

Cardiovascular management of septic shock

R. Phillip Dellinger, MD

This review will cover septic shock as a manifestation of severe sepsis. The reader is referred to other articles, which review the myriad multisystem dysfunctions associated with severe sepsis (1–4), and is reminded that as in all patients with sepsis early initiation of appropriate antibiotics and adequate source control are key components of septic shock treatment.

Ascertaining the incidence of septic shock is limited by the variability in definitions used in epidemiologic studies, the analysis of septic shock as a subset of patients with severe sepsis, and shortcomings of methods used to calculate the incidence of severe sepsis. In five recent large clinical trials that enrolled a total of 5,461 patients with severe sepsis (criteria = evidence of infection, systemic inflammatory response syndrome, and at least one organ dysfunction/hypoperfusion), the incidence of septic shock ranged from 52% to 71% of patients with severe sepsis, with a mean of 58% (5–9). A recent study used International Classification of Diseases (ICD)-9 hospital diagnostic codes for infection and acute organ dysfunction to estimate 751,000 cases of severe sepsis per annum in the United States (10). Taking the incidence of septic shock in severe sepsis from the five studies above, septic shock would, therefore, be predicted to occur annually in 435,580 patients in the United States. The mor-

tality of septic shock can be estimated more reliably. Table 1 shows a compilation of septic shock mortalities drawn from the placebo arms of clinical trials (8, 9, 11–22). Figure 1 shows improvement in septic shock mortality over time (23).

Historical Perspective

The word *sepsis* is derived from the Greek language (24). Sepsis was good, embodying the natural processes of maturation and fermentation. Sepsis, however, was bad and synonymous with putrefaction as characterized by bad smell. It was thousands of years later before Pasteur conclusively linked putrefaction to a bacterial cause. The word *shock* has its derivation from the French root “choquer,” meaning “to collide with.” Based on our current understanding of the pathophysiology of septic shock, the collision of the body’s defenses with the invading organism, this seems to be particularly appropriate terminology.

Current Definition of Septic Shock

In 1992, the ACCP/SCCM Consensus Conference Committee defined septic shock as follows: “. . .sepsis-induced hypotension (systolic blood pressure < 90 mm Hg or a reduction of \geq 40 mm Hg from baseline) despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may have a normalized blood pressure at the time that perfusion abnormalities are identified.” (25)

This definition has received general acceptance with the exception that most clinical trials have not considered inotropic therapy alone as a qualifier for sepsis-induced cardiovascular failure. As a gen-

eral rule, because most patients who remain hypotensive after volume resuscitation will be started on vasopressors, vasopressor requirement for sepsis-induced hypotension plus hypoperfusion abnormalities becomes a clinically useful surrogate definition for septic shock.

Pathophysiology and Associated Clinical Considerations

The hemodynamic profile of septic shock is influenced by multiple sepsis-induced physiologic changes (26–38) and characterized by components of hypovolemic, obstructive, cardiogenic, distributive, and cytotoxic shock (Table 2). This hemodynamic profile is modified by fluid resuscitation (Fig. 2). After adequate restoration of left ventricular filling, the presence and severity of hypotension are directly dependent on impairment of contractility (both sepsis-induced and baseline) and the degree of systemic vascular resistance lowering (39, 40). Persistent hypotension, despite adequate fluid resuscitation, mandates the use of vasopressors and is the hallmark of septic shock.

Even when cardiac output in septic shock has been normalized or is supranormal, hypoperfusion abnormalities (lactic acidosis, decreased urine output, or altered mental status) may persist. This “distributive shock” may be related to a maldistribution of blood flow at the organ level (decreased blood flow to the stomach, pancreas, and small bowel) or microvascular level (shunting) and may be associated with a cytotoxic component (sepsis-induced cellular deficiency in utilizing oxygen, despite adequate supply) (41–47).

Diagnosis

Septic shock is diagnosed when there is clinical evidence of infection, persistent sepsis-induced hypotension, despite volume resuscitation (or re-

From Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Section of Critical Care Medicine, Cooper Health System, Camden, NJ.

