Septic shock in the postoperative patient:

Three important management decisions

ALI JAHAN, MD

Septic shock is one of the most mismanaged forms of shock. This is primarily due to the lack of focus on the most important aspects: early diagnosis and early, aggressive volume resuscitation. For example, advances in the management of acute coronary syndromes and cerebral ischemic syndromes have resulted from a focus on early, aggressive identification and intervention.

This article provides guidance on three basic questions in the management of septic shock. In doing so, it underscores the clinical significance of early goal-directed therapy and the role for supranormal oxygen delivery, reviews vasopressor use in septic shock, and discusses new concepts in the clinical management of septic shock.

DEFINING SEPSIS

Clinicians need to have a high suspicion for sepsis because the mortality rate for septic shock remains high (30% to 50%). The rate remains unchanged despite advances in critical care medicine. The annual incidence of severe sepsis in the United States has been estimated at 751,000, with 215,000 deaths annually, more than lung and breast cancer combined.[1]

Sepsis is a systemic inflammatory response syndrome (SIRS) that occurs as a result of an infection. SIRS is characterized by the following:

- Temperature of ≥ 38°C or ≤ 36°C
- Heart rate of ≥ 90 beats per minute
- Respiratory rate of ≥ 20 respirations per minute
- White blood cell count of ≥12,000 cells/μL or ≤4,000 cells/μL.

Severe sepsis is defined as sepsis with acute organ dysfunction caused by the sepsis. Severe sepsis results from not only an inflammatory response but also a procoagulant response, which leads to endovascular injury, microvascular thrombosis, organ ischemia, multiorgan dysfunction, and ultimately death.

From the Department of General Anesthesiology, Cleveland Clinic Foundation, Cleveland, OH.

Address: Ali Jahan, MD, Department of General Anesthesiology, Cleveland Clinic Foundation, 9500 Euclid Avenue, G61, Cleveland, OH 44195; jahana@ccf.org.

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MANAGEMENT ISSUE 1: OXYGEN DELIVERY

Should supranormal oxygen levels be targeted?

Studies in which supranormal oxygen levels have been a target of therapy have been difficult to perform and have yielded mixed results. Three major problems with the design of these studies are patient selection, time of enrollment, and inability to reach targeted endpoints. First, the definition of a *high-risk* patient is unclear in many studies. Next, some studies enrolled pre-insult patients, some enrolled post-insult patients, and others enrolled both. Finally, most studies targeted an oxygen delivery level, a cardiac index, or a mixed venous level, but rarely were they able to attain those targeted goals. Not surprisingly, these problems have led to difficulties in interpreting data.

Clinical evidence for intervention. One of the first studies of supranormal oxygen delivery was conducted by Shoemaker and colleagues.[2] Having previously observed that survivors of shock had higher oxygen delivery levels compared with nonsurvivors, they hypothesized that increasing oxygen delivery to supranormal levels might improve outcome.

Although their findings showed that outcomes did indeed improve, the study had significant flaws. It consisted of a small number of relatively young trauma patients, the comparison groups were poorly matched, and the treatment regimens were unclear. Additionally, treatment goals were achieved with fluids alone in two thirds of the patients, with only a small number of patients requiring inotropic support. This study was later followed by other trials,[3–5] which continued to struggle with similar challenges with design, making it difficult to interpret the clinical applicability of their results.

Interpretation. Being able to generate normal or supranormal oxygen levels may be associated with improved outcomes, but having to augment cardiac output with inotropic support to reach supranormal levels is not necessarily beneficial.

Early goal-directed therapy

Early goal-directed therapy involves the early identification of patients with septic shock followed by immediate, aggressive fluid resuscitative efforts and use of antibiotics along with appropriate vasoactive medications.

In 2001, Rivers et al[6] evaluated early goal-directed therapy in emergency room patients with septic shock. They randomized patients to receive either standard therapy at the clinician's discretion or 6 hours of intensive goal-directed therapy.

