REVIEW

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Septic shock: The initial moments and beyond

■ ABSTRACT

Our understanding of the pathophysiology and treatment of sepsis has advanced over the last decade, and evidence-based protocols have improved its outcomes. Here, we review its management in the first hours and afterward, including topics of ongoing study and debate.

■ KEY POINTS

Managing septic shock in the first 6 hours involves prompt recognition, empiric antibiotic therapy, elimination of the source of infection (if applicable), fluid resuscitation titrated to specific goals, and vasopressor therapy.

A number of biomarkers have been proposed to help recognize septic shock early in its course.

A delay in starting appropriate antibiotic treatment is associated with higher risk of death.

The ideal measure of the adequacy of fluid resuscitation remains a topic of study and debate.

Preliminary studies suggest that norepinephrine should be the initial vasopressor.

Management after the first 6 hours is less well defined. Decisions in this period include whether to give further fluid resuscitation, further and additional hemodynamic therapies, adjunctive therapies, and antibiotics.

CONSIDERABLY FEWER PATIENTS who develop sepsis are dying of it now, thanks to a number of studies of how to reverse sepsis-induced tissue hypoxia.[1] The greatest strides in improving outcomes have been attributed to better early management, which includes prompt recognition of sepsis, rapid initiation of antimicrobial therapy, elimination of the source of infection, and early goal-directed therapy. Thus, even though the incidence of severe sepsis and septic shock is increasing,[2,3] the Surviving Sepsis Campaign has documented a significant decrease in unadjusted mortality rates (37% to 30.8%) associated with the bundled approach in the management of sepsis.[4] (We will talk about this later in the article.)

This review will summarize the evidence for the early management of septic shock and will evaluate the various treatment decisions beyond the initial phases of resuscitation.

■ INFLAMMATION AND VASODILATION

Sepsis syndrome starts with an infection that leads to a proinflammatory state with a complex interaction between anti-inflammatory and proinflammatory mediators, enhanced coagulation, and impaired fibrinolysis.[5,6]

Sepsis induces vasodilation by way of inappropriate activation of vasodilatory mechanisms (increased synthesis of nitric oxide and vasopressin deficiency) and failure of vasoconstrictor mechanisms (activation of ATP-sensitive potassium channels in vascular smooth muscle).[7] Thus, the hemodynamic abnormalities are multifactorial, and the resultant tissue hypoperfusion further contributes to the proinflammatory and procoagulant state, precipitating multiorgan dysfunction and, often, death.

TABLE 1

Resuscitation steps in early stages of severe sepsis and septic shock

In patients with two or more systemic inflammatory response syndrome (SIRS) criteria, ie:
Body temperature < 36°C (96.8°F) or > 38°C (100.4°F)
Heart rate > 90 beats per minute
Respiratory rate > 20 breaths per minute or an arterial partial pressure of carbon dioxide < 32 mm Hg
White blood cell count < 4,000 cells/mm³ (4 x 10⁹ cells/L) or > 12,000 cells/mm³ (12 x 10⁹ cells/L) or > 10% immature neutrophils (band forms)

AND a source of infection (suspected or documented)

AND hypotension (mean arterial pressure < 60 mm Hg):

• Obtain appropriate cultures, start broad-spectrum antibiotics, and eliminate the source of infection

• Check serum lactate and monitor urine output

• Give 30 mL/kg normal saline or Ringer's lactate as a bolus with a pressure bag

• If hypotension persists or the serum lactate is > 4 mmol/L, start goal-directed resuscitation and arrange to transfer the patient to the intensive care unit for invasive hemodynamic monitoring

• Place central venous catheter (subclavian or jugular) and begin continuous central venous pressure monitoring along with central venous oxygen saturation monitoring (intermittent or continuous)

• Give crystalloid fluid boluses (1,000 mL normal saline or Ringer's lactate) over 30 minutes until central venous pressure is > 8 mm Hg (12 mm Hg in mechanically ventilated patients)