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Address requests for reprints to: R. Phillip Dellinger, MD, Director, Section of Critical Care Medicine, Cooper Health System, One Cooper Plaza, Camden, NJ 08103. E-mail: Dellinger-Phil@cooperhealth.edu

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Table 1. Compilation of septic shock mortalities drawn from placebo arms of clinical trials

Author	Year	Study Type	Control Group Patients with Septic Shock	HMR (%)
Abraham et al. (11)	1998	RCT	930	398 (43)
Baudo et al. (12)	1998	RCT	23	20 (87)
Bollaert et al. (13)	1998	RCT	19	12 (63)
Briegel et al. (14)	1999	RCT	20	6 (30)
Angus et al. (15)	2000	RCT	317	145 (46)
Martin et al. (16)	2000	POS	97	70 (73)
Rank et al. (17)	2000	RCT	30	16 (53)
Abraham et al. (18)	2001	RCT	185	63 (34)
Warren et al. (8)	2001	RCT	544	235 (43)
Abraham et al. (19)	2001	RCT	46	19 (41)
Rivers et al. (9)	2001	RCT	70	40 (57)
Jensen et al. (20)	2002	POS	38	18 (47)
Cole et al. (21)	2002	RCT	12	4 (33)
Annane et al. (22)	2002	RCT	149	91 (61)
Total			2480	1137 (46)

HMR, hospital mortality rate; RCT, randomized, controlled trial; POS, prospective observational study.

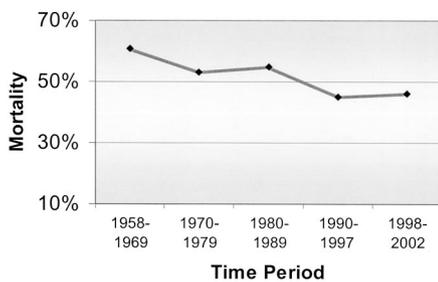


Figure 1. Changes in septic shock mortality (1958–2002). Adapted from Reference 23.

quirement for vasopressors), and evidence of sepsis-related organ hypoperfusion (lactic acidosis, decreased urine output, or altered mental status). Other causes of shock potentially associated with fever include pulmonary embolism, acute myocardial infarction, and adrenal crisis (48–50). In patients being hemodynamically monitored, cardiac output is decreased in pulmonary embolism and acute myocardial infarction but following volume resuscitation would typically be increased in septic and adrenal shock. Serum troponin may be elevated in septic shock, as well as shock due to myocardial infarction or pulmonary embolism, but markedly increased only in myocardial infarction (51–53). Bedside echocardiography is useful in differentiating shock due to pulmonary embolism (right ventricular dilation), acute myocardial infarction (focal wall motion abnormality), hypovolemic shock (poorly filled hyperdynamic left ventricle), and septic shock (global decrease in contractility).

Table 2. Septic shock—A melting pot of shock etiologies

Hypovolemic (loss of cardiac filling)
Capillary leak (absolute hypovolemia)
Venodilation (relative hypovolemia)
Cardiogenic
Decrease in contractility
Obstructive
Rise in pulmonary vascular resistance
Distributive (hypoperfusion, despite normal/increased cardiac output)
Macrovascular
Decreased splanchnic blood flow
Microvascular
Shunting
Cytotoxic
Cellular inability to utilize oxygen, despite adequate supply