Patients assigned to early goal-directed therapy had placement of a central venous catheter that measured central venous oxygen saturation (CVO_2), which was monitored continuously. If central venous pressure was less than 8 mm Hg, crystalloid was administered to achieve a central venous pressure of 8 to 12 mm Hg. If mean arterial pressure (MAP) was less than 65 mm Hg, vasopressors were administered to maintain a MAP of at least 65 mm Hg. If the MAP was greater than 90 mm Hg, vasodilators were given until it was 90 mm Hg or less. Once the targeted MAP was achieved, patients whose CVO_2 was less than 70% received transfusions to achieve a hematocrit of at least 30%. If the CVO_2 remained less than 70%, they were given dobutamine (Figure 1).

In-hospital mortality was significantly lower in the group assigned to goal-directed therapy (30%) than in those assigned to standard therapy (46%). Additionally, the critical endpoint of CVO_2 was achieved in 95% of patients assigned to goal-directed therapy. This is unprecedented since in most studies targeting supranormal oxygen delivery levels, equivalent endpoints have only been achieved in 20% to 25% of patients.

A significant finding in support of early, aggressive therapy is that during the first 6 hours of treatment, patients in the goal-directed therapy group received an average of 5 L of fluid, compared with only 3.5 L in the standard therapy group.

Comments. Early, aggressive intervention is important in order to avoid irreversible systemic damage, as demonstrated by the results of Rivers et al.[6] Early intervention may also explain why the hemodynamic goals were obtainable in 95% of patients. This study also suggests that a simple-to-obtain hemodynamic endpoint may have significant practical implications. While most studies require placement of a pulmonary artery catheter for hemodynamic measurement, this study effectively used the results obtained from a central line to guide therapy during the early phases of septic shock.

MANAGEMENT ISSUE 2: CHOICE OF VASOPRESSOR

Which vasopressor should be used?

Along with fluid resuscitation, vasopressors may be needed to help manage persistent hypotension associated with septic shock. Among norepinephrine, dopamine, phenylephrine, epinephrine and vasopressin, norepinephrine is the most appropriate first choice, for reasons reviewed below.

Norepinephrine, after initially developing a negative reputation (it was colloquially known as "Leave 'Em Dead" in a play on its brand name, Levophed), has evolved into the leading choice for vasopressor support in septic shock. Its initial negative reputation stemmed from a variety of factors, including its *potential* negative effect on splanchnic and renal blood flow, its association with renal failure when infused into the renal artery of dogs, and an association with digital ischemia. Consequently, norepinephrine was used as a last resort in many studies, resulting in predictably poor outcomes.

With additional evidence, however, it is now thought to be the least harmful vasopressor in compromising splanchnic perfusion and to contribute to increases in urine output and creatinine clearance. Furthermore, it contributes to preserving organ blood flow by maintaining if not increasing cardiac output.[7,8]

Dopamine. The Surviving Sepsis Campaign guidelines published in March 2004 state that norepinephrine and dopamine are appropriate first-choice drugs to support MAP.[9] In clinical practice, however, dopamine has fallen out of favor. Several studies suggest improved efficacy with norepinephrine when compared with dopamine.

In a 1993 crossover study by Martin et al,[7] 32 patients were randomized prospectively to receive dopamine or norepinephrine. Although dopamine was successful in reversing hemodynamic abnormalities in 5 of 16 patients, norepinephrine was beneficial in 15 of 16 patients. Also, 10 of the 11 nonresponders in the dopamine group responded to norepinephrine, while the one nonresponder in the norepinephrine group did not respond to dopamine. Survival was 59% in the norepinephrine compared with 17% in the dopamine group.

