between epinephrine dose and heart rate, mean arterial pressure, cardiac index, left ventricular stroke work index, and oxygen delivery and consumption. Epinephrine, however, has variable and often detrimental effects on splanchnic blood flow and causes transient de-

creases in pHi and increases in the P_{CO_2} gap (51, 63, 73). De Backer et al. (40) demonstrated in septic patients with severe shock that epinephrine increased cardiac index when compared with norepinephrine but that splanchnic blood flow was reduced and the mixed-venous–to–hepatic venous oxygenation gradient was increased, although P_{CO_2} gap remained unchanged, leading these authors to conclude that epinephrine was potentially detrimental.

Epinephrine administration has also been associated with increases in systemic and regional lactate concentrations (51, 71, 74), although the cause of these increases is unclear. As the monitoring periods in all these studies were short, it is unclear whether these increases are a transient phenomenon. In an animal sepsis model, Levy et al. (75) demonstrated that these changes may well be due to a direct effect on carbohydrate metabolism. Other adverse effects of epinephrine include tachyarrhythmias. In summary, epinephrine clearly increases blood pressure and cardiac output in patients unresponsive to other agents. However, because of its potentially negative effects on gastric blood flow and blood lactate concentrations, its use should be limited.

Phenylephrine is a selective α_1-adrenergic agonist and has been used in septic shock, although there are concerns about its potential to reduce cardiac output and lower heart rate in these patients. Doses of phenylephrine start at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and reach a maximum dose of 5–8 $\mu g \cdot kg^{-1} \cdot min^{-1}$. A few studies have evaluated the clinical use of phenylephrine in septic shock (76–78). Reinelt et al. (78) reported reduced splanchnic blood flow and oxygen delivery in six septic shock patients treated with phenylephrine compared with norepinephrine.

Question: Should vasopressin be administered as vasopressor in septic shock when conventional vasopressor therapy fails?

Uncertain; Grade E

Recommendations: Vasopressin use may be considered in patients with refractory shock despite adequate fluid resuscitation and high-dose conventional vasopressors. Pending the outcome of ongoing trials, it is not recommended as a replacement for norepinephrine or dopamine as a first-line agent. If used in adults, it should be administered at infusion rates of 0.01–0.04 units/min. It may decrease stroke volume.

Grade E

Rationale: There is increasing interest in the possible role of vasopressin as a therapeutic vasopressor in patients with septic shock. Landry et al. (79) reported that patients with severe septic shock had reduced vasopressin levels and demonstrated a marked response to exogenous infusion. Subsequently, there have been several small case series of the use of vasopressin to raise the blood pressure in septic patients (80, 81). Recently, Dunser et al. (82) prospectively randomized 48 patients with vasodilatory shock to receive either norepinephrine or norepinephrine plus vasopressin at 4 units/hr for 48 hrs. Mean arterial pressure, cardiac index, and left ventricular stroke work index were all significantly higher in the vasopressin group. Splanchnic perfusion as assessed by tonometry was better preserved in the vasopressin group, although serum bilirubin levels were also higher and increased significantly during the infusion period. However, in a separate report, the same group described a 30.2% rate (19 of 63 patients) of ischemic skin lesions in patients with septic shock receiving vasopressin infusions (83). Although these preliminary results are fascinating, there is still inadequate understanding as to the mechanisms and potential therapeutic risk/benefit ratio of the use of vasopressin in septic shock. At this stage, vasopressin should only be used as part of properly constructed clinical trials until more information is available.

Question: Is dobutamine the pharmacologic agent of choice to increase cardiac output in the treatment of septic shock?

Yes; Grade E

Recommendations: In patients with low cardiac output despite adequate fluid resuscitation, dobutamine may be used to increase cardiac output. If used in the presence of low blood pressure, it should be combined with vasopressor therapy.

Grade E

Rationale: Although the cardiac index is usually maintained in the volume-resuscitated septic shock patient, cardiac function is impaired (84). Characterized by ventricular dilation, a decreased ejection fraction, an impaired contractile response to volume loading, and a low peak systolic pressure/end-systolic volume (85, 86), the mechanism of the myocardial dysfunction is complex. Coronary blood flow is usually normal, and there is no net lactate production across the coronary vascular bed, so myocardial ischemia is not implicated. Alterations in intracellular calcium homeostasis and in β-adrenergic signal transduction may be contributory factors. Several inflammatory mediators have been shown to cause myocardial depression in various animal models, including cytokines (87), platelet-activating factor, and nitric oxide (88). Inotropic therapy in septic shock is thus not straightforward. Cardiac output is usually not decreased, and multiple factors may be involved in the depressed cardiac function.

Dobutamine is an adrenergic agonist that stimulates β_1- and β_2-adrenergic receptors. A number of studies have investigated the effect of dobutamine on cardiac function during sepsis or septic shock (89–93). The doses utilized ranged from 2 to 28 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The majority of these studies found increases in cardiac index combined with increases in stroke volume and heart rate.

Dopexamine is a dopamine analog that stimulates adrenergic and dopamine 1 and 2 receptors. It is not approved for use in the United States. Several studies have evaluated short-term infusions of dopexamine in sepsis or septic shock and demonstrated significant improvements in cardiac index and left ventricular stroke work index (94–96). In addition, mesenteric perfusion, as assessed by gastric tonometry, was improved compared with baseline values in initial studies (95), but this has not been confirmed in subsequent studies (97).

Phosphodiesterase inhibitors alone, such as amrinone and milrinone, have little place in the treatment of septic shock. They may be considered in combination with adrenergic agents. One study evaluating milrinone in pediatric patients with sepsis observed that cardiac index and right and left ventricular stroke work indices improved significantly, with little change in heart rate (98).

Calcium supplementation has been proposed in the management of myocardial dysfunction in septic shock. However, no consistent beneficial hemodynamic effect of calcium administration in septic patients has been reported (99), and increased mortality has been reported in animal models (100, 101). Digoxin has been reported to significantly

improve cardiac performance in hypodynamic septic patients (102). The new calcium-sensitizing agent levosimendan may also prove to have a role in the future, but there are no available data at present.

Question: Is it recommended to use inotropic agents for increasing cardiac output above physiologic levels?

No; Grade A

Recommendations: A strategy of increasing cardiac index to achieve an arbitrarily predefined elevated level is not recommended.

Grade A

Rationale: In patients with decreased cardiac output, the goals of therapy are relatively clear and are aimed at restoring normal physiology. Because of the complexity of assessment of clinical variables in septic patients, direct measurement of cardiac output by invasive hemodynamic monitoring is advisable, but other end points of global perfusion should be followed as well. When global hypoperfusion is manifest by a decreased $S\bar{V}o_2$, monitoring of $S\bar{V}o_2$ can be helpful to guide response to therapy. Similarly, although lactate production in sepsis is complex, a fall in blood lactate levels during inotropic therapy is a good prognostic sign (103).

In contrast to former reports (104, 105), two large prospective clinical trials that included critically ill patients who had severe sepsis failed to demonstrate benefit from increasing oxygen delivery to supranormal levels by use of dobutamine (106, 107). The goal of resuscitation should instead be to achieve adequate levels of oxygen delivery to avoid flow-dependent tissue hypoxia.

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