Invasive Monitoring

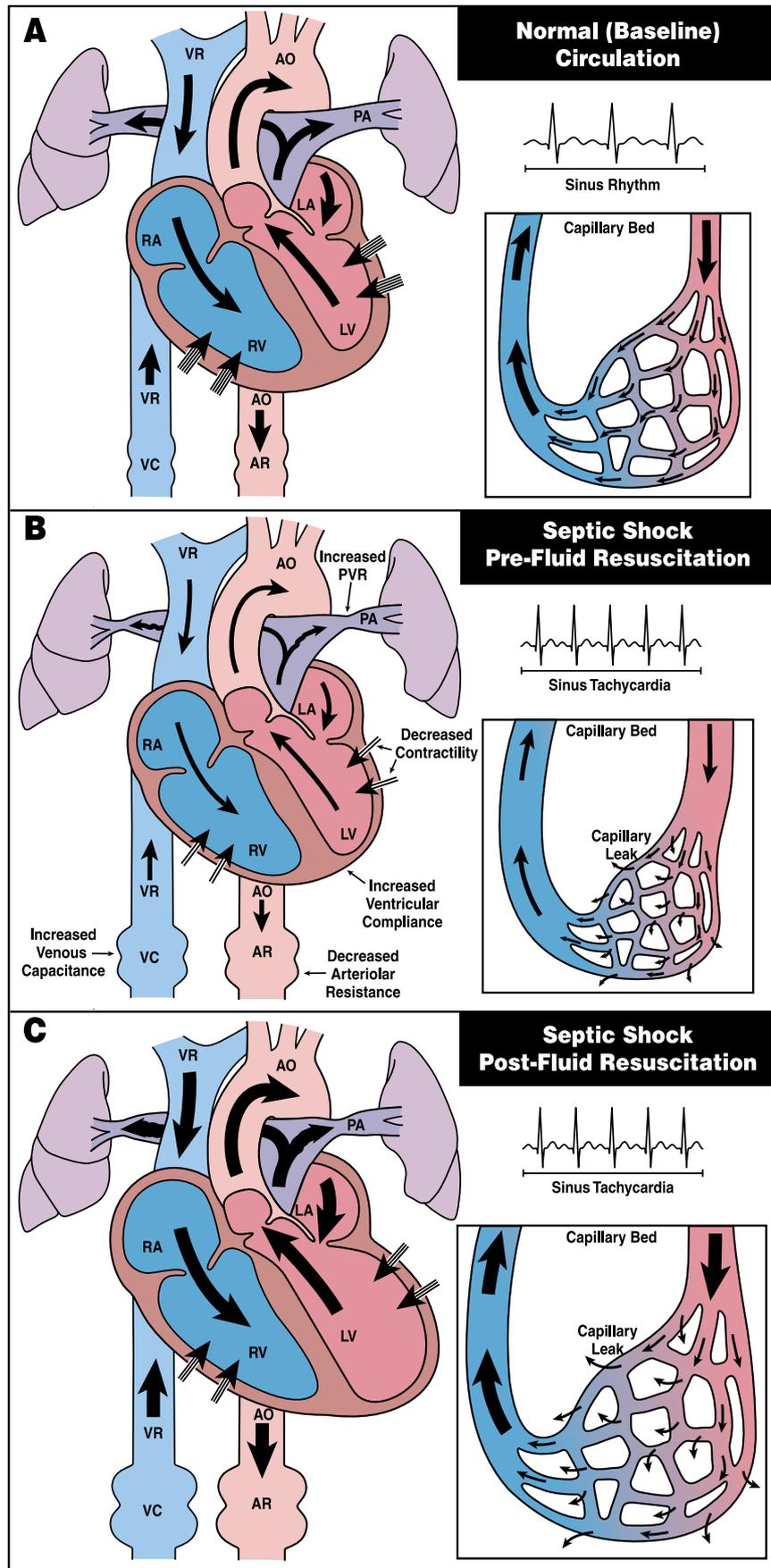
Because of the rapid changes in blood pressure that may occur in the presence of septic shock, arterial cannulation for continual monitoring of blood pressure is recommended. In addition, central venous catheters are needed to infuse vasopressors. The role of central hemodynamic monitoring is less clear. Although one retrospective analysis using paired cohorts suggested harm with pulmonary artery catheterization, randomized, prospective trials in patients with septic shock are lacking (54). A study using historical controls demonstrated improved survival when on-site intensivists were involved in the care of septic shock patients (55). Pulmonary artery catheters were used more frequently during the intensivist involvement period. It is now well established that use of the pulmo-

nary artery catheter (PAC) is frequently associated with inaccurate measurements (56). Furthermore, even when measurements are accurate, benefit could only be gained when appropriate decisions are made based on these measurements. It is likely that only a randomized, prospective trial in which both education on proper measurements and consensus treatment protocols are used will answer the question of whether the PAC offers potential benefit for patients with septic shock. Nevertheless, central hemodynamic monitoring technology continues to advance and less invasive alternatives for the estimation of cardiac output are being made available (57–62). Although trials with these technologies are encouraging as to performance, the ability to influence clinical outcome in septic shock is unknown.

Therapy

Fluid Resuscitation. Despite universal agreement on aggressive fluid resuscitation as the initial intervention in septic shock patients, the choice of optimum fluid resuscitation has been less clear. Although prospective studies of choice of fluid resuscitation in septic shock are lacking, meta-analyses of clinical studies comparing crystalloid and colloid resuscitation in general populations of primarily surgical nonseptic shock patients indicate no clinical outcome difference between colloids and crystalloids (63–65). Extrapolation of these results to septic shock patients is unclear. Although less fluid is required with colloids to achieve resuscitation goals and less edema results, it is unlikely that these nonoutcome-related events justify the added expense (66). An exception would be a clinical scenario in which hypotension is immediately life threatening and colloid infusion is judged to offer more rapid correction of volume deficit (limited access and low mL/min infusion rate capability).

