# Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update

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***Objective:*** **To provide the American College of Critical Care Medicine with updated guidelines for hemodynamic support of adult patients with sepsis.**

***Data Source:*** **Publications relevant to hemodynamic support of septic patients were obtained from the medical literature, supplemented by the expertise and experience of members of an international task force convened from the membership of the Society of Critical Care Medicine.**

***Study Selection:*** **Both human studies and relevant animal studies were considered.**

***Data Synthesis:*** **The experts articles reviewed the literature and classified the strength of evidence of human studies according to study design and scientific value. Recommendations were drafted and graded levels based on an evidence-based rating system described in the text. The recommendations were debated, and the task force chairman modified the document until <10% of the experts disagreed with the recommendations.**

***Conclusions:*** **An organized approach to the hemodynamic support of sepsis was formulated. The fundamental principle is that clinicians using hemodynamic therapies should define specific goals and end points, titrate therapies to those end points, and evaluate the results of their interventions on an ongoing basis by monitoring a combination of variables of global and regional perfusion. Using this approach, specific recommendations for fluid resuscitation, vasopressor therapy, and inotropic therapy of septic in adult patients were promulgated. (Crit Care Med 2004; 32:1928–1948)**

**KEY WORDS: sepsis; hemodynamic support; fluid resuscitation; vasopressor therapy; inotropic therapy**

Shock occurs when the circulatory system fails to maintain adequate cellular perfusion. Shock is a syndrome that may arise from any of several initiating causes; as this syndrome progresses, a common pattern comprising an array of symptoms, signs, and laboratory abnormalities that result from hypoperfusion emerges. If shock is not reversed, irreversible cellular damage may ensue.

Septic shock results when infectious agents or infection-induced mediators in the bloodstream produce hemodynamic decompensation. Septic shock is primarily a form of distributive shock and is characterized by ineffective tissue oxygen delivery and extraction associated with inappropriate peripheral vasodilation despite preserved or increased cardiac output (1). In septic shock, a complex interaction between pathologic vasodilation, relative and absolute hypovolemia, myocardial dysfunction, and altered blood flow distribution occurs due to the inflammatory response to infection. Even after the restoration of intravascular volume, microcirculatory abnormalities may persist and lead to maldistribution of cardiac output (2). About half of the patients who succumb to septic shock die of multiple organ system failure (1). Most of the rest have progressive hypotension with low systemic vascular resistance refractory to vasopressor agents (3). Although myocardial dysfunction is not uncommon, death from myocardial failure is rare (1).

Cellular dysfunction in sepsis is the final outcome of a process with multiple stimuli. Prominent mechanisms include cellular ischemia, disruption of cellular metabolism by the effects of inflammatory mediators, and toxic effects of free radicals (3). Activation of caspases and induction of heat shock proteins may lead to apoptotic cell death. In early shock, compensatory mechanisms are activated in an attempt to restore pressure and flow to vital organs. When these compensatory mechanisms begin to fail, damage to cellular membranes, loss of ion gradients, leakage of lysosomal enzymes, proteolysis due to activation of cellular proteases, and reductions in cellular energy stores occur and may result in cell death (3). Once enough cells from vital organs have reached this stage, shock can become irreversible, and death can occur despite eradication of the underlying septic focus.

The American College of Critical Care Medicine (ACCM), which honors individuals for their achievements and contributions to multidisciplinary critical care medicine, is the consultative body of the Society of Critical Care Medicine (SCCM) that possesses recognized expertise in the practice of critical care. The College has developed administrative guidelines and clinical practice parameters for the critical care practitioner. New guidelines and practice parameters are continually developed, and current ones are systematically reviewed and revised.

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Therapy of septic shock may be viewed as having three main components. The initial priority in managing septic shock is to maintain a reasonable mean arterial pressure and cardiac output to keep the patient alive. Then the nidus of infection must be identified and eliminated, using antimicrobial therapy in all cases and surgical drainage whenever indicated. 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. The purpose of this practice parameter is to provide guidelines for hemodynamic support in sepsis to maintain adequate organ system and cellular perfusion.

## PURPOSE AND STRUCTURE OF PRACTICE PARAMETERS FOR HEMODYNAMIC SUPPORT IN SEPSIS

These practice parameters were developed by a panel convened by the American College of Critical Care Medicine of the Society of Critical Care Medicine, and updated by a similar panel, to assist health care providers in the management of hemodynamic support for patients with sepsis and septic shock. These guidelines are intended for adult patients and do not cover all conceivable clinical scenarios. Nonetheless, they do represent an attempt to review the state of knowledge concerning hemodynamic therapy of sepsis and to supplement specific therapeutic recommendations with guidelines about how to optimize therapy and how to evaluate the results of therapeutic interventions. The information and recommendations are predicated upon an expert-based review of the available scientific data, clinical investigations, and outcomes research. Where such data are unavailable or limited in scope, consensus was attained by considering published expert opinion and discussion among a wide range of experts. The citations of human studies have been annotated into levels of scientific support as per Cochrane group recommendations (4) as follows:

Level I: large, randomized trials with clear-cut results; low risk of false-positive ($\alpha$) error or false-negative ($\beta$) error

Level II: small, randomized trials with uncertain results; moderate to high risk of false-positive ($\alpha$) error and/or false-negative ($\beta$) error

Level III: nonrandomized, contemporaneous controls

Level IV: nonrandomized, historical controls and expert opinion

Level V: case series, uncontrolled studies, and expert opinion

The strength of the recommendations has been graded as modified from the guidelines of Evidence-Based Medicine Working Group as follows: (5)

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

Hemodynamic therapy of sepsis has been considered in each of three categories: fluid resuscitation, vasopressor therapy, and inotropic therapy. Since the initial formulation of the guidelines, a randomized, double-blind, placebo-controlled, multiple-center trial of recombinant human activated protein C has been completed (6). Although this trial showed that treatment with recombinant activated protein C is effective in patients with septic shock, activated protein C is not a hemodynamic therapy per se, nor was hemodynamic instability a requisite for inclusion in the trial. Thus, consideration of activated protein C and other therapies not directed at hemodynamic stabilization is outside the scope of these practice parameters.

An algorithm outlining an approach to hemodynamic support of patients with septic shock based on the recommendations in these parameters is shown in Figure 1.

## BASIC PRINCIPLES

Septic shock requires early, vigorous resuscitation. An integrated approach directed at rapidly restoring systemic oxygen delivery and improving tissue oxygenation has been demonstrated to improve survival significantly in septic shock (7). Although the specific approach that is used may vary, there are critical elements that should be incorporated in 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 concentrations of hemoglobin, and using vasoactive agents directed to physiologic and clinical end points.

Patients with septic shock should be treated in an intensive care unit. Continuous electrocardiographic monitoring should be performed for detection of rhythm disturbances, and pulse oximetry is useful to detect fluctuations in arterial oxygenation. Urine output is monitored continuously as well. Laboratory measurements such as arterial blood gases, serum electrolytes, complete blood counts, coagulation variables, and lactate concentrations should be done early and repeated as indicated.

In shock states, estimation of blood pressure using a cuff is commonly inaccurate, and use of an arterial cannula provides a more appropriate and reproducible measurement of arterial pressure (3). These catheters also allow beat-to-beat analysis so that decisions regarding therapy can be based on immediate and reproducible blood pressure information. Such monitoring facilitates the administration of large quantities of fluids and potent vasopressor and inotropic agents to critically ill patients (3).

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

### Goals and End Points of Hemodynamic Support in Septic Patients

Shock represents the failure of the circulatory system to maintain adequate delivery of oxygen and other nutrients to tissues, causing cellular and then organ dysfunction. Thus the ultimate goals of hemodynamic therapy in shock are to



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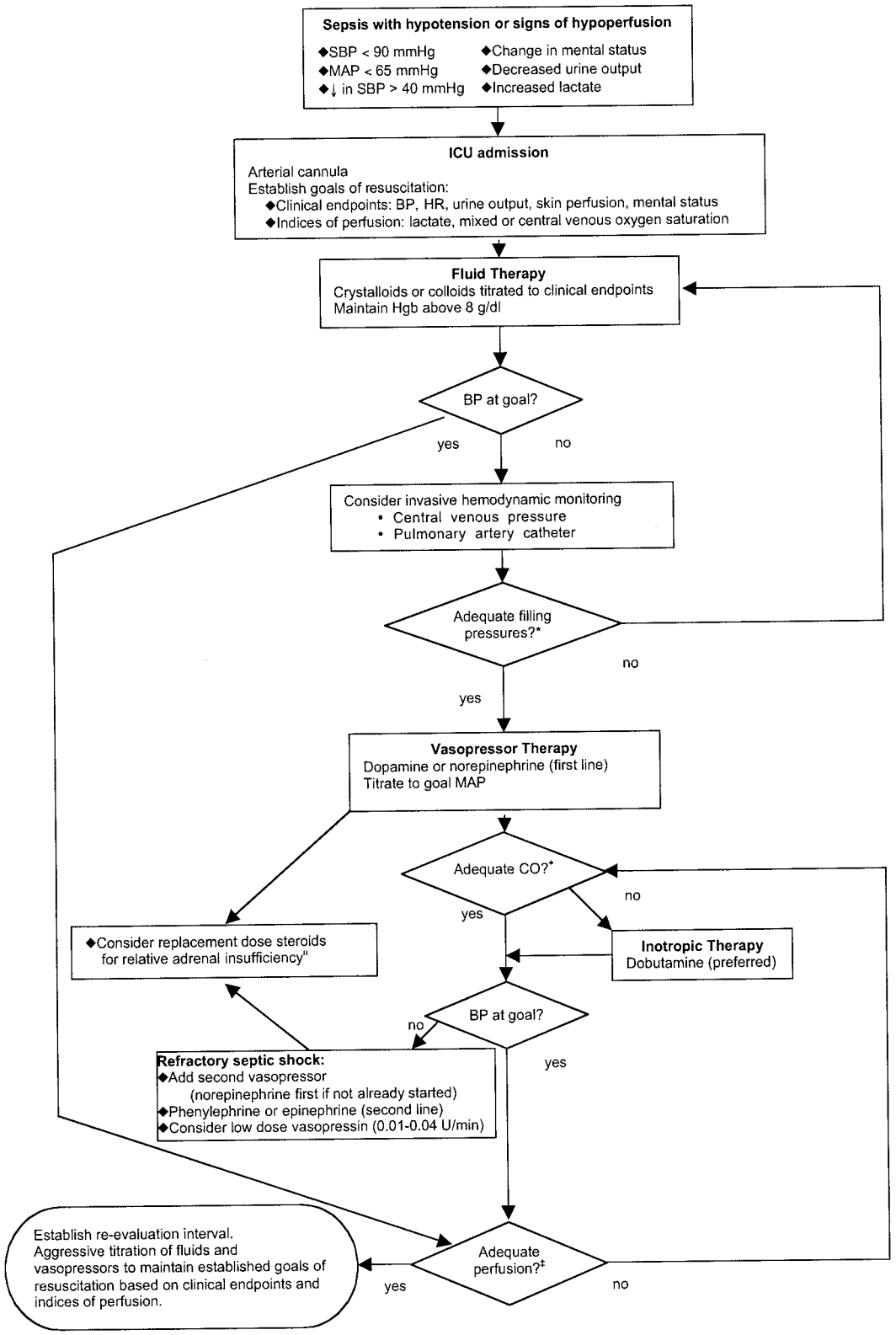