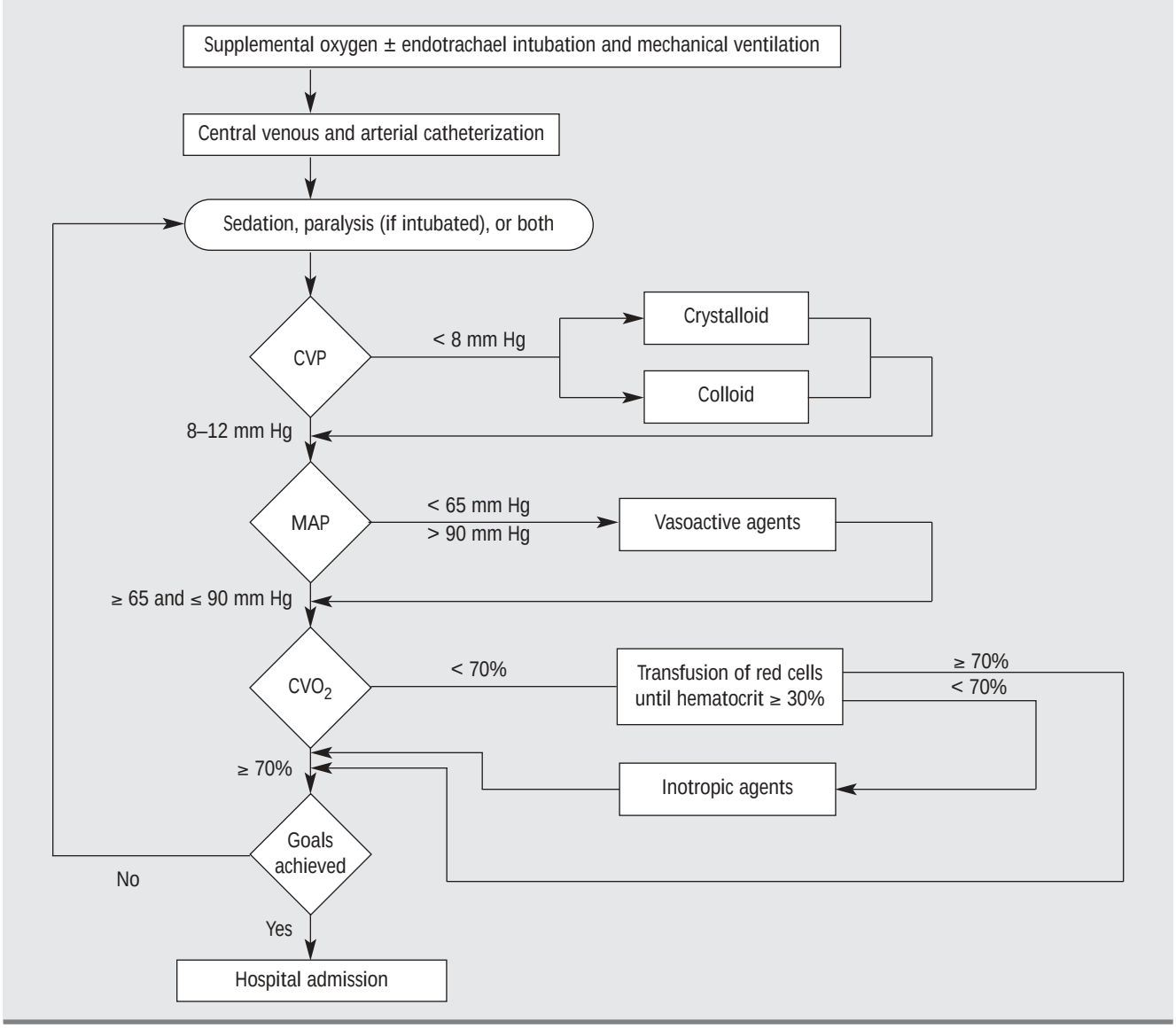

FIGURE 1. Early goal-directed therapy uses a central venous catheter to monitor central venous oxygen saturation (CVO_2) continuously. Interventions are then directed to achieve predefined goals for central venous pressure (CVP), mean arterial pressure (MAP), and CVO_2. Reprinted, with permission, from Rivers E, et al, N Engl J Med 2001; 345:1368–1377. Copyright © 2001 Massachusetts Medical Society. All rights reserved.

The same group of investigators later published an observational study that sought to identify factors associated with outcome among 97 patients with septic shock who were treated with either norepinephrine or high-dose dopamine.[8] Among various factors assessed, the only one that was associated with a favorable outcome was the use of norepinephrine as part of hemodynamic support.

Furthermore, low-dose dopamine is no longer recommended for renal protection. This recommendation is based on the results of a large randomized controlled trial that revealed no clinically significant benefit of dopamine against renal failure[10] and on concerns over potential reductions in secretion of several important hormones, potentiation of immune suppression, and possible splanchnic mucosal ischemia.