Over the years, there has been considerable interest in targeting filling pressures for fluid resuscitation therapy in patients with central venous or pulmonary artery catheters. This has included targeting absolute values of central venous pressure between 8 and 14 mm Hg or pulmonary artery occlusive pressure between 14 and 18 mm Hg. Establishing a narrow range for these filling pressures is difficult because left ventricular filling may vary based on physiology other than



filling pressure (such as ventricular wall compliance, intrathoracic pressure, and in the case of right-sided filling pressure, pulmonary vascular resistance). In addition, the potential negative effects of increasing pulmonary capillary leak in the presence of acute lung injury must also be considered as filling pressures are increased. Fluid resuscitation of septic shock often occurs in the absence of central hemodynamic monitoring. In that circumstance, bolus fluid therapy (250–1000 mL crystalloid over 5–15 mins), repeated as long as the patient remains hypotensive or until early clinical manifestation of high left-sided filling pressures occur (crackles on auscultation of lungs or a drop in oxyhemoglobin saturation), is appropriate. This approach is safer in patients mechanically ventilated or those with good oxygen transfer and of greater risk in nonintubated patients already receiving significant supplemental oxygen.

Vasopressor and Inotropic Therapy

Indications and Targets of Vasopressor Therapy. Following adequate intra-

Figure 2. Cardiovascular changes associated with septic shock and the effects of fluid resuscitation. *A*, normal (baseline) state. *B*, in septic shock, left ventricular blood return is reduced due to a combination of capillary leak (*inset*), increased venous capacitance (*VC*), and increased pulmonary vascular resistance. The stroke volume is further compromised by a sepsis-induced decrease in left and right ventricular (*RV*) contractility. Tachycardia and increased left ventricular compliance serve as countermeasures to combat low cardiac output, the latter by increasing left ventricular preload. However, cardiac output remains low to normal. Finally, a decrease in arteriolar (systemic vascular) resistance allows a higher stroke volume at any given contractility and left ventricular filling state, but also the potential for severe hypotension, despite restoration of adequate left ventricular filling. *C*, aggressive fluid resuscitation compensates for capillary leak, increased venous capacitance, and increased pulmonary vascular resistance by re-establishing adequate left ventricular blood return. Decreased arteriolar resistance (*AR*), tachycardia, and increased left ventricular compliance compensate for decreased ejection fraction. Ejection fraction increases as left ventricular filling increases. The net result is that after adequate volume resuscitation, most patients with severe sepsis have a high cardiac output, low systemic vascular resistance state. *VR*, venous return; *RA*, right atrium; *LA*, left atrium; *LV*, left ventricle; *AO*, aorta; \rightarrow , blood flow (cardiac output); $=>$, contractility.

vascular volume repletion, the continued presence of hypotension warrants the use of vasopressor therapy (defined as an intravenous drug that raises blood pressure partially or totally through a direct arteriolar constrictive effect). A combined inotrope/vasopressor may be chosen (1). Minimal data exist to guide selection of the threshold for blood pressure maintenance. Arbitrary values of a systolic blood pressure of 90 mm Hg or a mean arterial blood pressure of 60–65 mm Hg have traditionally been chosen. Mean arterial pressure is a better reflection of arterial pressure-head, but in the absence of an arterial line, systolic blood pressure is likely to be a more accurate pressure measurement and is typically used. One study demonstrated that mean arterial pressures between 65 and 85 mm Hg were associated with no difference in organ perfusion variables (67). Because increasing blood pressure through vasoconstriction may be associated with a decrease in cardiac output, trade-off may exist between raising blood pressure and decreasing cardiac index that varies based on the choice of vasopressor or combined inotrope/vasopressor.

Vasopressor Agents

Dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressin have been demonstrated to be effective in raising blood pressure in patients with septic shock (68–73) (Table 3). Dopamine and epinephrine are more likely to induce or exacerbate tachycardia than norepinephrine and phenylephrine. Because of intense venoconstriction and associated right atrial baroreceptor stimulation, norepinephrine does not usually induce or exacerbate tachycardia. As a pure α agonist, phenylephrine should not produce tachycardia. Dopamine typically raises both blood pressure and cardiac index, as does norepinephrine, although the rise in cardiac output with dopamine is greater. Phenylephrine, as a pure α agonist, might be expected to decrease

cardiac output (CO) as it raises blood pressure. However, at least one study documented an increase in CO with phenylephrine (68). Although only one small single-center, prospective, randomized study has shown benefit of norepinephrine over dopamine, recent literature reports some potential advantages of norepinephrine (74). The potential advantages of norepinephrine, compared with dopamine, include minimal tachycardia response and no interference with hypothalamic pituitary axis (67, 75). In addition, despite concerns in the past of vasoconstriction-induced digital ischemia and decreased renal perfusion, there is no evidence that these occur and data in humans and animals demonstrate a norepinephrine-induced increase in cardiac output, renal blood flow, and urine output when used in septic shock (76–78). Norepinephrine is a more potent agent than dopamine in refractory septic shock (74, 79). An observational study also reports a survival advantage of norepinephrine over other vasopressor choices in septic shock (80).