**Figure 1.** Suggested algorithm for hemodynamic support of adult patients with severe sepsis and septic shock. *SBP*, systolic blood pressure; *MAP*, mean arterial pressure; *ICU*, intensive care unit; *BP*, blood pressure; *HR*, heart rate; *Hgb*, hemoglobin. *Adequate cardiac filling pressures can be assessed by response of cardiac output (*CO*) to increases of pulmonary artery occlusion pressure. Maximal benefit is usually achieved at pulmonary artery occlusion pressure 12–15 mm Hg. Variation in arterial pressure with respiration can also be used to identify patients who would benefit from increased fluid administration. +Cardiac output can be assessed by echocardiography or by measuring cardiac index and/or mixed-venous oxygen saturation with a pulmonary artery catheter. ‡Perfusion can be assessed using a combination of clinical and laboratory variables, as described in the text. ‖A corticotropin stimulation test is recommended. See text for details.



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restore effective tissue perfusion and to normalize cellular metabolism.

In hypovolemic, cardiogenic, and extracardiac obstructive shock, hypotension results from a decrease in cardiac output, with consequent anaerobic tissue metabolism. Septic shock, the prototypical form of distributive shock, is different and more complicated. In septic patients, tissue hypoperfusion results not only from decreased perfusion pressure attributable to hypotension but also from abnormal shunting of a normal or increased cardiac output (3). Cellular alterations may also occur. Hemodynamic support of sepsis thus requires consideration of both global and regional perfusion.

The practical import of the complexity of hemodynamics in sepsis is that the goals of therapy are much more difficult to define with certainty than in other forms of shock in which global hypoperfusion is the dominant pathology. In cardiogenic shock, for example, the goal of therapy is to increase cardiac output, although the degree of hypoperfusion may vary in different organs. Indexes of regional perfusion usually correlate well with indexes of global perfusion, and both can be used to monitor the effects of therapy. In sepsis, maldistribution of a normal cardiac output can impair organ perfusion, and maldistribution of blood flow within organs due to perturbation of resistance vessel tone or microvascular obstruction can exacerbate organ dysfunction. To add to the complexity, mediators of sepsis can perturb cellular metabolism, leading to inadequate utilization of oxygen and other nutrients despite adequate perfusion. One would not expect such abnormalities to be corrected by hemodynamic therapy.

Despite the complexity of the pathophysiology of sepsis, an underlying approach to the hemodynamic support of sepsis can be formulated, with the understanding that the basic principles of the approach are more important than the specific recommendations, which will certainly change as our understanding of sepsis improves. For example, although which variables most accurately reflect the effects of therapy in septic patients may be uncertain, it should be apparent that therapeutic efficacy should be assessed by monitoring a combination of variables. Similarly, although specific end points may be arguable, 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.

An important recent trial supports early goal-directed therapy in sepsis. A total of 263 patients with severe sepsis or septic shock were randomized to receive either 6 hrs of early goal-directed therapy or standard therapy in the emergency department before admission to the intensive care unit (7). The resuscitation strategy involved rapid administration of intravenous fluids targeted to a central venous pressure of 8–12 mm Hg, correction of anemia to a hematocrit ≥30%, vasopressor agents as necessary to maintain mean arterial pressure ≥65 mm Hg, and administration of dobutamine in an attempt to achieve a central venous oxygen saturation ≥70%. Patients assigned to early goal-directed therapy had a significantly higher central venous oxygen saturation, lower lactate concentration and base deficit, and significantly lower Acute Physiology and Chronic Health Evaluation II scores, indicating less severe organ dysfunction (7). More importantly, in-hospital mortality rate was significantly decreased in the group assigned to early goal-directed therapy, from 46.5% to 30.5% ($p = .009$) (7). This study provides strong support for the notion that therapy for sepsis should be initiated as early as possible and should be directed toward clearly defined goals.

## Indexes of Global Perfusion

Bedside clinical assessment provides a good indication of global perfusion. Septic shock is by definition characterized by hypotension, which generally refers to a mean arterial pressure below 60–70 mm Hg in adults. Mean arterial pressure is preferable to systolic pressure because of its closer relationship to the autoregulatory limits of organ blood flow (3). In interpreting any given level of arterial pressure, however, the chronic level of pressure must be considered. Hypotension is usually accompanied by tachycardia.

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.

In most forms of shock, elevated blood lactate concentrations reflect anaerobic metabolism due to hypoperfusion, but the interpretation of blood lactate concentrations in septic patients is not always straightforward. Some studies in animal models of sepsis have found normal high-energy phosphate concentrations (8) but others have not (9); the differences may relate 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. A number of studies have indicated that increasing either global (10) or regional (11) oxygen delivery fails to alter elevated lactate concentrations in patients with sepsis. A number of studies have suggested that elevated lactate may result from cellular metabolic alterations rather than from global hypoperfusion in sepsis (12, 13). Accelerated glycolysis with high pyruvate production (14), inhibited pyruvate dehydrogenase, and decreased clearance by the liver may contribute to elevated lactate concentrations. Nonetheless, although lactate concentrations should not be considered to represent tissue hypoxia in the strict sense, the prognostic value of elevations of blood lactate has been well established in septic shock patients (15–17). The trend of lactate concentrations is a better indicator than a single value (15, 16). It is also of interest to note that blood lactate concentrations are a better prognostic indicator than oxygen-derived variables (calculated oxygen delivery and consumption) (18).

Mixed venous oxyhemoglobin saturation ($Svo_2$) can be measured in patients with a right heart catheter in place, either intermittently by sampling blood from the pulmonary artery port or continuously using a fiberoptic oximeter. $Svo_2$ is dependent on cardiac output, oxygen demand, hemoglobin, and oxygen saturation. $Svo_2$ reflects the balance between oxygen delivery and consumption and can decrease when oxygen delivery falls in relation to the oxygen requirements of the tissues. The normal $Svo_2$ value is 70–75% in critically ill patients, but $Svo_2$ can be elevated in septic patients due to maldistribution of blood flow, and so values must be interpreted in the context of the wider hemodynamic picture. Nonetheless, If $Svo_2$ remains low despite achievement of other end points of resuscitation, this suggests increased oxygen extraction and therefore potentially incomplete resuscitation. A



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recent study showed that monitoring of central venous oxygen saturation ($Scvo_2$) can be a valuable guide to early resuscitation (7).

### Indexes of Regional Perfusion

Adequacy of regional perfusion is usually assessed clinically by evaluating indexes of organ function, such as myocardial ischemia, decreased urine output, increased blood urea nitrogen and creatinine, an abnormal sensorium, increased serum concentrations of transaminases, lactic dehydrogenase, and bilirubin, and prolonged clotting tests (3). Methods of measuring regional perfusion more directly have been under investigation, with a focus on the splanchnic circulation, for several reasons. First, the hepatosplanchnic circulation may be compromised early in acute circulatory failure. Measurements of oxygen saturation in the hepatic vein have revealed oxygen desaturation in a subset of septic patients, suggesting that hepatosplanchnic oxygen supply may be inadequate in some patients, even when more global variables appear adequate (19). Second, the gut (especially the stomach) may be accessible to monitoring systems. Third, the countercurrent flow in the gut microcirculation increases the risk of mucosal hypoxia. Finally, the gut may have a higher critical oxygen delivery threshold than other organs (20), and gut ischemia increases intestinal permeability.

Gastric tonometry is a method to assess regional perfusion in the gut that employs a balloon in the stomach to measure intramucosal $Pco_2$. Gastric mucosal $Pco_2$ is influenced directly by systemic arterial $Pco_2$, however, and so use of gastric-arterial $Pco_2$ difference has been proposed as the primary tonometric variable of interest, although even this measure is not a simple measure of gastric mucosal hypoxia (21). Despite its complexity, tonometry is a reasonably good predictor for the ultimate outcome of critically ill patients (22–26). Its utility to guide therapy in patients with sepsis and septic shock, however, has not been proven. More recently, capnography in the sublingual area, a technique that is less invasive and easier to use, has been shown to yield tissue $Pco_2$ measurements that correlate with those obtained by gastric tonometry (27).

## FLUID RESUSCITATION IN SEPSIS

### Goals and Monitoring of Fluid Resuscitation

Septic shock is characterized by decreased effective capillary perfusion resulting from both global and distributive abnormalities of systemic and microcirculatory blood flow. An important factor contributing to the impairment in tissue perfusion is hypovolemia (13, 28–30). The initial phases of experimental and clinical septic shock present as a low cardiac output syndrome with low filling pressures and evolve to a hyperdynamic state only after volume repletion (13, 28). Increased blood and plasma volumes are associated with increased cardiac output and enhanced survival from septic shock (31). Failure to appreciate the degree of underlying hypovolemia may result in a low cardiac output.

Large fluid deficits exist in patients with septic shock. Up to 6–10 L of crystalloid solutions or 2 to 4 L of colloid solutions may be required for initial resuscitation in the first 24 hrs (7, 32). Volume repletion in patients with septic shock produces significant improvement in cardiac function and systemic oxygen delivery, thereby enhancing tissue perfusion and reversing anaerobic metabolism (33). Despite sepsis-induced myocardial depression, cardiac index will usually improve by 25–40% during fluid resuscitation (34). In approximately 50% of septic patients who initially present with hypotension, fluids alone will reverse hypotension and restore hemodynamic stability (35).

In sepsis, increases in interstitial fluid volume may already exist and venous capacitance changes play a major role in contributing to hypovolemia, and so repleting the interstitial space, which may have a role in hemorrhagic shock, does not appear to be as important. Intravascular volume can be repleted through the use of packed red cells, crystalloid solutions, and colloid solutions.