Phenylephrine. Few clinical data are available on the use of phenylephrine for hypotension, but its use usually results in an increase in vascular resistance and a subsequent decrease in cardiac output. This decrease in cardiac output leads to reduced splanchnic blood flow and oxygen delivery. Furthermore, a practical concern is that it is frequently ineffective in patients with septic shock.

Epinephrine is not recommended for use as a vasopressor or as an inotropic agent because it compromises splanchnic blood flow, increases lactate production, and potentiates dysrhythmias. Dobutamine is the preferred inotropic agent for use in septic shock if one is needed. For patients with significant hypotension and compromised contractility, the combination of dobutamine and norepinephrine is a reasonable choice.

Vasopressin. The use of vasopressin for management of hypotension associated with septic shock is relatively new. Circulating levels of vasopressin have been found to be inappropriately low in patients with septic shock. Several case reports indicate that when vasopressin is used in patients who remain hypotensive, blood pressure may improve to the point that they can be weaned off norepinephrine. Vasopressin, therefore, should be considered in situations in which escalating doses of norepinephrine are required. However, because vasopressin can have potential adverse effects on splanchnic perfusion and can reduce cardiac output, caution needs to be taken when considering its use. Because of these concerns and a lack of outcomes data, vasopressin is not recommended as a first-line agent for hypotension in septic shock.

MANAGEMENT ISSUE 3: USE OF STEROIDS, ACTIVATED PROTEIN C

Should other interventions be considered?

Consider empiric use of steroids as well as early use of activated protein C, if the clinical condition is appropriate.

Steroids. Preclinical studies conducted in the 1960s suggested that high-dose steroids would improve overall survival for septic shock. However, subsequent human trials have produced inconsistent results, and three meta-analyses conducted in the 1990s suggested no benefit, if not a worsening of outcomes.[11–13]

A renewed interest in steroids was prompted by the realization that severe sepsis may be associated with relative adrenal insufficiency. Also, several studies showed that prolonged treatment with relatively low doses of hydrocortisone improved time to vasopressor therapy withdrawal.

In 2002, Annane et al[14] conducted a study of 300 patients with septic shock who were randomized to a 7-day course of steroids or placebo. Patients were diagnosed with relative adrenal insufficiency if cortisol levels increased by 9 µg/dL or less following stimulation with 250 µg of adrenocorticotropic hormone analog. Steroid treatment reduced the risk of death significantly in the patients with septic shock and relative adrenal insufficiency.

Although these findings are encouraging, long-term outcomes studies are still needed, as well as studies to determine optimal dosing, duration of therapy, and the best means of tapering steroid treatment. An ongoing National Institutes of Health study of 800 patients will address some of these issues.[15]

Activated protein C. Activated protein C (drotrecogin alfa activated) is an endogenous protein that acts as an anti-inflammatory, inhibits thrombosis, and promotes fibrinolysis in sepsis. Evaluating its benefits, the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study[16] found a 6.1% absolute reduction and a 19.1% relative reduction in the risk of death with activated protein C compared with placebo. This difference in risk translates into one additional life saved for every 16 patients with sepsis who are treated with activated protein C.

The Surviving Sepsis Campaign Management Guidelines Committee[9] recommends using activated protein C in patients at high risk of death from sepsis (Acute Physiology and Chronic Health Evaluation [APACHE] score ≥ 25). Its use is contraindicated in patients whose risk of death would further increase if bleeding were to occur. Accordingly, the primary patient group in the PROWESS study was nonsurgical. No breakdown was provided for bleeding events related to surgery; however, a significantly higher incidence of severe bleeding occurred in the group randomized to activated protein C.

The Surviving Sepsis Campaign committee also recommended aggressive glucose control, management of acute respiratory distress syndrome using lower tidal volumes, daily stoppage of sedation for assessment of need, stress ulcer prophylaxis, prevention of deep vein thrombosis, and prevention of ventilator-related pneumonia.

SUMMARY

The medical consultant should have a high index of suspicion for sepsis. Early goal-directed therapy is recommended and includes early, aggressive fluid resuscitation, antibiotics, and vasoactive agents, if needed. CVO_2 may be helpful in guiding therapy, but targeting supranormal levels of oxygen delivery is not necessary. Empiric use of steroids and early use of activated protein C also need to be considered. Vasopressin should be considered if hypotension persists or if the situation requires escalating doses of norepinephrine.

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