Role of Vasopressin

Although high endogenous levels of vasopressin in nonshock states (inappropriate antidiuretic hormone syndrome) do not produce hypertension, in shock states, vasopressin stimulation of vascular V1 receptors appears to be an important mechanism of blood pressure rise (81, 82). Recent literature supports vasopressin as an option to raise blood pressure in septic shock and to wean more traditional vasopressors already in place. Septic shock-associated exhaustion of neurohypophyseal stores due to intense and prolonged stimulation, as well as impairment of baroreflex-mediated stimulation of vasopressin release, may lead to inappropriately low levels of serum vasopressin (81, 83, 84). Low doses of vasopressin targeted to achieve serum vasopressin levels, similar to that present in cardiogenic shock, have been demonstrated to produce a significant rise in mean arterial pressure in septic shock, often leading to the discontinuation of traditional vasopressors (85–88). The effect of this strategy on clinical outcome is unknown, because no randomized, prospective clinical outcome trials exist. If vasopressin is given, it seems most appropriate in patients requiring high-dose vasopressors, especially when blood pressure remains inadequate. Dosing should be limited to 0.01 to 0.04 units/minute because higher doses put the patient at a

greater risk for splanchnic and coronary artery ischemia, as well as a decrease in cardiac output (81).

Vasopressor Impact on Clinical Outcome

A rise in blood pressure may or may not be a surrogate of clinical benefit. In a large placebo-controlled clinical trial, administration of the nonselective nitric oxide inhibitor N^G-methyl-L-arginine in septic shock produced both significant increases in blood pressure and significant increases in mortality (89). The effects of vasopressor choice on other variables, such as renal blood flow, glomerular filtration pressure, splanchnic blood flow, hypothalamic-pituitary axis, and cerebral perfusion pressure, are likely to be important issues.

Inotropic Support

Decreased global contractility is expected in patients with septic shock. Despite this decrease in ejection fraction, the typical hemodynamic profile in septic shock following fluid resuscitation is an increased cardiac output. In the presence of severe depression of cardiac contractility and low normal or decreased cardiac output, inotropic therapy, i.e., dobutamine, may be considered in an attempt to maintain a high normal range of cardiac output. In the presence of hypotension, dobutamine would be administered under the cover of vasopressor therapy. This should be distinguished from the institution of dobutamine to increase cardiac output to high levels, even when already elevated, as part of empirical supranormal oxygen delivery (see discussion below).

Bicarbonate Therapy

In years past, intravenous bicarbonate became routine therapy for septic shock-induced anion gap acidosis based on the following: a) the inherent concept that acidemia is bad and that it can be corrected with intravenous bicarbonate; b) the widespread belief that vasopressors are not as effective in an acidic environment; and c) whole and isolated heart muscle animal studies that suggest acidemia suppresses cardiac performance (90–94). However, there has been a recent paradigm shift in the use of bicarbonate therapy for septic shock because of the following: a) the awareness that

Table 3. Vasopressor agents for use in septic shock

Agent	Typical Intravenous Dose Range
Dopamine	6–25 $\mu\text{g}/\text{kg}/\text{min}$
Epinephrine	1–10 $\mu\text{g}/\text{min}$
Norepinephrine	1–30 $\mu\text{g}/\text{min}$
Phenylephrine	40–180 $\mu\text{g}/\text{min}$
Vasopressin	0.01–0.04 units/min

patients with septic shock are not dying from lactic acidemia but are dying from the inability of the cell to receive or utilize oxygen, i.e., the acidemia is cosmetic; b) in the presence of peripheral hypoperfusion, the generation of CO_2 ($\text{H}^+ + \text{HCO}_3^- \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2$), which may not be adequately cleared from poorly perfused peripheral tissues, is problematic; and c) clinical studies, including one randomized, prospective trial, failed to show any hemodynamic benefit from bicarbonate therapy either to increase cardiac output or to decrease the vasopressor requirement, regardless of degree of acidemia (91, 95, 96). Other forms of base therapy, Carbicarb and dichloroacetate with buffering profiles that might offer advantages over bicarbonate have also been studied in lactic acidosis. Carbicarb has demonstrated mixed results as to hemodynamic benefit, and the only large randomized trial studied the potential benefit of dichloroacetate and failed to show a clinical outcome benefit (97, 98).

Oxygen Delivery in Septic Shock: How Much Is Enough?