The goal of fluid resuscitation in septic shock is restoration of tissue perfusion and normalization of oxidative metabolism. Increasing cardiac output and oxygen delivery is dependent on expansion of blood and plasma volume. Fluid infusion is best initiated with predetermined boluses (250–500 mL every 15 mins) titrated to clinical end points of heart rate, urine output, and blood pressure. Patients who do not respond rapidly to initial fluid boluses or those with poor physiologic reserve should be considered for invasive hemodynamic monitoring. Filling pressures should be increased to a level associated with maximal increases in cardiac output. In most patients with septic shock, cardiac output will be optimized at pulmonary artery occlusion pressures between 12 and 15 mm Hg (34). Increases above this range usually do not significantly enhance end-diastolic volume or stroke volume and increase the risk for developing pulmonary edema. If only central venous pressure is available, levels of 8–12 mm Hg should be targeted (7).

In patients requiring mechanical ventilation, changes in arterial pressure during mechanical breaths may also serve as a useful indicator of underlying hypovolemia (36–38). The effects of increased pleural pressure on ventricular filling are accentuated in preload-deficient states, resulting in cyclic decreases in systolic arterial pressure and widening of the arterial pulse pressure. When these changes are present, they appear to be predictive of fluid responsiveness in septic patients with circulatory failure (37, 38). These measurements require that the patient have minimal or absent spontaneous respiratory efforts, which may necessitate the use of neuromuscular blocking agents (37, 38).

Far more important than the specific method of monitoring is the use of that method in a dynamic fashion. Evaluation of the response to fluid infusion is much more useful than one measurement at a single time point. This is particularly true in unstable patients, since cardiac and vascular compliance may change over time.

Resuscitation should be titrated to end points of oxygen metabolism and organ function. Associations have been observed between improved survival and increased levels of central venous oxygen saturation, systemic oxygen delivery, reversal of lactic acidosis, and increases in gastric intramucosal pH (7, 18, 24, 39). However, the specific choice of end points remains controversial.

### Fluid Resuscitation Therapies

*Crystalloids.* The crystalloid solutions used most commonly for resuscitation are 0.9% sodium chloride (normal saline) and lactated Ringer's solution. The lactate content of Ringer's solution is rapidly metabolized during resuscitation and



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does not significantly affect the use of arterial lactate concentration as a marker of tissue hypoperfusion (40).

The volume of distribution of normal saline and Ringer's lactate is the extracellular compartment. Under ideal conditions, approximately 25% of the infused amount will remain intravascular while the rest is distributed to the extravascular space. Clinically, 100–200 mL of intravascular volume expansion can be expected after the infusion of 1 L of isotonic crystalloids (41, 42). Resuscitation from septic shock frequently requires crystalloid volumes ranging from 6 to 10 L during the initial 24-hr period, which results in significant hemodilution of plasma proteins and decreases in colloid osmotic pressure.

Hypertonic saline solutions have a sodium content ranging from 400 to 2400 mOsm/L. Hypertonic solutions have potentially advantageous physiologic effects including improved cardiac contractility and precapillary vasodilation (43). The primary risk when using these fluids is iatrogenically induced hypertonic states due to sodium load. Experience with hypertonic solutions in septic shock is limited.

*Colloids.* Many different colloidal solutions are available, including plasma protein fraction, albumin, gelatins, dextrans, and hydroxyethyl starch. The principal solutions used in clinical resuscitation are albumin and hydroxyethyl starch.

Albumin is a naturally occurring plasma protein that accounts for approximately 80% of the plasma colloid osmotic pressure in normal subjects. Human serum albumin is available in the United States in 5% and 25% solutions; other concentrations are available in Europe. The 5% solution, rather than the 25% solution, should be used for initial resuscitation. After 1 L of 5% albumin, plasma volume expansion ranges from 500 to 1000 mL (41, 42). Mobilization of extravascular volume is required for effective increases in intravascular volume when using 25% albumin. If fluid is successfully mobilized from the interstitial space, a 100-mL aliquot can produce increases of 400–500 mL in the intravascular volume 1 hr after infusion (42). In the setting of increased vascular permeability such as septic shock, significantly smaller amounts of fluid may be mobilized.

The recently completed Saline versus Albumin Fluid Evaluation (SAFE) trial randomized 6,997 critically ill patients to resuscitation with albumin or saline. There was no difference in 28-day mortality rate (20.9% with albumin vs. 21.1% with saline) (44).

Hydroxyethyl starch is a synthetic colloid formed from hydroxyethyl-substituted branched-chain amylopectin. It is available in the United States a 6% solution of normal saline with a colloid osmotic pressure of approximately 30 mOsm/L (45). One liter of hydroxyethyl starch solution expands plasma volume by 700 mL to 1 L with as much as 40% of maximum volume expansion persisting for 24 hrs (41)

There have been reports suggesting that hydroxyethyl starch molecules may adversely affect renal function by causing tubular injury (46, 47). In patients with sepsis, resuscitation with hydroxyethyl starch solution, as compared with gelatin, resulted in significantly higher serum creatinine concentrations without associated differences in the need for renal replacement (47). Studies in other groups of patients have not observed differences in renal function when hydroxyethyl starch solution was compared with other fluids (48–51). Importantly, these studies were done with a variety of hydroxyethyl starch solutions, each with different physical properties that may have different effects on renal tubular cells. Additional investigations are required to reconcile these divergent observations.

Hydroxyethyl starch can cause dose-dependent decreases in factor VIII activity and prolongation of partial thromboplastin time. Although these changes appear to be primarily dilutional, there have been reports of increased bleeding, primarily in patients undergoing cardiac surgery (52). However, only minor clotting abnormalities and no increased incidence of bleeding have been noted in patients with hypovolemic and septic shock (52).

## Efficacy

Patients with septic shock can be successfully resuscitated with either crystalloid or colloids. Increases in cardiac output and systemic oxygen delivery are proportional to the expansion of intravascular volume achieved. When crystalloids and colloids are titrated to the same level of filling pressure, they are equally effective in restoring tissue perfusion (32). Resuscitation with crystalloid solutions will require two to four times more volume than colloids and may require slightly longer periods to achieve desired hemodynamic end points. Colloid solutions are much more expensive than crystalloid solutions. Five percent albumin and 6% hydroxyethyl starch solution are equivalent with respect to the amount of fluid required during resuscitation.

## Complications

The major complications of fluid resuscitation are pulmonary and systemic edema. These complications are related to three principal factors: a) increases in hydrostatic pressures; b) decreases in colloid osmotic pressure; and c) increases in microvascular permeability associated with septic shock. The controversy concerning crystalloid and colloid resuscitation revolves around the importance of maintaining plasma colloid osmotic pressure. Large volume crystalloid resuscitation results in significant decreases in plasma colloid osmotic pressure, whereas plasma colloid osmotic pressure is maintained with colloid infusion (32). In experimental studies, decreases in plasma colloid osmotic pressure increase extravascular fluid flux in the lungs and lower the level of hydrostatic pressure associated with lung water accumulation (53, 54). Some, but not all, clinical reports have observed a correlation between decreases in the colloid osmotic pressure-pulmonary artery occlusion pressure gradient and the presence of pulmonary edema (55–57). Several clinical studies have randomized subjects to crystalloid or colloid infusion and examined the development of pulmonary edema with mixed results, demonstrating either no differences between solutions or an increased incidence of pulmonary edema with crystalloids (32, 58, 59). Experimental reports in septic models demonstrate no increase in extravascular lung water when hydrostatic pressures are maintained at low levels, indicating that in sepsis the primary determinant of extravascular fluid flux appears to be microvascular pressure rather than colloid osmotic pressure (60). Together, these data suggest that when lower filling pressures are maintained there is no significant difference in the development of pulmonary edema with crystalloids or colloids. However, if higher filling pressures are required to optimize cardiac performance in patients with ventricular dysfunction, colloids may mitigate against extravascular fluid flux (32).



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The acute respiratory distress syndrome occurs in 30–60% of patients with septic shock. Of concern has been the possibility that in the setting of increased microvascular permeability, colloid particles could migrate into the interstitium where they would favor fluid retention in the lung and worsen pulmonary edema. A number of studies, including a variety of models of increased microvascular permeability, as well as clinical studies in patients with septic shock and the acute respiratory distress syndrome, have not found evidence of increased lung water or compromised lung function with colloids (32, 61–63).

Systemic edema is a frequent complication of fluid resuscitation. The relative roles of increased microvascular permeability, increases in hydrostatic pressure, and decreases in plasma colloid osmotic pressure in the development of this complication during sepsis are unclear. Tissue edema may reduce tissue oxygen tensions by increasing the distance for diffusion of oxygen into cells. During experimental peritonitis, crystalloid therapy was associated with increased endothelial cell swelling and decreased systemic capillary cross-sectional area when compared with colloid infusion (64). In contrast, other studies comparing the impact of large volume crystalloid infusion on skeletal muscle and intestinal oxygen metabolism have observed no impairment of oxidative metabolism despite significant edema formation (60, 65). The integrity of the gastrointestinal mucosa as a barrier to bacterial translocation also does not appear to be affected by decreases in colloid osmotic pressure and the development of tissue edema following crystalloid resuscitation. A comparison of crystalloid and colloid resuscitation in thermal injury found that the extent of resuscitation and not the choice of fluids was the major determinant of bacterial translocation (66).

Finally, there have been multiple meta-analyses of the clinical studies comparing crystalloids with colloids, which have examined the effect of resuscitation with these solutions on mortality rate. The results have been conflicting, with some of the reports suggesting differences in mortality rate favoring crystalloids, whereas others have shown no differences (67–69). These differences reflect the poor quality of many of the underlying studies, the heterogeneity in patient populations, and the fact that none of the clinical studies was ever designed with mortality as an end point.

## Transfusion Therapy

The optimal hemoglobin and hematocrit for patients with septic shock is uncertain. This is a major clinical issue since hemoglobin concentrations usually range between 8 and 10 g/dL in patients with septic shock. The decrease in hemoglobin is related to several factors including ineffective erythropoiesis and hemodilution. Decreases in hemoglobin in the range of 1–3 g/dL can be expected during resuscitation of septic shock with either crystalloids or colloids (32).

In most patients, this degree of anemia is well tolerated because the associated decrease in blood viscosity decreases afterload and increases venous return thereby increasing stroke volume and cardiac output. The decrease in blood viscosity may also compensate for other rheologic changes that occur in patients with septic shock and may enhance microvascular blood flow. However, several factors may affect the ability of the patient to tolerate the decrease in hematocrit and should be considered. Cardiac dysfunction will limit the increase in cardiac output in response to decreased viscosity and may result in inadequate levels of systemic oxygen delivery. In markedly hypermetabolic states, the increase in cardiac output may not be adequate to compensate for the decrease in arterial oxygen content, potentially compromising systemic oxygen metabolism. The inability to extract oxygen, related either to anatomical abnormalities such as in coronary artery diseases or physiologic abnormalities in sepsis, may result in greater dependence on oxygen content to maintain oxidative metabolism (70, 71).