• Start norepinephrine via central venous catheter if hypotension persists with ongoing fluid infusion, and try to wean from vasopressors as soon as possible after aggressive fluid resuscitation

• If central venous oxygen saturation is < 70% after fluid resuscitation with central venous pressure > 8 mm Hg, consider packed red blood cell transfusion if hematocrit < 30% and dobutamine infusion if hematocrit is > 30% (validated only during the first 6 hours of presentation)

■ DEFINITIONS

- Sepsis—infection together with systemic manifestation of inflammatory response
- Severe sepsis—sepsis plus induced organ dysfunction or evidence of tissue hypoperfusion
- Septic shock—sepsis-induced hypotension persisting despite adequate fluid resuscitation.

■ EARLY MANAGEMENT OF SEPTIC SHOCK

Early in the course of septic shock, the physician's job is to:
- Recognize it promptly
- Begin empiric antibiotic therapy quickly
- Eliminate the source of infection, if applicable, eg, by removing an infected central venous catheter
- Give fluid resuscitation, titrated to specific goals
- Give vasopressor therapy to maintain blood pressure, organ perfusion, and oxygen delivery (**TABLE 1**).

The line between "early" and "late" is not clear. Traditionally, it has been drawn at 6 hours from presentation, and this cutoff was used in some of the studies we will discuss here.

Recognizing severe sepsis early in its course

The diagnosis of severe sepsis may be challenging, since up to 40% of patients may present with cryptic shock. These patients may not be hemodynamically compromised but may show evidence of tissue hypoxia, eg, an elevated serum lactate concentration or a low central venous oxygen saturation ($Scvo_2$), or both.[8] In view of this, much effort has gone into finding a biomarker that, in addition to clinical features, can help identify patients in an early stage of sepsis.

Procalcitonin levels rise in response to severe bacterial infection,[9] and they correlate with sepsis-related organ failure scores and outcomes.[10,11] Thus, the serum procalcitonin level may help in assessing the severity of sepsis, especially when combined with standard clinical and laboratory variables. However, controversy exists about the threshold to use in making decisions about antibiotic therapy and the value of this test in differentiating severe noninfectious inflammatory reactions from infectious causes of shock.[12] Therefore, it is not widely used in clinical practice.

Serum lactate has been used for decades as a marker of tissue hypoperfusion. It is typically elevated in patients with severe sepsis and septic shock, and although the hyperlactatemia could be a result of global hypoperfusion, it can also be secondary to sepsis-induced mitochondrial dysfunction,[13] impaired pyruvate dehydrogenase activity,[14] increased aerobic glycolysis by catecholamine-stimulated sodi-

um-potassium pump hyperactivity,[15] and even impaired clearance.[16]

But whatever the mechanism, elevated lactate in severe sepsis and septic shock predicts a poor outcome and may help guide aggressive resuscitation. In fact, early lactate clearance (ie, normalization of an elevated value on repeat testing within the first 6 hours) is associated with better outcomes in patients with severe sepsis and septic shock.[17,18]

Panels of biomarkers. A literature search revealed over 3,000 papers on 178 different biomarkers in sepsis.[19] Many of these biomarkers lack sufficient specificity and sensitivity for clinical use, and thus some investigators have suggested using a panel of them to enhance their predictive ability. Shapiro et al[20] evaluated 971 patients admitted to the emergency department with suspected infection and discovered that a panel of three biomarkers (neutrophil gelatinase-associated lipocalin, protein C, and interleukin-1 receptor antagonist) was highly predictive of severe sepsis, septic shock, and death.