Studies in septic shock patients demonstrating that increasing oxygen consumption as normal oxygen delivery was increased to higher than normal values supported the concept of “supranormal O_2 delivery” being potentially beneficial in the treatment of septic shock to replete an oxygen deficit as the cause of lactic acidosis. Detractors from this approach argued that the observed effect was due to mathematical coupling because the same key variables were used in calculating both oxygen delivery and consumption, causing movement in the same direction (99). Numerous studies have demonstrated that the lactate/pyruvate ratio, expected to increase in the face of oxygen debt, remains unchanged in septic shock and hyperlactatemia (100–102).

Clinical studies of “supranormal oxygen delivery” demonstrate that the ability to increase oxygen delivery with volume resuscitation and inotropic therapy in a patient with septic shock identifies a better prognosis (103–107). However, two large randomized, multiple-centered, prospective clinical trials failed to demonstrate a benefit of supranormal oxygen delivery (108, 109). Targeting a specific threshold of high oxygen delivery is not recommended as therapy of septic shock.

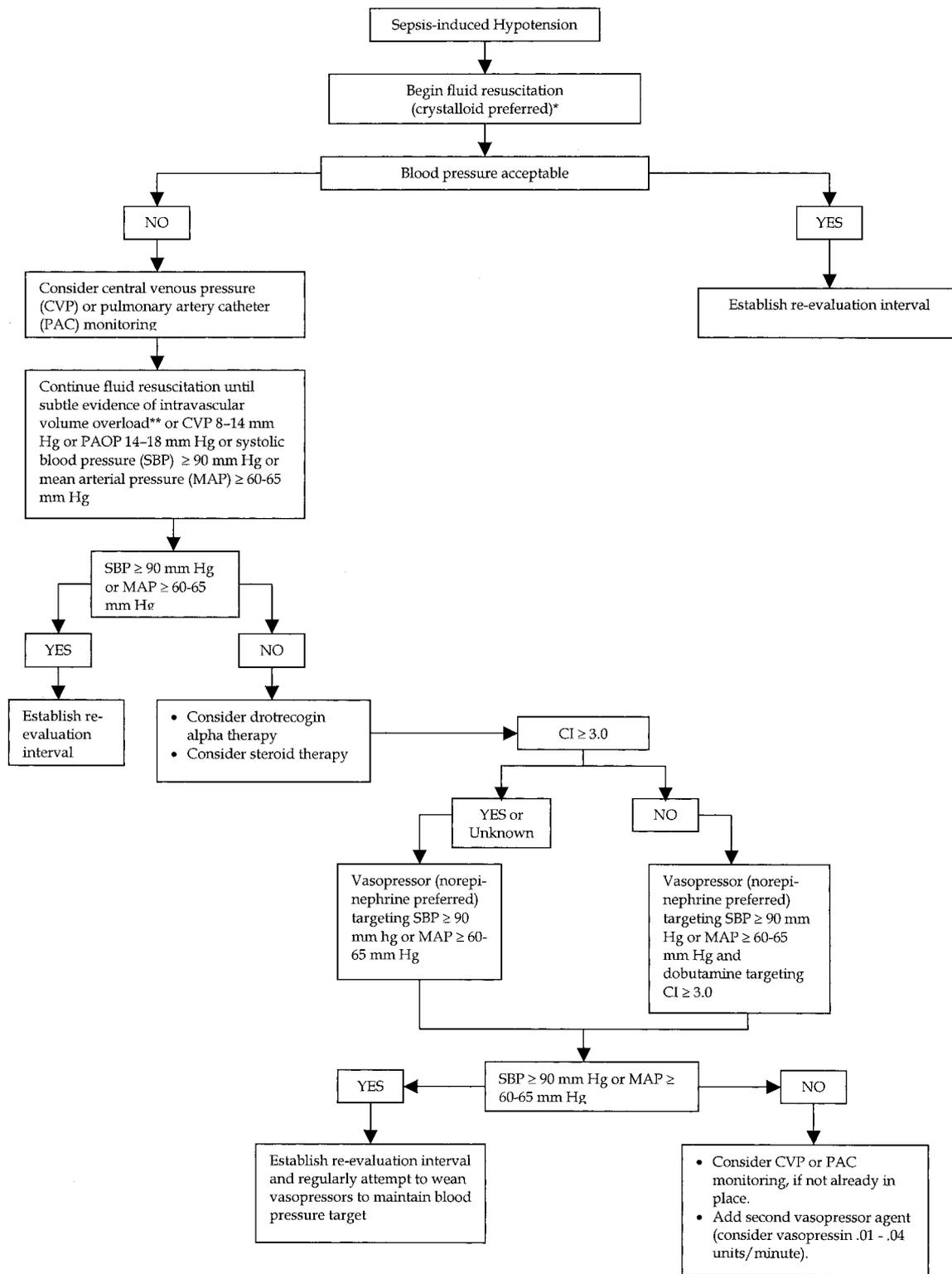
Early Goal-Directed Therapy

A recent single-institution clinical trial of 263 randomized patients presented to the emergency department with septic shock to receive 6 hrs of either traditional therapy consisting of volume resuscitation (targeting a central venous pressure of 8–12 mm Hg), followed by vasopressor therapy (if required), to maintain a mean arterial pressure of 65 mm Hg or “early goal-directed (EGT) therapy,” which required a central venous catheter with the capability to measure central venous oxyhemoglobin saturation (CVO_2 sat), used to dictate further resuscitation measures (9). If, following volume resuscitation, the CVO_2 sat remained at $<70\%$, EGT therapy involved, first, transfusion of packed red blood cells to a hematocrit of 30% and, then, if CVO_2 sat remained at $<70\%$, institution of dobutamine therapy (blinded as to cardiac output because no PAC was in place) to a maximum of 20 $\mu\text{g}/\text{kg}/\text{min}$ in an attempt to achieve a CVO_2 sat of 70%. A significant clinical outcome benefit was demonstrated in the EGT group with a 16% absolute reduction in 28-day mortality. Several points concerning this trial are worthy of emphasis. The protocol treatments were applied during the first 6 hrs of septic shock management, which likely provided more organized state-of-the-art medical attention than the typical septic shock patient receives during that time period. The primary difference between the two treatment groups was in red blood cell transfusion. This is contrary to recent studies that showed no benefit of red blood cell transfusion in general intensive care unit (ICU) populations (110). This early approach of increasing oxygen delivery in septic shock patients by targeting a monitor of the oxygen supply/demand relationship is significantly different from the supranormal O_2 delivery approach that targeted a specific oxygen delivery target in general ICU patients. Although these results are encouraging, larger multiple-centered studies are needed to validate this approach. Use of this approach requires measurement of CVO_2 sat.