To date, studies examining the effects of transfusing critically ill patients with hemoglobin concentrations in the range of 8–10 g/dL have not demonstrated any consistent benefit in tissue perfusion. The majority of trials have demonstrated no significant increase in systemic oxygen consumption when the major effect of transfusion therapy is to increase oxygen content (72–74). Other studies suggest that increasing oxygen content by transfusion therapy is not as effective in restoring splanchnic perfusion as it is in increasing cardiac output (75). Indeed, the transfusion of aged, more rigid, red cells has been associated with decreased gastric intramucosal pH and may accentuate the rheologic abnormalities seen in sepsis (76). Blood transfusion may also have immunosuppressive effects (77). Moreover, a study randomizing critically ill patients to transfusion thresholds of 7 or 10 g/dL failed to demonstrate any differences in clinically significant outcomes (78).

Accordingly, the optimal hemoglobin for patients with hemodynamically significant sepsis has not been defined. Most patients will tolerate hemoglobin concentrations in the range of 8–10 g/dL. Some patients, however, may have clinical variables that suggest a need for increased oxygen delivery, including excessive tachycardia, cardiac dysfunction, significant underlying cardiac or pulmonary disease, severe mixed venous oxygen desaturation, or failure to clear lactic acidosis. Patients with sepsis and hemodynamic instability tend to be in the second category. Such patients were excluded from the randomized trials of transfusion thresholds and may benefit from higher hemoglobin concentrations. Although no data exist to support transfusion to a predefined threshold, most experts recommend maintenance of hemoglobin concentrations in the 8–10 g/dL range in patients with sepsis and hemodynamic instability.

## Vasopressor 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 (79). 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. Potential agents include dopamine, norepinephrine, phenylephrine, epinephrine, and vasopressin.

Arterial pressure is the end point of vasopressor therapy, and the restoration of adequate pressure is the criterion of effectiveness. Blood pressure, however, does not always equate to blood flow, and the precise level of mean arterial pressure to aim for is not necessarily the same in all patients. Animal studies suggest that below a mean arterial pressure of 60 mm Hg, autoregulation in the coronary, renal, and central nervous system vascular beds is compromised. When organ autoregulation is lost, organ flow becomes linearly dependent on pressure (80, 81).



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Thus, maintenance of a mean arterial pressure of 60 mm Hg is usually required to maintain and optimize flow (82–84). Loss of autoregulation can occur at different levels in different organs, however, and thus some patients may require higher blood pressures to maintain adequate perfusion. In addition, the degree to which autoregulation is intact in septic patients is uncertain. It is important to supplement end points such as blood pressure with assessment of regional and global perfusion by a combination of the methods outlined previously.

Particular attention should be paid to certain peripheral circulations during vasopressor infusion. 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; the targeted mean blood pressure varied but was as high as 75 mm Hg (85–95). However, significant improvements in renal function with an increase in renal perfusion pressure have not been demonstrated in prospective, randomized studies. A recent study compared vasopressor therapy targeted to 65, 75, and 85 mm Hg in patients with septic shock and found no significant effect on systemic oxygen metabolism, skin microcirculatory blood flow, urine output, or splanchnic perfusion (96). Vasopressors should be titrated to the minimum level required to optimize urine flow; in some patients this can be achieved with a mean arterial pressure of 60 or 65 mm Hg.

The gastrointestinal tract, particularly perfusion of the splanchnic bed and the integrity of the gut mucosa, occupies a key position in the pathogenesis of multiple organ failure in sepsis. The effects of vasopressor agents on splanchnic circulation may play a role in their selection for a given patient.

Whether a potent vasopressor also has positive inotropic effects is of clinical importance in patients with low cardiac output (97). If vasopressor infusion impairs stroke volume, addition of an inotropic agent such as dobutamine should be considered (91).

## Individual Vasopressor Agents

*Dopamine.* Dopamine is the natural precursor of norepinephrine and epinephrine. Dopamine possesses several distinct dose-dependent pharmacologic effects. At doses $<5$ $\mu g \cdot kg^{-1} \cdot min^{-1}$, the predominant effect of dopamine is to stimulate dopaminergic $DA_1$ and $DA_2$ receptors to cause vasodilation in the renal, mesenteric, and coronary beds. Infusion of low doses of dopamine increases glomerular filtration rate, renal blood flow, and sodium excretion (98, 99). At doses of 5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, $\beta_1$-adrenergic effects predominate, increasing cardiac contractility and heart rate. Dopamine causes the release of norepinephrine from nerve terminals, which contributes to its effects on the heart. At doses $>10$ $\mu g \cdot kg^{-1} \cdot min^{-1}$, $\alpha_1$-adrenergic effects predominate, leading to arterial vasoconstriction and an increase in blood pressure. It should be recognized, however, that there is a great deal of overlap in these effects, particularly in critically ill patients.

The hemodynamic effects of dopamine in patients with septic shock have been reported in a number of open labeled trials. Dopamine has been shown to produce a median increase in mean arterial pressure of 24% in patients who remained hypotensive after optimal fluid resuscitation (29, 100–111). 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 (29, 100–111). The median dose of dopamine required to restore blood pressure was 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In most studies central venous, pulmonary artery, and pulmonary occlusion pressures, systemic vascular resistance index, and pulmonary artery resistance index were unchanged. In patients with elevated pulmonary artery occlusion pressures, dopamine may further increase occlusion pressure by increasing venous return. Patients receiving dopamine infusion rates $>20$ $\mu g \cdot kg^{-1} \cdot min^{-1}$ did show increases in right heart pressures as well as heart rate. Dopamine has been shown to improve right ventricular contractility in patients with underlying right ventricular failure (112).

Dopamine increases pulmonary shunt fraction, probably due to the increase in cardiac output, which can reopen vessels in poorly ventilated areas of the lung, (104, 110). $Pao_2$, however, remains relatively constant, which may be due to hemodynamic improvement and/or an increased mixed venous oxygen saturation (104, 105, 110).

Dopamine has been shown to increase oxygen delivery, but its effects on calculated or measured oxygen consumption have been mixed (100–102). Oxygen extraction ratio typically decreases, suggesting no improvement in tissue oxygenation (100, 102). This may be due to a failure to improve microcirculatory flow in vital organs or lack of a meaningful tissue oxygen debt in some patients (102).

The effect of dopamine on splanchnic perfusion as assessed by gastric tonometric variables has also been mixed. Increases in splanchnic blood flow have been reported but have not always been associated with increases in splanchnic oxygen consumption or effects on gastric intramucosal pH (100, 103, 113, 114). One pilot study reported that despite an increase in both systemic oxygen delivery and systemic oxygen consumption with dopamine, gastric intramucosal pH was reduced (101). The authors speculated that dopamine might have redistributed blood flow within the gut, reducing mucosal blood flow and increasing mucosal oxygen debt. Decreased gastric mucosal blood flow was reported with dopamine in another study, but gastric $Pco_2$, gastric-arterial $Pco_2$ difference, and calculated intramucosal pH were unchanged (115).

In laboratory animals and healthy volunteers, low doses of dopamine increase renal blood flow and glomerular filtration rate and inhibit proximal-tubular resorption of sodium, which result in natriuresis (116). With this physiologic rationale, low-dose dopamine is commonly administered to critically ill patients in the belief that it reduces the risk of renal failure by increasing renal blood flow. This issue has now been addressed by an adequately powered randomized clinical trial, which enrolled 328 critically ill patients with early renal dysfunction (urine output $<0.5$ $mL \cdot kg^{-1} \cdot hr^{-1}$ over 4 hrs, creatine $>150$ $\mu mol/L$ or an increase of $>80$ $\mu mol/L$ over 24 hrs) (117). Patients were randomized to low ("renal") dose dopamine (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or placebo, and the primary end point was peak serum creatinine. No difference was found in either the primary outcome (peak serum creatinine 245 vs. 249 $\mu mol/L$, $p = .92$), other renal outcomes (increase in creatinine, need for renal replacement), urine output (increased in both groups, perhaps due to furosemide administration), time to recovery of normal renal function, or secondary outcomes (survival to either intensive care unit or hospital discharge, intensive care unit stay, hospital stay, arrhythmias) (117). Thus, the available data do not support administration



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of low doses of dopamine solely to maintain renal function.

In summary, dopamine appears to be very effective in increasing mean arterial pressure in patients who remain hypotensive after optimal volume expansion. Since mean arterial pressure increases primarily as a result of increasing cardiac index, dopamine may be particularly useful in patients who are hypotensive with compromised cardiac function or cardiac reserve. The major undesirable effects of dopamine are tachycardia and arrhythmogenesis, both of which are more prominent than with other vasopressor agents. Other side effects include increased pulmonary artery occlusion pressure, increased pulmonary shunt, and the potential for decreased prolactin release and consequent immunosuppression (118).

*Norepinephrine.* Norepinephrine is a potent α-adrenergic agonist with less pronounced β-adrenergic agonist effects. Norepinephrine usually causes a clinically significant increase in mean arterial pressure attributable to its vasoconstrictive effects, with little change in heart rate or cardiac output, leading to increased systemic vascular resistance. Norepinephrine generally increases cardiac output by 10–20% and increases stroke volume by 10–15% (85, 86, 89, 91, 93, 119). Clinical studies have reported either no change (85, 86, 89, 93, 112) or modest increases (1–3 mm Hg) (92, 94, 101, 103, 106) in pulmonary artery occlusion pressure. Mean pulmonary arterial pressure is either unchanged (86, 89, 91, 94, 106) or increased slightly (93, 94, 106, 112). The combination of norepinephrine with dobutamine may be attractive in the setting of sepsis. In one study, addition of norepinephrine in patients with septic shock unresponsive to dobutamine significantly improved both mean arterial pressure and cardiac output (120).

Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in septic shock patients. In open labeled trials, norepinephrine has been shown to increase mean arterial pressure in patients who remained hypotensive after fluid resuscitation and dopamine (86, 89, 91, 93, 94, 103, 106, 112, 121). Reported doses have ranged from 0.01 to 3.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (91, 93). Thus, large doses of the drug may be required in some patients with septic shock, possibly due to α-receptor down-regulation in sepsis (122).