Starting empiric antibiotic therapy early

As soon as severe sepsis and septic shock are recognized, it is imperative that adequate empiric antibiotic treatment be started, along with infectious source control if applicable.[21] The Surviving Sepsis Campaign guidelines recommend starting intravenous antibiotics as early as possible—within the first hour of recognition of severe sepsis with or without septic shock.[22]

Kumar et al,[23] in a multicenter retrospective study of patients with septic shock, found that each hour of delay in giving appropriate antimicrobial agents in the first 6 hours from the onset of hypotension was associated with a 7.6% decrease in the in-hospital survival rate.

In a similar study,[24] the same investigators analyzed data from 5,715 septic shock patients regarding the impact of starting the right antimicrobial therapy. Appropriate antimicrobial agents (ie, those having in vitro activity against the isolated pathogens) were given in 80.1% of cases, and the survival rate in those who received appropriate antibiotics was drastically higher than in those who received inappropriate ones (52.0% vs 10.3%, $P < .0001$).

In addition, two recent studies evaluated the importance of early empiric antibiotic therapy in conjunction with resuscitative protocols.[25,26] In a preplanned analysis of early antimicrobial use in a study comparing lactate clearance and $ScvO_2$ as goals of therapy, Puskarich et al[26] found that fewer patients who received antibiotics before shock was recognized (according to formal criteria) died. Similarly, in a retrospective study in patients presenting to the emergency department and treated with early goal-directed therapy (defined below), Gaieski et al[25] found that the mortality rate was drastically lower when antibiotics were started within 1 hour of either triage or initiation of early goal-directed therapy.

In short, it is imperative to promptly start the most appropriate broad-spectrum antibiotics to target the most likely pathogens based on site of infection, patient risk of multidrug-resistant pathogens, and local susceptibility patterns.

Goal-directed resuscitative therapy

As with antimicrobial therapy, resuscitative therapy should be started early and directed at defined goals.

Rivers et al[27] conducted a randomized, controlled study in patients with severe sepsis or septic shock presenting to an emergency department of an urban teaching hospital. The patients were at high risk and had either persistent hypotension after a fluid challenge or serum lactate levels of 4 mmol/L or higher.

Two hundred sixty patients were randomized to receive either early goal-directed therapy in a protocol aimed at maximizing the intravascular volume and correcting global tissue hypoxia or standard therapy in the first 6 hours after presentation. The goals in the goal-directed therapy group were:
- Central venous pressure 8 to 12 mm Hg (achieved with aggressive fluid resuscitation with crystalloids)
- Mean arterial blood pressure greater than 65 mm Hg (maintained with vasoactive drugs, if necessary)
- $ScvO_2$ above 70%. To achieve this third goal, packed red blood cells were infused to reach a target hematocrit of greater than 30%. For patients with a hematocrit higher than 30% but still with an $ScvO_2$

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less than 70%, inotropic agents were added and titrated to the $Scvo_2$ goal of 70%.

Goal-directed therapy reduced the in-hospital mortality rate by 16% (the mortality rates were 30.5% in the goal-directed group and 46.5% in the standard therapy group, $P = .009$) and also reduced the 28- and 60-day mortality rates by similar proportions.[27]

Subsequent studies of a protocol for early recognition and treatment of sepsis have concluded that early aggressive fluid resuscitation decreases the ensuing need for vasopressor support.[28] A resuscitation strategy based on early goal-directed therapy is a major component of the initial resuscitation bundle recommended by the Surviving Sepsis Campaign.[22] (A "bundle" refers to the implementation of a core set of recommendations involving the simultaneous adaptation of a number of interventions.)

Areas of debate. However, concerns have been raised about the design of the study by Rivers et al and the mortality rate in the control group, which was higher than one would expect from the patients' Acute Physiology and Chronic Health Evaluation II (APACHE II) scores.[29] In particular, the bundled approach they used precludes the ability to differentiate which interventions were responsible for the outcome benefits. Indeed, there were two major interventions in the early goal-directed therapy group: a protocol for achieving the goals described and the use of $Scvo_2$ as a goal.