Steroids

Based on positive reports from animal and single-center clinical studies, as well as the anecdotal use of steroids for severe infection (111–118), two multiple-center clinical trials were performed in the

1980s, each giving large “industrial strength” doses of steroids targeting day 1 of septic shock (119, 120). These trials failed to show a clinical outcome benefit, and empirical steroid therapy of septic shock in the absence of the identification of traditional adrenal insufficiency (very low baseline serum cortisol in the face of the stress of shock or failing to achieve a specific serum cortisol level following the corticotropin [ACTH] stimulation test) was largely abandoned (121, 122). In the late 1990s, several single-center studies of septic shock using stress (low) doses of steroids intravenously for 5–8 days showed promising results (123, 124). In 2000, a prospective observational study used the response to a high-dose ACTH stimulation test (250 μg) to characterize the adrenal status of patients in septic shock (125). A baseline cortisol measurement was followed up by post-ACTH stimulation cortisol levels at 30 and 60 mins. The highest value of the two post-ACTH stimulation cortisol levels was compared with the baseline level and suggested that the inability to raise cortisol following the ACTH stimulation test by 10 $\mu\text{g}/\text{dL}$ or greater was more predictive of a poor outcome than the basal level itself. This group of patients was called “nonresponders” and was identified as having “relative adrenal insufficiency.” Based on these findings, a 300-patient multicenter, prospective, randomized, blinded study of stress-dose steroid therapy targeting this group of nonresponders was performed and published in 2002 (126). Patients with septic shock were randomized within the first 8 hrs of presentation to receive either 50 mg of intravenous hydrocortisone every 6 hrs every day plus 50 μg by mouth of the mineralocorticoid fludrocortisone every day or placebo. Treatment continued for 7 days. The primary analysis group was nonresponders to ACTH, defined as the failure to increase serum cortisol levels by 10 $\mu\text{g}/\text{dL}$ or greater following ACTH stimulation. Use of stress-dose (low-dose) steroids in nonresponders was associated with decreased mortality and decreased vasopressor usage. There was no benefit of steroids in responders to ACTH. The benefit in nonresponders was best seen in the Kaplan-Meier survival curve analysis, in which death was both decreased and prolonged by steroids. There was no statistically significant difference in the 28-day chi-square point mortality, but statistical significance was reached when logistic regression adjustment (baseline