In the only randomized trial comparing vasopressor agents, 32 volume-resuscitated patients with hyperdynamic sepsis syndrome were prospectively randomized to receive either dopamine or norepinephrine to achieve and maintain normal hemodynamic and oxygen transport parameters for ≥6 hrs (106). Dopamine administration (10–25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) resulted in successful treatment in only 31% of patients whereas norepinephrine administration ($1.5 \pm 1.2$ $\mu g \cdot kg^{-1} \cdot min^{-1}$) was successful in 93% ($p < .001$). Of the 11 patients who did not respond to dopamine, ten responded when norepinephrine was added (106).

In patients with hypotension and hypovolemia, that is, during hemorrhagic or hypovolemic shock, the vasoconstrictive effects of norepinephrine can have detrimental effects on renal hemodynamics, with the potential for renal ischemia (123–125). The situation may differ in hyperdynamic septic shock (92). Norepinephrine has a greater effect on efferent than afferent renal arteriolar resistance and increases the filtration fraction. Several studies have shown increases in urine output, creatinine clearance, and osmolar clearance in patients with septic shock treated with norepinephrine alone or norepinephrine added to dobutamine (29, 85, 88, 92, 94, 101, 106, 112). These studies support the hypothesis that in fluid-resuscitated patients with septic shock, norepinephrine may optimize renal blood flow and renal vascular resistance (85, 92, 94).

Although early studies in patients with only mildly elevated serum lactate concentrations showed no significant changes over a relatively short period of time (1–3 hrs) with norepinephrine, (89, 101, 103, 112) in a later study in which initial lactate concentrations were elevated ($4.8 \pm 1.6$ mmol/L), a statistically and clinically significant decrease ($2.9 \pm 0.8$ mmol/L) was observed at the end of the 6-hr study period (106). The results of these studies suggest that the use of norepinephrine does not worsen and can even improve tissue oxygenation of patients with septic shock.

Results of studies of the effects of norepinephrine on splanchnic blood flow in patients with septic shock have been mixed. In one study, the effect of norepinephrine on splanchnic blood flow was unpredictable (103), whereas another study showed that septic patients who switched from dobutamine to norepinephrine or from dobutamine and norepinephrine to norepinephrine alone had a decrease in cardiac output and a parallel decrease in splanchnic blood flow (100). In these studies, however, splanchnic oxygen consumption remained unchanged (100, 103, 126). One pilot study found that gastric mucosal pHi was significantly increased during a 3-hr treatment with norepinephrine whereas it was significantly decreased during treatment with dopamine (101). A more recent study compared the effects of norepinephrine, epinephrine, and dopamine in 20 patients with septic shock (127). In the ten patients with moderate shock, no differences in splanchnic blood flow or gastric-arterial $P_{CO_2}$ difference were observed (127). In the ten with severe shock, cardiac index was higher and the effects of norepinephrine and dopamine were similar, but splanchnic blood flow was lower despite a higher cardiac index with epinephrine than with norepinephrine (127).

In summary, the clinical experience with norepinephrine in septic shock patients strongly suggests that this drug can successfully increase blood pressure without causing a deterioration in cardiac index and organ function (128). Used in doses of 0.01–3 $\mu g \cdot kg^{-1} \cdot min^{-1}$, norepinephrine reliably improves hemodynamic variables in most patients with septic shock. The effect of the drug on oxygen transport variables cannot be determined fully from the available data. However, other clinical variables of peripheral perfusion, such as urine flow and lactate concentration, are significantly improved in most studies. Unfortunately, only one report was controlled (106), and whether using norepinephrine in septic shock patients affects mortality rate as compared with dopamine or epinephrine still requires a prospective clinical trial. The available data do not support a detrimental effect of norepinephrine, however. In a recent multivariate analysis including 97 septic shock patients, mortality rate was favorably influenced by the use of norepinephrine as part of the hemodynamic management; use of high-dose dopamine, epinephrine, or dobutamine had no significant effect (129). When the use of norepinephrine is contemplated, it should be used early and not withheld as a last resort (130).

*Phenylephrine.* Phenylephrine, a selective α-1 adrenergic agonist, has been used by rapid intravenous administration to treat supraventricular tachycardia by causing a reflex vagal stimulation to the heart resulting from a rapid increase in



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blood pressure. It is also used intravenously in anesthesia to increase blood pressure. Its rapid onset, short duration, and primary vascular effects make it an attractive agent in the management of hypotension associated with sepsis. However, there are concerns about its potential to reduce cardiac output and lower heart rate in these patients.

Unfortunately, only a few studies have evaluated the use of phenylephrine in hyperdynamic sepsis. As such, guidelines on its clinical use are limited. One study in normotensive hyperdynamic septic patients showed that short-term administration of phenylephrine at a dosage of 70 μg/min increased mean arterial pressure, cardiac output, and stroke volume (131). In a dose-response study, phenylephrine administered to normotensive hyperdynamic septic patients in incremental doses of 0.5–8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increased mean arterial pressure, systemic vascular resistance, and stroke index, whereas no change was seen in cardiac index (132). Heart rate was slightly but significantly lower, with a decrease ranging from 3 to 9 beats/min. This study found no statistically significant changes in either oxygen delivery or consumption overall, but a clinically significant (>15%) increase in oxygen consumption was seen in eight of ten patients in at least one dosage.

Only one study has evaluated the effects of phenylephrine in treating hypotension associated with sepsis (95). In a small study of 13 patients with hyperdynamic septic shock (baseline cardiac index 3.3 $L \cdot min^{-1} \cdot m^{-2}$) receiving either low-dose dopamine or dobutamine, who remained hypotensive despite fluid administration (mean arterial pressure 57 mm Hg), phenylephrine was begun at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and was titrated to maintain a mean arterial pressure >70 mm Hg. Patients required phenylephrine for an average of 65 hrs, and the maximum dosage in each patient averaged 3.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (range 0.4–9.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Phenylephrine resulted in an increase in mean arterial pressure, systemic vascular resistance, cardiac index, and stroke index. There was no change in heart rate. A significant increase in urine output without a change in serum creatinine was observed during phenylephrine therapy.

The limited information available with phenylephrine suggests that this drug can increase blood pressure modestly in fluid-resuscitated septic shock patients. In addition, phenylephrine therapy does not impair cardiac or renal function. Phenylephrine may be a good choice when tachyarrhythmias limit therapy with other vasopressors. An increase in oxygen consumption and delivery may occur during therapy.

*Epinephrine.* In patients unresponsive to volume expansion or other catecholamine infusions, epinephrine can increase mean arterial pressure, primarily by increasing cardiac index and stroke volume with more modest increases in systemic vascular resistance and heart rate (90, 133–135). The dose-response relationship is more predictable in some studies (134) than others (90, 133). In patients with right ventricular failure, epinephrine increases right ventricular function by improving contractility (136). Epinephrine can increase oxygen delivery, but oxygen consumption may be increased as well (133–137).

Epinephrine decreases splanchnic blood flow, with transient increases in arterial, splanchnic, and hepatic venous lactate concentrations, decreases in pHi, and increases in $P_{CO_2}$ gap (100, 121, 138). These effects may be due to a reduction in splanchnic oxygen delivery to a level that impairs nutrient blood flow and results in a reduction in global tissue oxygenation, (100, 121) and may potentially be reversed by the concomitant administration of dobutamine (121). Alternatively, $CO_2$ production secondary to the thermogenic effect of epinephrine may play a role. These studies have been limited by the concurrent use of other catecholamines. Two more recent studies, however, found increased gastric mucosal perfusion with epinephrine compared with norepinephrine alone, to an extent similar to that of norepinephrine in combination with dobutamine (139, 140). In a recent study of 20 patients with septic shock, dopamine was replaced by either norepinephrine or epinephrine. In ten patients with severe shock (mean arterial pressure <65 mm Hg despite high-dose dopamine), epinephrine increased global oxygen delivery and consumption but caused a lower absolute and fractional splanchnic blood flow and lower indocyanine green clearance, thus validating the adverse effects of epinephrine alone on the splanchnic circulation (127).

Epinephrine administration has been associated with increases in systemic and regional lactate concentrations (121, 133, 137). Despite respiratory compensation and decreased arterial $P_{CO_2}$, the increase in plasma lactate was associated with decreases in arterial pH and base excess (137). The monitoring periods were short, and so it is unclear if these increases are transient; in the one longer study, arterial lactate and pHi returned to normal values within 24 hrs (121). Other adverse effects of epinephrine include increases in heart rate, but electrocardiographic changes indicating ischemia or arrhythmias have not been reported in septic patients (133, 134). Epinephrine has had minimal effects on pulmonary artery pressures and pulmonary vascular resistance in sepsis (133, 134).

In summary, epinephrine clearly increases blood pressure in patients unresponsive to traditional agents. However, because of its effects on gastric blood flow and its propensity to increase lactate concentrations, its use should be limited to patients who fail to respond to traditional therapies for increasing or maintaining blood pressure.

*Corticosteroids.* Corticosteroids exert important actions on various elements of the cardiovascular system including the capillaries, the arterioles, and the myocardium. Topical glucocorticoids constrict the dermal vessels, provoking blanching (141), although the mechanisms of this vasoconstriction remain poorly understood. Corticosteroids may up-regulate the sympathetic nervous system and the renin-angiotensin system (142, 143) and also enhance vascular responses to norepinephrine and angiotensin II, possibly through stimulation of the phosphoinositide signaling system in smooth muscle cells (144). Glucocorticoids also inhibit nitric oxide production by inducible nitric oxide synthase (145). Corticosteroids may potentiate catecholamine activity by several mechanisms: increasing phenylethanolamine N-methyltransferase activity and epinephrine synthesis (146), inhibiting catecholamine reuptake in neuromuscular junctions and decreasing their metabolism (147), increasing binding capacity and affinity of β-adrenergic receptors in arterial smooth muscle cells (148), and potentiating receptor G coupling and catecholamine-induced cyclic adenosine monophosphate synthesis (149). Corticosteroids also increase angiotensin II type I receptor expression in vascular smooth muscles (150) and significantly enhance central pressor effects of exogenous angiotensin II (151).

Numerous studies in various animal models, in healthy volunteers challenged with lipopolysaccharide, and in patients



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consistently show that corticosteroids enhance vascular responsiveness to vasoactive agents. In a rodent endotoxemia model, pretreatment with dexamethasone prevented endotoxin-induced vascular hyporesponsiveness to norepinephrine (152), probably by inhibiting extracellular release of lipocortin-1 (153). In a rodent model of hypotensive and hypokinetic septic shock, dexamethasone administration resulted in a complete reversal of hypotension, improvement in aortic blood flow, and reduced plasma lactate and nitrite/nitrate concentrations without affecting myocardial β-adrenergic receptor numbers or myocardial cyclic adenosine monophosphate, suggesting an effect on inducible nitric oxide synthase rather than on adrenergic receptor sensitivity (154). In healthy volunteers, the profound reduction in venous contractile response to norepinephrine induced by local instillation of endotoxin was completely prevented with pretreatment with 100 mg of oral hydrocortisone (155).