Aggressive fluid resuscitation is considered the most critical aspect of all the major interventions, and there is little argument on its value. The debate centers on central venous pressure as a preload marker, since after the publication of the early goal-directed therapy trial,[27] several studies showed that central venous pressure may not be a valid measure to predict fluid responsiveness (discussed later in this paper).[30,31]

The choice of colloids or crystalloids for fluid resuscitation is another area of debate. Clinical evidence suggests that albumin is equivalent to normal saline in a heterogeneous intensive care unit population,[32] but subgroup analyses suggest albumin may be superior in patients with septic shock.[33] Studies are ongoing (NCT00707122, NCT01337934, and NCT00318942). The use of hydroxyethyl starch in severe sepsis is associated with higher rates of acute renal failure

and need for renal replacement therapy than Ringer's lactate,[34] and is generally not recommended. This is further substantiated by two recent randomized controlled studies, which found that the use of hydroxyethyl starch for fluid resuscitation in severe sepsis, compared with crystalloids, did not reduce the mortality rate (and even increased it in one study), and was associated with more need for renal replacement therapy.[35,36]

The use of $Scvo_2$ is yet another topic of debate, and other monitoring variables have been evaluated. A recent study assessed the noninferiority of incorporating venous lactate clearance into the early goal-directed therapy protocol vs $Scvo_2$.[37] Both groups had identical goals for central venous pressure and mean arterial pressure but differed in the use of lactate clearance (defined as at least a 10% decline) or $Scvo_2$ (> 70%) as the goal for improving tissue hypoxia. There were no significant differences between groups in their in-hospital mortality rates (17% in the lactate clearance group vs 23% in the $Scvo_2$ group; criteria for noninferiority met). This suggests that lactate may be an alternative to $Scvo_2$ as a goal in early goal-directed therapy. However, a secondary analysis of the data revealed a lack of concordance in achieving lactate clearance and $Scvo_2$ goals, which suggests that these parameters may be measuring distinct physiologic processes.[38] Since the hemodynamic profiles of septic shock patients are complex, it may be prudent to use both of these markers of resuscitation until further studies are completed.

Given the debate, a number of prospective randomized trials are under way to evaluate resuscitative interventions. These include the Protocolized Care for Early Septic Shock trial (NCT00510835), the Australasian Resuscitation in Sepsis Evaluation trial (NCT00975793), and the Protocolised Management of Sepsis (ProMISe) trial in the United Kingdom (ISRCTN 36307479). These three trials will evaluate, collectively, close to 4,000 patients and will provide considerable insights into resuscitative interventions in septic shock.

Vasopressors: Which one to use?

If fluid therapy does not restore perfusion, vasopressors should be promptly initiated, as the

It is imperative to promptly start the most appropriate broad-spectrum antimicrobial agents

longer that hypotension goes on, the lower the survival rate.[39]

But which vasopressor should be used? The early goal-directed therapy protocol used in the study by Rivers et al[27] did not specify which vasopressor should be used to keep the mean arterial pressure above 65 mm Hg.

The Surviving Sepsis Campaign[22] recommends norepinephrine as the first-choice vasopressor, with dopamine as an alternative only in selected patients, such as those with absolute or relative bradycardia.

The guidelines also recommend epinephrine to be added to or substituted for norepinephrine when an additional catecholamine is needed to maintain adequate blood pressure.[22] Furthermore, vasopressin at a dose of 0.03 units/min can be added to norepinephrine with the intent of raising the blood pressure or decreasing the norepinephrine requirement. Higher doses of vasopressin should be reserved for salvage therapy.

Regarding phenylephrine, the guidelines recommend against its use except when norepinephrine use is associated with significant tachyarrhythmias, cardiac output is known to be higher, or as a salvage therapy.[22]

This is a topic of debate, with recent clinical studies offering further insight.