*250 - 1000 ml boluses of crystalloid, each over 5-15 minutes

**Basilar crackles on lung auscultation or increase in pulse oximetry O₂ saturation

Figure 3. Flow diagram for guidance in management decisions in septic shock.

cortisol, cortisol response, McCabe classification, Logistic Organ Dysfunction Score, arterial lactate level, and PaO₂/FIO₂) was performed. Although validation

of this study of 300 patients is clearly needed (and is being done in the European CORTICUS trial), in the interim, it is reasonable to consider stress-dose ste-

roids in select patients with early septic shock. Patients most appropriate to target for this therapy would be those who are requiring high-dose or increasing va-

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sopressor therapy within the first 8 hrs of septic shock. In those patients, a reasonable approach would be to give dexamethasone, 3 mg intravenously every 6 hrs (does not interfere with cortisol assay), until the high-dose ACTH stimulation test can be performed. Hydrocortisone and fludrocortisone would then be started and continued or discontinued based on the results of the ACTH stimulation test. If the ACTH stimulation test is not available, then empirical stress-dose steroids should be considered.

Some investigators question the choice of the 250- μ g ACTH stimulation test for the evaluation of adrenal reserve in the critically ill patient and judge it to be supraphysiologic and potentially overestimating of adrenal reserve (127). They recommend a 1- to 2- μ g ACTH dose as more appropriate. The precise threshold for separating responders and nonresponders with the lower ACTH dose is, however, unknown.

Activated Protein C

Extreme clinical manifestations of disseminated intravascular coagulation, such as purpura fulminans or digital ischemia, have long been identified as a poor prognostic sign of septic shock. However, subclinical manifestations of disseminated intravascular coagulation are present in essentially all patients with septic shock (some combination of increased D-dimers, decreased protein C, thrombocytopenia, and increased prothrombin time), and consumptive coagu-

lopathy is likely an important facet of pathophysiology in septic shock. The activation of protein C from its inactive zymogen is thought to be an important body mechanism for modulating sepsis-induced consumptive coagulopathy. In patients with meningococemia, the ability to activate protein C is impaired (128). Drotrecogin alfa (recombinant activated protein C) is the first innovative therapy to be approved by the Food and Drug Administration (FDA) for the treatment of severe sepsis and septic shock. Rationale for the use of recombinant activated protein C (rhAPC) relates to its anticoagulant and profibrinolytic effect, which targets the consumptive coagulopathy of septic shock. A large prospective, randomized and blinded clinical trial studied the effect of 96 hrs of continuous infusion of drotrecogin alpha (recombinant activated protein C) given at 24 μ g/kg/hr vs. placebo, with 75% of 1,690 severely septic patients receiving vasopressors at the time of study entry (7). Mortality was significantly reduced from 30.8% with placebo to 24.7% in those receiving drotrecogin alfa (activated) (a 6.3% absolute reduction in mortality). Although debate continues about some aspects of the trial design and patient selection, rhAPC appears to have a significant role in the treatment of septic shock (129–131). A *post hoc* subgroup analysis of the four stratified Acute Physiology and Chronic Health Evaluation (APACHE) II quartiles revealed enhanced drug performance in the higher two APACHE II quartiles (APACHE II \geq 25, with 13% absolute reduction in mortality vs. placebo) and no evidence of overall activity in the lowest of the four APACHE II quartiles, where slightly more deaths occurred in the drotrecogin alpha (activated) group. A recent cost-benefit analysis suggests the higher two APACHE II quartiles as the optimum target for therapy (132). The FDA's labeling for drotrecogin alpha (activated) recommends that it be given to patients with severe sepsis and with a high risk of death, such as APACHE II \geq 25. Septic shock is itself indicative of a high risk of death and, if no contraindication exists, identifies a good candidate for rhAPC. The benefit of rhAPC in septic shock must be weighed against the risk of rhAPC-induced bleeding, which are well characterized in the FDA's labeling instructions. Other anticoagulant strategies, promising early trials, failed to show a clinical benefit in larger trials (19, 133, 134).

Experimental Therapies

Available therapies that remain “experimental” for the management of septic shock without enough literature support for integration into clinical practice include high-volume hemofiltration, plasmapheresis, and intravenous immunoglobulin (135–142).

SUMMARY

The intensivist provides ICU management and coordination across the total spectrum of organ dysfunctions and support; however, no other disorder likely requires the level of complex on-site physician skills needed for the successful treatment of septic shock. After many years in which there was more “opinion and debate,” than prospective scientific literature to guide therapy, multiple studies now allow the potential for integration into critical care practice. Figure 3 depicts a decision tree capturing integration of both traditional thought and recent advancements in management guidelines for septic shock.

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