In another experiment, hydrocortisone given before or concurrent with an intravenous endotoxin challenge in 23 healthy subjects prevented the decreases in blood pressure and increases in heart rate and circulating epinephrine concentrations (156). In nine patients with septic shock, the relationship between the cortisol response to corticotropin (ACTH; defined by an increment in plasma cortisol concentrations of less than 9 μg/dL (250 nmol/L) after an intravenous bolus of 250 μg of ACTH) and pressor response to norepinephrine was investigated; five of the nine had such an impaired response (157). These five patients had a profound decrease in pressor response to incremental dose of norepinephrine (difference of 7 mm Hg at a norepinephrine infusion rate of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 20 mm Hg at a rate of 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, $p = .028$) when compared with the other four. In addition, the maximal increase in mean arterial pressure during norepinephrine infusion correlated positively with the maximal increment in plasma cortisol concentrations after corticotropin ($r = .783$, $p = .013$). In the patients with a cortisol response to ACTH <9 μg/dL, a single intravenous bolus of 50 mg of hydrocortisone normalized the pressor response to norepinephrine. Another study investigated the effects of a single intravenous bolus of 50 mg of hydrocortisone on phenylephrine-mean arterial pressure response curves in 12 patients with septic shock and 12 healthy volunteers (158). Septic patients had decreased maximum responses to phenylephrine compared with healthy volunteers, an effect that was mostly reversed by hydrocortisone. In this experiment, the effects of hydrocortisone did not correlate with circulating catecholamines concentrations, plasma renin activity, or cyclic guanosine monophosphate concentrations.

Prolonged treatment (≥5 days) with intravenous hydrocortisone at stress doses (around 300 mg daily) increases mean systemic arterial pressure and systemic vascular resistance with no significant change in pulmonary hemodynamics and cardiac index. In three phase II (159–161) and one phase III trial (162) of patients with vasopressor-dependent septic shock, prolonged treatment with a low dose of corticosteroids was associated with a significant reduction in the duration of shock.

In patients with septic shock, the effects of corticosteroids on systemic and pulmonary hemodynamics vary according to concomitant vasopressor therapy. In septic shock not treated by vasoconstrictors, intravenous administration of 50 mg of hydrocortisone had little effect on systemic blood pressure (157, 158). In one randomized, placebo-controlled, double-blind trial, the hemodynamic effects of 100 mg of hydrocortisone every 8 hrs for 5 days were investigated in 41 septic shock patients (159). In this study, mean arterial pressure increased in the hydrocortisone group (+10% at peak effects) and decreased (−7% at peak effects) in the placebo group, with no effect on cardiac output. In a second randomized, placebo-controlled, double-blind trial, the hemodynamic effects of a continuous infusion of hydrocortisone (0.18 $mg \cdot kg^{-1} \cdot hr^{-1}$) for 6 days were investigated in 40 hyperdynamic septic shock patients (160). In this study, as compared with placebo, hydrocortisone increased mean arterial pressure from study day 1 (+7 mm Hg) to study day 5 (+8 mm Hg). Cardiac output decreased in the hydrocortisone group (−25%) compared with the placebo group (+6%), and systemic vascular resistance was increased (by 260 and 369 $dynes \cdot sec/cm^5 \cdot m^2$ at study day 1 and 5, respectively). In a third randomized, placebo-controlled trial, the hemodynamic effects of a continuous infusion of hydrocortisone (10 mg/hr) were investigated in 40 septic shock patients (163). As compared with placebo, hydrocortisone significantly improved mean arterial pressure (+14 mm Hg vs. + 1 mm Hg at peak effect), again with a slight decrease in cardiac output in the hydrocortisone group (−11%) as compared with the placebo group (+9%) and an increase in systemic vascular resistance (+237 vs. + 10 $dynes \cdot sec/cm^5 \cdot m^2$ at peak effect).

The favorable effect of corticosteroids on vascular responsiveness to vasopressor agents is manifested at the bedside by a shortening of the time on vasoconstrictor drugs. Five randomized, placebo-controlled, double-blind trials have investigated the effects of prolonged (>3 days) treatment with moderate doses of hydrocortisone (200–300 mg per day) on shock duration and vasopressor withdrawal in septic shock. In one study, hydrocortisone significantly reduced the amount of catecholamine needed to maintain adequate systemic hemodynamics on day one (−40% from baseline vs. + 43%) and shortened mean time to cessation of vasopressor therapy (4 days vs. 13) (159). At study day 7, the rate of shock reversal was 68% in the hydrocortisone group and 21% in the placebo group. In a second study, at study day 7, the rate of shock reversal was 85% in the hydrocortisone group and 60% in the placebo group. The median time to vasopressor therapy withdrawal was 2 days in the treated group and 7 days in the placebo group (160). In a third study, hydrocortisone increased the rate of shock reversal at study day 3 compared with placebo (70% vs. 33%) and decreased the median time to cessation of vasopressor therapy (3 days vs. 5 days) (161). In a fourth study, at study day 3, the rate of shock reversal was 70% in the hydrocortisone group and 30% in the placebo group (163). Finally, in the fifth study, a phase III randomized placebo-controlled, double-blind trial of 300 septic shock patients, hydrocortisone combined with fludrocortisone significantly reduced the time on vasopressors in nonresponders to ACTH (increment in plasma cortisol concentrations of <9 μg/dL [248 nmol/L]) with a median time to vasopressor therapy withdrawal of 7 vs. 10 days (log rank $p = .009$). The rate of shock reversal at study day 7 was 70% vs. 50% (162). These effects were not seen in septic shock patients who had a cortisol increment of >9 μg/dL (248 nmol/L) in response to ACTH.

High doses of corticosteroids (i.e., 30 mg/kg of methylprednisolone or equivalent) once to four times had no effect on survival in severe sepsis or septic shock



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(164). By contrast, in septic shock, low doses ranging from 200 to 300 mg daily of corticosteroids given for a prolonged period of time (>5 days) have been shown to improve outcome in several controlled clinical trials. In 18 critically ill patients, compared with standard treatment alone, 100 mg twice daily of hydrocortisone dramatically improved intensive care unit survival rate (90% vs. 12.5%) (165). In another study of 41 septic shock patients, as compared with placebo, a 100-mg bolus of hydrocortisone every 8 hrs for 5 days improved the 28-day survival rate (68% vs. 37%) (159). Similar findings have been reported in another study in abstract form (161). Finally, a phase III, multiple-center, placebo-controlled, randomized, double-blind study evaluated the efficacy and safety of a combination of hydrocortisone (50-mg intravenous bolus four times per day) and fludrocortisone (50 μg orally once a day) given for 7 days in 300 patients with septic shock (162). In this trial, nonresponders to ACTH were more likely to benefit from cortisol replacement, with 30-day survival rates 47% vs. 37% (log rank $p = .02$), intensive care unit survival rates 42% vs. 30% (log rank $p = .01$), and hospital survival rates 39% vs. 28% (log rank $p = .02$). Patients who responded normally to ACTH (cortisol increment of >9 μg/dL [250 nmol/L] after 250 μg of corticotropin) had no benefit from corticosteroid therapy (1-month mortality rates: 61% vs. 53%, log rank $p = .81$).

*Vasopressin.* Vasopressin is a peptide hormone synthesized in the hypothalamus and then transported to and stored in the pituitary gland. Vasopressin is 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 (166). Vasopressin may also increase blood pressure by inhibition of vascular smooth muscle NO production (167) and $K^+$-ATP channels (168).

Normal concentrations of vasopressin have little effect on blood pressure in physiologic conditions (166), but vasopressin helps maintain blood pressure during hypovolemia, (169) and seems to restore impaired hemodynamic mechanisms and also inhibit pathologic vascular responses in shock. Increased concentrations of vasopressin have been documented in several types of shock (170, 171), but a growing body of evidence indicates that this response is abnormal or blunted in septic shock. One study found markedly increased concentrations of circulating vasopressin in 12 patients with cardiogenic shock but much lower concentrations in 19 patients with septic shock, concentrations that were hypothesized to be inappropriately low (172). One potential mechanism for this relative vasopressin deficiency would be depletion of pituitary stores, possibly in conjunction with impaired synthesis. Depletion of vasopressin stores in the neurohypophysis evaluated by magnetic resonance imaging has in fact been described in a small group of septic shock patients (173). A recent prospective cohort study of patients with septic shock found that vasopressin concentrations were almost always elevated in the initial hours of septic shock and decreased afterward; one third of patients developed relative vasopressin deficiency as defined by the investigators (174).

Given this theoretical rationale, several small observational studies have examined the effects of addition of vasopressin to catecholamines in patients with pressor-refractory septic shock. The first report showed that with infusion of low dose of vasopressin (0.04 units/min) in five patients with septic shock, vasopressin plasma concentrations reached 100 pg/mol (a concentration commensurate with those in patients with normal stress responses), and blood pressure increased significantly (172). Discontinuation of vasopressin was followed by a marked decrease in the arterial pressure. Similar findings were noted by the same group with low-dose vasopressin administration in the 19 patients with sepsis and low vasopressin concentrations in the study cited previously (172). Other studies have tested longer infusions. One report examined the effects of infusion of 0.04 units/min of vasopressin for 16 hrs in 16 patients with catecholamine-refractory septic shock and found an increase in mean arterial pressure in 14–16, with stable cardiac output, and increased urine output in the ten patients who were not anuric on study entry (175). In another report, in 50 patients with severe septic shock who had received continuous vasopressin infusion for 48 hrs, mean arterial pressure increased by 18% in the 4 hrs after the beginning of the infusion and then stabilized at 24 and 48 hrs; catecholamine doses were reduced by 33% at the 4th hour ($p = .01$) and by 50% at the 48th hour (166). Of note, five of the six patients with cardiac arrest during the study had received vasopressin doses >0.05 units/min (166).

Randomized studies of vasopressin infusion have been small. In one, ten patients with hyperdynamic septic shock on catecholamines were randomized to a low dose of vasopressin (0.04 units/min) or placebo (176). The patients who received vasopressin had a significant increase in systolic arterial pressure (from 98 to 125 mm Hg, $p < .05$) with successful weaning of catecholamines. No variation in arterial pressure was noted in the placebo group. The cardiac index did not differ in the two groups. Before termination of the study at 24 hrs, two of the five patients in the placebo group died of refractory hypotension; there were no deaths during the study in vasopressin-treated patients. Another group randomized 24 patients with septic shock on high-dose vasopressors to a 4-hr infusion of either norepinephrine or vasopressin, with open-label titration of vasopressors to maintain mean arterial pressure (177). In the vasopressin group, norepinephrine doses were significantly reduced at the 4th hour (25 to 5 μg/min, $p < .001$). Vasopressin doses varied between 0.01 and 0.08 units/min. In the norepinephrine group, doses were not significantly modified. Mean arterial pressure and cardiac index were maintained in both groups, and the gastric $CO_2$ gradient was unchanged as well. Urine output and creatinine clearance increased significantly in the vasopressin group but did not vary in the norepinephrine group (177).