De Backer et al[40] compared the effects of dopamine vs norepinephrine for the treatment of shock in 1,679 patients, 62% of whom had septic shock. Overall, there was a trend towards better outcomes with norepinephrine, but no significant difference in mortality rates at 28 days (52.5% with dopamine vs 48.5% with norepinephrine, $P = .10$). Importantly, fewer patients who were randomized to norepinephrine developed arrhythmias (12.4% vs 24.1%, $P < .001$), and the norepinephrine group required fewer days of study drug (11.0 vs 12.5, $P = .01$) and open-label vasopressors (12.6 vs 14.2, $P = .007$). Of note, patients with cardiogenic shock randomized to norepinephrine had a significantly lower mortality rate than those randomized to dopamine. Although no significant difference in outcome was found between the two vasopressors in the subgroup of patients with septic shock, the overall improvements in secondary surrogate markers suggest that norepinephrine should be the first-line agent.

Norepinephrine has also been compared with "secondary" vasopressors. Annane et al,[41] in a prospective multicenter randomized controlled study, evaluated the effect of norepinephrine plus dobutamine vs epinephrine alone in managing septic shock. There was no significant difference in the primary outcome measure of 28-day mortality (34% with norepinephrine plus dobutamine vs 40% with epinephrine alone, $P = .31$). However, the study was powered to evaluate for an absolute risk reduction of 20% in the mortality rate, which would be a big reduction. A smaller reduction in the mortality rate, which would not have been statistically significant in this study, might still be considered clinically significant. Furthermore, the group randomized to norepinephrine plus dobutamine had more vasopressor-free days (20 days vs 22 days, $P = .05$) and less acidosis on days 1 to 4 than the group randomized to epinephrine.

Norepinephrine was also compared with phenylephrine as a first-line vasopressor in a randomized controlled trial in 32 patients with septic shock. No difference was found in cardiopulmonary performance, global oxygen transport, or regional hemodynamics between phenylephrine and norepinephrine.[42]

While encouraging, these preliminary data need to be verified in a larger randomized controlled trial with concrete outcome measures before being clinically adapted. Taken together, the above studies suggest that norepinephrine should be the initial vasopressor of choice for patients with septic shock.

◼ CONTINUED MANAGEMENT OF SEPTIC SHOCK

How to manage septic shock after the initial stages is much less defined.

Uncertainty persists about the importance of achieving the early goals of resuscitation in patients who did not reach them in the initial 6 hours of treatment. Although there are data suggesting that extending the goals beyond the initial 6 hours may be beneficial, clinicians should use caution when interpreting these results in light of the observational design of the studies.[43,44] For the purpose of this discussion, "continued management" of septic shock will mean after the first 6 hours and after all the early goals are met.

As with antibiotics, resuscitative therapy should be started early and directed by defined goals

TABLE 2

Treatment strategies beyond the initial stages of severe sepsis and septic shock

Consider dynamic measures of fluid responsiveness if in doubt about the adequacy of fluid resuscitation after the first 6 hours of resuscitation, especially after initial large-volume infusion to target central venous pressure or in patients who are showing signs of pulmonary edema or in those who remain vasopressor-dependent with a goal central venous pressure

Consideration of adjunctive hemodynamic therapy should include:
Adding vasopressin when norepinephrine requirements are > 10 µg/min
Changing or limiting initial catecholamine choice if evidence of adverse effects (eg, tachycardia, ischemia) is seen
Evaluating left ventricular function and augmenting with inotropic therapy as necessary

Consider other adjunctive therapies:
Assess the need for and give low-dose corticosteroids (if arterial hypotension is not responding to vasopressors)
Maintain adequate glycemic control (< 180 mg/dL)
Assess initial empiric antibiotics and adjust as necessary

The clinical decisions necessary after the initial stages of resuscitation include:

- Whether further fluid resuscitation is needed
- Assessment for further and additional hemodynamic therapies
- Consideration of adjunctive therapies
- Reevaluation of antibiotic choices (**TABLE 2**).