All of the previously cited studies infused arginine-vasopressin, the vasopressin that is naturally present in humans. Lysine-vasopressin or terlipressin, the vasopressin present in the pig, has been evaluated in patients with septic shock in one reported study (178). Terlipressin administered as a single bolus of 1 mg to eight patients with septic shock refractory to catecholamines, hydrocortisone, and methylene blue improved blood pressure during the first 5 hrs and enabled partial or total weaning of catecholamines (178).

In summary, vasopressin plays an important role in normalizing blood pressure in states of shock. There is evidence that in septic shock, a relative deficiency of vasopressin may contribute to persis-



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tent hypotension. Current evidence demonstrates that in catecholamine-resistant septic shock, the addition of low-dose vasopressin (0.01–0.04 units/min) by continuous infusion to catecholamines can be used to increase blood pressure and decrease catecholamine doses. There is concern, however, that vasopressin infusion in septic patients may either decrease splanchnic perfusion or redistribute blood flow away from the splanchnic mucosa (179, 180). Data examining outcomes and clinical side effects are limited.

### Complications of Vasopressor Therapy

All of the catecholamine vasopressor agents can cause significant tachycardia, especially in patients who are inadequately volume resuscitated. 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 vasoconstriction can decrease stroke volume, cardiac output, and oxygen delivery. Should this occur, the dose of vasopressor should be lowered, or the addition of an inotropic agent such as dobutamine should be considered (91). Vasopressors can also cause limb ischemia and necrosis.

Administration of vasopressors may impair blood flow to the splanchnic system, and this can be manifested by stress ulceration, ileus, malabsorption, and even bowel infarction (121, 137). 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. If possible, episodes of intramucosal acidosis, which might be detected either by a decrease in gastric mucosal pHi or an increase in gastric mucosal $P_{CO_2}$, should be avoided, although no prospective randomized controlled trial has demonstrated a decrease in mortality rate with pHi or gastric $P_{CO_2}$-directed care in the management of patients with septic shock.

## INOTROPIC THERAPY IN SEPSIS

### Overview

Sepsis is characterized by a hyperdynamic state with normal to low blood pressure, normal to high cardiac index, and a low systemic vascular resistance (1, 29). Although cardiac output is usually maintained in the volume-resuscitated septic patient, a number of investigations have demonstrated that cardiac function is impaired (97, 181, 182). This myocardial dysfunction is characterized by a decreased ejection fraction, ventricular dilation, impaired contractile response to volume loading, and a low peak systolic pressure/end-systolic volume ratio (a relatively load-independent measure of ventricular function) (183–185). The mechanism of this cardiac dysfunction is complex. Myocardial ischemia is unlikely, as coronary blood flow is normal and there is no net lactate production across the coronary vascular bed (186, 187). Animal studies of endotoxemia or bacterial infection have suggested that myocardial edema (188), alterations in sarcolemmal or intracellular calcium homeostasis (189), and uncoupling or disruption of β-adrenergic signal transduction may contribute to the cardiac contractile dysfunction (190). A variety of inflammatory mediators, including prostanoids (191), platelet-activating factor (65), tumor necrosis factor-α, interleukin-1 and interleukin-2, (192), and nitric oxide (193, 194) have been shown to cause myocardial depression in a number of animal models, possibly through the sphinomyelinase pathway (195). Although it is clear that myocardial performance is altered during sepsis and septic shock, end points for cardiac resuscitation are uncertain.

Inotropic therapy in septic shock is complex, because different approaches endeavor to achieve different goals. In patients with decreased cardiac output, the goals of therapy are straightforward and are aimed at restoring normal physiology. Because of the complexity of assessment of clinical variables in septic patients, measurement of cardiac output is advisable. Such measurements need to be interpreted in the clinical context; a patient with preexisting cardiac disease may have a limited ability to increase cardiac output, and thus values within the normal range or even slightly below normal may actually represent a hyperdynamic response for that particular patient. Thus, other end points of global perfusion should be followed as well. When global hypoperfusion is manifested by decreased mixed venous oxygen saturation, this measure may be followed as an index of the efficacy of inotropic therapy. Similarly, although lactate production in sepsis is complex, a decrease in blood lactate concentrations concomitant with increased cardiac output is a good prognostic sign. To further complicate matters, the pharmacokinetics and pharmacodynamics of inotropic agents in septic patients can be quite complex and variable (196, 197).

Some critically ill septic patients are hypermetabolic and may require high levels of oxygen delivery to maintain oxidative metabolism. Data from the 1980s and early 1990s suggested that a linear relationship between oxygen delivery and oxygen consumption ("pathologic supply dependency") was common in septic patients, (33, 198) with the inference that oxygen delivery was insufficient to meet the metabolic needs of the patient. These observations led to the hypothesis that resuscitation to predetermined elevated end points of cardiac index and oxygen delivery and consumption ("hyperresuscitation") might improve patient outcome. Retrospective analyses showed that achievement of cardiac index $>4.5$ $L \cdot min^{-1} \cdot m^{-2}$, oxygen delivery $>600$ $mL \cdot min^{-1} \cdot m^{-2}$, and oxygen consumption $>170$ $mL \cdot min^{-1} \cdot m^{-2}$ correlated with improved survival (39). Other investigations, however, have challenged the concept of pathologic supply-dependency and hyperresuscitation (199–202). Although cardiac index and oxygen delivery are correlated with outcome (39), it is unclear if increases in these variables are the cause of increased survival or represent the underlying physiologic reserve of the patient. Randomized studies to test the practice of routinely increasing oxygen delivery to these predefined levels in all critically ill patients have produced conflicting results (199–201, 203, 204), and it is unclear if increases in cardiac index and oxygen delivery are the cause of increased survival or represent underlying physiologic reserve of the patient. Thus, a strategy of routinely increasing oxygen delivery to predetermined elevated end points of cardiac index and oxygen delivery cannot be recommended on the basis of current data (205). Nonetheless, some clinicians believe that this issue has not been settled definitively in



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Table 1. Summary of cardiac effects of inotropes used in sepsis and septic shock: Physiologic values are reported as percent change from baseline

| Drug | Dose Range, $\mu g \cdot kg^{-1} \cdot m^{-1}$ | Heart Rate | Cardiac Index | Stroke Volume Index | SVRI | LVSWI | References |
|---|---|---|---|---|---|---|---|
| Isoproterenol | 1.5 to 18 μg/min | 11 to 20 | 47 to 119 | 22 to 89 | −24 to −44 | 74 to 157 | (29, 230) |
| Dopamine | 2 to 55 | 1 to 23 | 4 to 44 | 7 to 32 | −6 to 18 | 5 to 91 | (102, 104, 105, 107, 109, 110, 112–114, 138, 211–214) |
| Epinephrine | 0.06 to 0.47 | −6 to 27 | 24 to 54 | 12 | −7 to 34 | 32 to 95 | (135, 136, 138) |
| Norepinephrine | 0.03 to 3.3 | −6 to 8 | −3 to 21 | 5 to 15 | 13 to 111 | 42 to 142 | (91, 94, 102, 104, 107, 113, 120) |
| Dobutamine | 2 to 28 | 9 to 23 | 12 to 61 | 15 | −6 to −21 | 23 to 58 | (16, 92, 203, 215–218) |
| Milrinone[a] | 0.5 | 1 | 41 to 49 | 47 | −30 to −35 | 51 to 56 | (228, 229) |

SVRI, systemic vascular resistance index; LVSWI, left ventricular stroke work index.
[a]With other inotropes including dopamine, dobutamine, norepinephrine and/or epinephrine.

those patients with septic shock and argue that a subset of these patients may benefit from therapy aimed at supranormal oxygen delivery.

Uncertainty exists in regard to other end points for inotropic therapy. Deficits in oxygen delivery can clearly cause a lactic acidosis, but the converse is not true: elevated lactate concentrations in patients with sepsis or septic shock do not necessarily reflect deficits in oxygen delivery (206). In adequately resuscitated septic patients, mixed venous oxygen saturation is usually normal or high, this value correlates poorly with cardiac output, and several studies have questioned the value of $Svo_2$ as the end point for inotropic therapy in critically ill patients (207, 208). Low mixed venous oxygen saturation may indicate decreased global oxygen delivery, however (207).

Despite seemingly adequate resuscitation, some septic shock patients develop multiple organ failure, resulting in death. It has been argued that even after hypotension has been corrected and global oxygen delivery is adequate in patients with septic shock, blood flow and tissue perfusion can remain suboptimal. Gastric tonometry and sublingual capnometry monitor gastric and sublingual $Pco_2$ as a proxy for determining the adequacy of gut perfusion. Although these monitors serve as good predictors for the ultimate outcome of critically ill patients (22–25), their utility to guide therapy in patients with sepsis and septic shock has not been proven. In dysoxic states with normal or elevated blood flow, these monitors generally fail to detect an elevated intramucosal-arterial $Pco_2$ gap (209). No current evidence supports improved outcome with empirical therapy to raise cardiac output in patients with normal blood pressure, but a subpopulation of patients might have regional hypoperfusion that would respond to additional therapy. One would want to titrate such therapy to an index of regional perfusion, although the precise end points are uncertain. In this context, it is important to realize that different interventions to increase oxygen delivery, such as fluid resuscitation, blood transfusion, or infusion of vasoactive agents, can have different effects on regional perfusion (101, 112, 121). Different vasoactive agents have been shown to have divergent effects on gastric intramucosal pH.

An inotropic agent should be considered to maintain an adequate cardiac index, mean arterial pressure, $Svo_2$, and urine output. Cardiac output can be measured using a pulmonary artery catheter, by echocardiography, with an esophageal Doppler probe, or by pulse contour analysis. Regardless of the measurement method chosen, clinicians should define specific goals and desired end points of inotropic therapy in septic patients and titrate therapy to those end points. These goals and end points should be refined at frequent intervals as patients' clinical status changes.

## Therapies and Efficacy

Most investigations evaluating inotropic agents have been observational and have used the baseline hemodynamic characteristics of the patient as the controls. The majority of these studies have used heart rate, cardiac index or output, and/or stroke volume or stroke volume index as the outcome variables. Only a few studies have assessed ventricular function by reporting left (or right) ventricular stroke work index. The results are summarized in Table 1.