Is more fluid needed? How can we tell?

There is considerable debate about the ideal method for assessing fluid responsiveness. In fact, one of the criticisms of the early goal-directed therapy study[27] was that it used central venous pressure as a marker of fluid responsiveness.

Several studies have shown that central venous pressure or pulmonary artery occlusion pressure may not be valid measures of fluid responsiveness.[45] In fact, in a retrospective study of 150 volume challenges, the area under the receiver-operating-characteristics curve of central venous pressure as a marker of fluid responsiveness was only 0.58. (Recall that the closer the area under the curve is to 1.0, the better the test; a value of 0.50 is the same as chance.) The area under the curve for pulmonary artery occlusion pressure was 0.63.[46]

> If fluid therapy does not restore perfusion, a vasopressor should be given promptly

In contrast, several dynamic indices have been proposed to better guide fluid resuscitation in mechanically ventilated patients.[31] These are based on changes in stroke volume, aortic blood flow, or arterial pulse pressure in response to the ventilator cycle or passive leg-raising. A detailed review of these markers can be found elsewhere,[31] but taken together, they have a sensitivity and specificity of over 90% for predicting fluid responsiveness. Clinicians may consider using dynamic markers of fluid responsiveness to determine when to give additional fluids, particularly after the first 6 hours of shock, in which data supporting the use of central venous pressure are lacking.

Optimal use of fluids is particularly important, since some studies suggest that "overresuscitation" has negative consequences. In a multicenter observational study of 1,177 patients with sepsis, after adjusting for a number of comorbidities and baseline severity of illness, the cumulative fluid balance in the first 72 hours after the onset of sepsis was independently associated with a worse mortality rate.[47]

Furthermore, in a retrospective analysis of a randomized controlled trial of vasopressin in conjunction with norepinephrine for septic shock, patients in the highest quartile of fluid balance (more fluid in than out) at 12 hours and 4 days after presentation had significantly higher mortality rates than those in the lowest two quartiles.[48] The worse outcome with a positive fluid balance might be explained by worsening oxygenation and prolonged mechanical ventilation, as demonstrated by the Fluid and Catheter Treatment Trial in patients with acute lung injury or acute respiratory distress syndrome (ALI/ARDS).[49] Indeed, when fluid balance in patients with septic shock-induced ALI/ARDS was evaluated, patients with both adequate initial fluid resuscitation and conservative late fluid management had a lower mortality rate than those with either one alone.[50]

In view of these findings, especially beyond the initial hours of resuscitation, clinicians should remember that further unnecessary fluid administration may have detrimental effects. Therefore, given the superior predictive abilities of dynamic markers of fluid responsiveness, these should be used to determine the need for further fluid boluses.

In cases in which patients are no longer fluid-responsive and need increasing levels of hemodynamic support, clinicians still have a number of options. These include increasing the current vasopressor dose or starting an additional therapy such as an alternative catecholamine vasopressor, vasopressin, inotropic therapy, or an adjunctive therapy such as a corticosteroid. The intervention could also be a combination of the above choices.

Adding catecholamines

The optimal time point or vasopressor dose at which to consider initiating additional therapies is unknown. However, the Vasopressin and Septic Shock Trial (VASST) provides some insight.[51]

This study compared two strategies: escalating doses of norepinephrine vs adding vasopressin to norepinephrine. Overall, adding vasopressin showed no benefit in terms of a lower mortality rate. However, in the subgroup of patients with norepinephrine requirements of 5 to 14 µg/min at study enrollment (ie, **a** low dose, reflecting less-severe sepsis) vasopressin was associated with a lower 28-day mortality rate (26.5% vs 35.7%, P = .05) and 90-day mortality rate (35.8% vs 46.1%, P = .04). Benefit was also noted in patients with other markers of lower disease severity such as low lactate levels or having received a single vasopressor at baseline.[51]

Although subgroup analyses should not generally be used to guide treatment decisions, a prospective trial may never be done to evaluate adding vasopressin to catecholamines earlier vs later. Thus, clinicians who choose to use vasopressin may consider starting this therapy when catecholamine doses are relatively low or before profound hyperlactatemia from prolonged tissue hypoxia has developed.