## Individual Inotropic Agents

*Isoproterenol.* Isoproterenol is a $\beta_1$- and $\beta_2$-adrenergic agonist. Few studies have evaluated isoproterenol in sepsis and septic shock. In septic shock patients with a low cardiac index (mean $<2.0$ $L \cdot min^{-1} \cdot m^{-2}$), isoproterenol (2–8 μg/min) will significantly increase cardiac index without decreasing blood pressure but at the expense of increasing heart rate (29, 210). In patients with a normal cardiac index, however, isoproterenol can decrease blood pressure through its $\beta_2$-adrenergic effects. In addition, the chronotropic effects of $\beta_1$-adrenergic stimulation can precipitate myocardial ischemia.

*Dopamine.* Dopamine is an adrenergic agonist with predominant dopaminergic properties at doses $<5$ $\mu g \cdot kg^{-1} \cdot min^{-1}$ and increased β and α activity at doses $>5$ $\mu g \cdot kg^{-1} \cdot min^{-1}$. However, even at low doses, significant α and β agonism may occur since the pharmacokinetics of dopamine in critically ill patients is highly variable (197).

In patients with severe sepsis and/or septic shock, most studies have shown that dopamine will increase cardiac index with a range from 4% to 44%, left ventricular stroke work index by 5–91%, and right ventricular stroke work index by a modest 5–10% (101, 103, 104, 106, 108, 109, 111–113, 137, 210–213). These improvements in cardiac performance come at the expense of an increase in the heart rate of approximately 15% (range up to 23%). The greatest increase in these variables occurs at doses ranging from 3 to 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$. At higher doses, the rate of improvement in cardiac function decreases. Although dopamine may increase mesenteric blood flow, it may also decrease mesenteric oxygen consumption (113). It is not clear whether effects of dopamine are superior to any other adrenergic agent.

*Dobutamine.* Dobutamine is a racemic mixture of two isomers, a D isomer with $\beta_1$- and $\beta_2$-adrenergic effects, and an L isomer with $\beta_1$- and $\alpha_1$-adrenergic ef-



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fects; its predominant effect is inotropic via stimulation of $\beta_1$ receptors, with a variable effect on blood pressure.

A number of studies have investigated the effect of dobutamine on cardiac function during sepsis or septic shock at doses ranging from 2 to 28 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (91, 202, 214–218). In these studies, increases in cardiac index ranged from 12% to 61%. However, heart rate increases, often significantly (9–23%). Two studies reported that left ventricular stroke work index increased by 23–58% at mean dobutamine doses of 5–12 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (214, 215). Similar increases in right ventricular stroke work were also observed in these studies.

Although dobutamine does not influence the distribution of blood flow, therapy is often aimed at increasing blood flow to organs such as the gut or the kidneys.

*Epinephrine.* Epinephrine stimulates both α and β receptors. At low doses, the β-adrenergic effects predominate. A few recent studies have examined the hemodynamic effects of epinephrine in septic shock at doses ranging from 0.1 to 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (134, 135, 137). The increase in cardiac index varied from 24% to 54%, and the heart rate response was variable. Increases in left ventricular stroke work index as high as 95% have been noted (135). Other studies indicated that lactic acidosis is increased and perfusion to the gut is altered with the use of epinephrine (121, 127, 137).

*Norepinephrine.* Like epinephrine, norepinephrine stimulates both α and β receptors; however, the α-adrenergic response is the predominant effect. The effect of norepinephrine on cardiac index is modest, with the majority of studies showing no change or increases of up to 21% while heart rate is unaffected or even decreases by up to 8% (91, 93, 101, 103, 106, 112, 119). However, several studies have shown a marked increase in left and right ventricular stroke work index due to increased blood pressure (93, 101, 112, 119).

*Combination and Comparative Studies.* A number of studies have investigated catecholamine combinations (86, 94, 121, 126, 219–222). The majority of these studies did not study the catecholamine combination in a standardized fashion, thus limiting the conclusions that can be drawn about the effects of these catecholamine combinations on cardiac function. Patients who do not respond to dopamine with an increase in cardiac index may reach the desired end point with a dopamine/norepinephrine combination (106). Dobutamine and norepinephrine appear to be an effective combination to improve cardiac index and blood pressure (91) In addition, some (223) but not all (224, 225) studies have shown that dobutamine or a dobutamine/norepinephrine combination will also enhance mesenteric perfusion.

A few investigations have been performed comparing different inotropic regimens (87–90, 101, 112, 121, 137). Epinephrine appears to be as good if not better at improving cardiac performance than dopamine or a dobutamine/norepinephrine combination (121, 137). However, with one exception (140), studies have shown that when epinephrine is compared with other adrenergic agents or their combinations, there are increases in arterial lactate and decreases in gastric intramucosal pH, suggesting that perfusion to regional vascular beds may be impaired (121, 127, 137, 139, 226). In several studies, dopamine increased cardiac index and stroke volume index to a greater extent than norepinephrine, but increases in left and right ventricular stroke volume index were about the same with the two agents (101, 112). There was less prominent tachycardia with norepinephrine, and one unconfirmed pilot study suggested that mesenteric perfusion is impaired with dopamine compared with norepinephrine (101, 112).

*Phosphodiesterase Inhibitors.* Phosphodiesterase inhibitors are vasodilators with long half-lives, raising the potential for prolonged decreases in blood pressure when used in septic patients. There are a few small studies of these agents in patients with sepsis, but meaningful conclusions cannot be made because of the size of the studies and the concomitant use of disparate adrenergic agents (227–230).

### Complications

In the septic patient who has been inadequately volume resuscitated, all of the inotropic agents can cause significant tachycardia and other cardiac arrhythmias (77). In patients with coexisting coronary disease, the change in myocardial oxygen consumption may precipitate myocardial ischemia and infarction (199). Excessive doses of catecholamines can also result in myocardial band necrosis independent of the presence of coronary disease.

Sole use of inotropic agents that also have vasodilatory activity (e.g., isoproterenol, milrinone) is likely to reduce blood pressure. These reductions can be long-lasting with agents that have long half-lives.

Administration of inotropic agents that have pressor activity may impair blood flow to other organ beds, such as the splanchnic circulation (121, 137). Efforts to ensure adequate volume resuscitation and to assess end-organ function must be made.

## RECOMMENDATIONS FOR HEMODYNAMIC SUPPORT OF SEPTIC PATIENTS

### Basic Principles

1. Resuscitation of patients with sepsis should be initiated expeditiously and pursued vigorously. Measures to improve tissue and organ perfusion are most effective when applied early.
2. Patients with septic shock should be treated in an intensive care unit, with continuous electrocardiographic monitoring and monitoring of arterial oxygenation.
3. Arterial cannulation should be performed in patients with shock to provide a more accurate measurement of intra-arterial pressure and to allow beat-to-beat analysis so that decisions regarding therapy can be based on immediate and reproducible blood pressure information.
4. Resuscitation should be titrated to clinical end points of arterial pressure, heart rate, urine output, skin perfusion, and mental status, and indexes of tissue perfusion such as blood lactate concentrations and mixed venous oxygen saturation.
5. Assessment of cardiac filling pressures may require central venous or pulmonary artery catheterization. Pulmonary artery catheterization also allows for assessment of pulmonary artery pressures, cardiac output measurement, and measurement of mixed venous oxygen saturation. Echocardiography may also be useful to assess ventricular volumes and cardiac performance.



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*The fundamental principle is that clinicians using hemodynamic therapies should define specific goals and end points, titrate therapies to those end points, and evaluate the results of their interventions on an ongoing basis by monitoring a combination of variables of global and regional perfusion.*

### Fluid Resuscitation

*Recommendation 1—Level B.* Fluid infusion should be the initial step in hemodynamic support of patients with septic shock. Initial fluid resuscitation should be titrated to clinical end points.

*Recommendation 2—Level B.* Isotonic crystalloids or iso-oncotic colloids are equally effective when titrated to the same hemodynamic end points.

*Recommendation 3—Level D.* Invasive hemodynamic monitoring should be considered in those patients not responding promptly to initial resuscitative efforts. Pulmonary edema may occur as a complication of fluid resuscitation and necessitates monitoring of arterial oxygenation. Fluid infusion should be titrated to a level of filling pressure associated with the greatest increase in cardiac output and stroke volume. For most patients, this will be a pulmonary artery occlusion pressure in the range of 12–15 mm Hg. An increase in the variation of arterial pressure with respiration may also be used to identify patients likely to respond to additional fluid administration.

*Recommendation 4—Level C.* Hemoglobin concentrations should be maintained between 8 and 10 gm/dL. In patients with low cardiac output, mixed venous oxygen desaturation, lactic acidosis, widened gastric-arterial $P_{CO_2}$ gradients, or significant cardiac or pulmonary disease, transfusion to a higher concentration of hemoglobin may be desirable.

### Vasopressor Therapy

*Recommendation 1—Level C.* Dopamine and norepinephrine are both effective for increasing arterial blood pressure. It is imperative to ensure that patients are adequately 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.

*Recommendation 2—Level D.* Phenylephrine is an alternative to increase blood pressure, especially in the setting of tachyarrhythmias. Epinephrine can be considered for refractory hypotension, although adverse effects are common, and epinephrine may potentially decrease mesenteric perfusion.

*Recommendation 3—Level B.* Administration of low doses of dopamine to maintain renal function is not recommended.

*Recommendation 4—Level C.* Patients with hypotension refractory to catecholamine vasopressors may benefit from addition of replacement dose steroids.

*Recommendation 5—Level D.* Low doses of vasopressin given after 24 hrs as hormone replacement may be effective in raising blood pressure in patients refractory to other vasopressors, although no conclusive data are yet available regarding outcome.

### Inotropic Therapy

*Recommendation 1—Level C.* Dobutamine is the first choice for patients with low cardiac index and/or low mixed venous oxygen saturation and an adequate mean arterial pressure following fluid resuscitation. Dobutamine may cause hypotension and/or tachycardia in some patients, especially those with decreased filling pressures.

*Recommendation 2—Level B.* In patients with evidence of tissue hypoperfusion, addition of dobutamine may be helpful to increase cardiac output and improve organ perfusion. A strategy of routinely increasing cardiac index to predefined "supranormal" levels ($>4.5$ $L \cdot min^{-1} \cdot m^{-2}$) has not been shown to improve outcome.

*Recommendation 3—Level C.* A vasopressor such as norepinephrine and an inotrope such as dobutamine can be titrated separately to maintain both mean arterial pressure and cardiac output.

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