There is less evidence to guide clinicians who are considering adding a different catecholamine. The theoretical concerns of splanchnic ischemia and cardiac arrhythmia associated with higher doses of catecholamines are usually the impetus to limit a single catecholamine to a "maximum" dose. However, studies that have evaluated combination catecholamine therapies have generally studied combinations of vasopressors with inotropes and lacked standardization in their protocols, thus making them difficult to interpret.[52–54] One could also argue

that additional catecholamine therapies, which all function similarly, may have additive effects and cause even more adverse effects. As such, adding another vasopressor should be reserved for patients experiencing noticeable adverse effects (such as tachycardia) on first-line therapy.

Inotropic support

Left ventricular function should be assessed in all patients who continue to be hypotensive despite adequate fluid resuscitation and vasopressor therapy. In a study of patients with septic shock in whom echocardiography was performed daily for the first 3 days of hemodynamic support, new-onset left ventricular hypokinesia was found in 26 (39%) of 67 patients on presentation and in an additional 14 patients (21%) after at least 24 hours of norepinephrine.[55] Adding inotropic support with dobutamine or epinephrine led to decreases in vasopressor dose and enhanced left ventricular ejection fraction.

In short, left ventricular hypokinesia is common in septic shock, may occur at presentation or after a period of vasopressor support, and is usually correctable with the addition of inotropic support.

Corticosteroids

Beyond hemodynamic support with fluids and catecholamines or vasopressin (or both), clinicians should also consider adjunctive corticosteroid therapy. However, for many years the issue has been controversial for patients with severe sepsis and septic shock.

Annane et al[56] conducted a large, multicenter, randomized, double-blind, placebo-controlled trial to assess the effect of low doses of corticosteroids in patients with refractory septic shock. Overall, the 28-day mortality rate was 61% in the treatment group and 55% in the placebo group, which was not statistically significant (adjusted odds ratio 0.65, 95% confidence interval 0.39–1.07, P value .09). However, when separated by response to cosyntropin stimulation, those with a change in cortisol of 9 ug/dL or less (nonresponders) randomized to receive corticosteroids had significantly higher survival rates in the short term (28 days) and the long term (1 year). The positive results of this study led to the adoption of low-dose hydrocortisone as standard practice

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in most patients with septic shock.[57]

But then, to evaluate the effects of corticosteroids in a broader intensive-care population with septic shock, another trial was designed: the Corticosteroid Therapy of Septic Shock (CORTICUS) trial.[58] Surprisingly, this multicenter, randomized, double-blind, placebo-controlled trial found no significant difference in survival between the group that received hydrocortisone and the placebo group, regardless of response to a cosyntropin stimulation test.

Taking into account the above studies and other randomized controlled trials, the 2012 Surviving Sepsis Campaign guidelines and the International Task Force for the Diagnosis and Management of Corticosteroid Insufficiency in Critically Ill Adult Patients recommend intravenous hydrocortisone therapy in adults with septic shock whose blood pressure responds poorly to fluid resuscitation and vasopressor therapy. These consensus statements do not recommend the cosyntropin stimulation test to identify patients with septic shock who should receive corticosteroids.[22,59] The guidelines, however, do not explicitly define poor response to initial therapy.

Of note, in the Annane study, which found a lower mortality rate with corticosteroids, the patients were severely ill, with a mean baseline norepinephrine dose of 1.1 µg/kg/min. In contrast, in the CORTICUS study (which found no benefit of hydrocortisone), patients had lower baseline vasopressor doses, with a mean norepinephrine dose of 0.5 µg/kg/min.

While corticosteroids are associated with a higher rate of shock reversal 7 days after initiation,[59] this has not translated into a consistent reduction in the death rate. If a clinician is considering adding corticosteroids to decrease the risk of death, it would seem prudent to add this therapy in patients receiving norepinephrine in doses above 0.5 µg/kg/min.

The ideal sequence and combination of the above therapies including fluids, catecholamine vasopressors, vasopressin, inotropes, and vasopressors have not been elucidated. However, some preliminary evidence suggests an advantage with the combination of vasopressin and corticosteroids. In a subgroup analysis of the VASST study, in patients who received corticosteroids, the combination of vasopressin plus norepinephrine was associated with a lower 28-day mortality rate than with norepinephrine alone (35.9% vs 44.7%, *P* = .03).[60] These findings have been replicated in other studies,[61,62] prompting suggestions for a study of vasopressin with and without corticosteroids in patients on norepinephrine to elucidate the role of each therapy individually and in combination.

Tight glycemic control

As with corticosteroids, the pendulum for tight glycemic control in critically ill patients has swung widely in recent years. Enthusiasm was high at first after the publication of a study by van den Berghe et al, which described a 3.4% absolute reduction in mortality with intensive insulin therapy to maintain blood glucose at or below 110 mg/dL.[63] However, the significant benefits found in this study were never replicated.

In fact, recent evidence suggests that tight glycemic control is associated with no benefit and a higher risk of hypoglycemia.[34,64] In the largest randomized controlled trial of this topic, with more than 6,000 patients, intensive insulin therapy with a target blood glucose level of 81 to 108 mg/dL was associated with a significantly higher mortality rate (odds ratio 1.14, 95% confidence interval 1.02–1.28, *P* = .02) than with a target glucose level of less than 180 mg/dL.[65] Furthermore, in a recent follow-up analysis,[66] moderate hypoglycemia (serum glucose 41–70 mg/dL) and severe hypoglycemia (serum glucose < 41 mg/dL) were associated with a higher rate of death in a dose-response relationship.[66]

Taking this information together, clinicians should be aware that there is no additional benefit in lowering blood glucose below the range of 140 to 180 mg/dL, and that doing so may be harmful.

Drotecogin alfa

Drotecogin alfa (Xigris) was another adjunctive therapy that has fallen from favor. It was approved for the treatment of severe sepsis in light of promising findings in initial studies.[67]

However, on October 25, 2011, drotecogin alfa was voluntarily withdrawn from the market by the manufacturer after another study found no beneficial effect on the mortality rates at 28 days or at 90 days.[68] Furthermore, no difference

When to consider additional therapies is unknown, but VASST provides some insight

could be found regarding any predetermined primary or secondary outcome measures.

Continued antibiotic therapy

The decision whether to continue initial empiric antimicrobial coverage, broaden it, or de-escalate must be faced for all patients with septic shock, and is ultimately clinical.

The serum procalcitonin level has been proposed to guide antibiotic discontinuation in several clinical settings, although there are still questions about the safety of such an approach. The largest randomized trial published to date reported that a procalcitonin-guided strategy to treat suspected bacterial infections in nonsurgical patients could reduce antibiotic exposure with no apparent adverse outcomes.[69] On the other hand, other data discourage the use of procalcitonin-guided antimicrobial escalation, as this approach

did not improve survival and worsened organ function and length of stay in the intensive care unit.[70]

The Surviving Sepsis Campaign guidelines recommend combination antibiotic therapy for no longer than 3 to 5 days and limiting the duration of antibiotics in most cases to 7 to 10 days.[22]

■ TRIALS ARE ONGOING

The understanding of the pathophysiology and treatment of sepsis has greatly advanced over the last decade. Adoption of evidence-based protocols for managing patients with septic shock has improved outcomes. Nevertheless, many multicenter trials are being conducted worldwide to look into some of the most controversial therapies, and their results will guide therapy in the future. ■

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