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REVIEW

Review of recent guidelines for the management of severe sepsis and septic shock

Jin-Nong ZHANG (✉)[1], MD, Bo PENG[1], BA, Jamile WOODS[2], MD, Wei PENG[2], MD, PhD

1 Pulmonary Division of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
2 Department of Pulmonary and Sleep Medicine, Salt Lake Regional Medical Center, Iasis Healthcare, Salt Lake City, UT 84102, USA

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Abstract Severe sepsis and septic shock affect millions of patients and are major causes of mortality worldwide. Advancements in treatment and disease management led to a decline in in-hospital mortality from 27.8% (1979–1984) to 17.9% (1995 to 2000). In this article, we systemically review recent guidelines for the management of severe sepsis and septic shock published in 2008 by the International Surviving Sepsis Campaign Guidelines Committee. The 2008 Surviving Sepsis guidelines recommend protocolized resuscitation with goals to maintain central venous pressure $\geqslant$ 8–12 mmHg, mean arterial pressure $\geqslant$ 65 mmHg, urine output $\geqslant$ 0.5 mL·kg^{-1}·h^{-1} and central venous oxygen saturation $\geqslant$ 70% (or mixed venous $\geqslant$ 65%). Further fluid administration, transfusion of packed red blood cells to achieve a hematocrit of $\geqslant$ 30% and/or infusion of dobutamine max 20 μg·kg^{-1}·min^{-1} are advised if venous O_2 saturations remain below 70%. In patients with decreased ventricular compliance or mechanical ventilation, a target central venous pressure of 12–15 mmHg is recommended. Intravenous antibiotic administration within the first hour of recognizing severe sepsis and septic shock is essential, while use of corticosteroids in sepsis is controversial. The mechanisms by which activated protein C improves clinical outcomes in sepsis are unknown. Therapy with activated protein C is approved for patients with severe sepsis and an increased risk of death [Acute Physiology and Chronic Health Evaluation II (APACHE II) > 25]. Bicarbonate therapy is discouraged. Intravenous insulin should be used to control hyperglycemia in patients with severe sepsis following stabilization in the intensive care unit.

Keywords sepsis; septic shock; hemodynamics; guidelines

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E-mail: zjnwhhb@163.com

1 Introduction

In general, sepsis is a systemic inflammatory response to infection and characterized by reduced global tissue perfusion and hypoxia. When sepsis leads to organ dysfunction due to low blood pressure or insufficient blood flow to one or more organs, it is called severe sepsis. Septic shock is severe sepsis with persistent hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities [1]. Although the lack of uniform definitions for this heterogeneous condition has influenced the interpretation of epidemiologic data, severe sepsis and septic shock affect millions of patients and are major causes of mortality worldwide [2,3].

The incidence of septicemia, estimated by the Centers for Disease Control, was 73.6 per 100 000 in 1979, rising to 175.9 per 100 000 in 1989 [4]. Data from over 10 million cases of sepsis in the United States for over a 22-year period revealed that the annualized incidence of sepsis has been increased by 8.7. In-hospital mortality has fallen from 27.8% during the period from 1979 to 1984 to 17.9% during the period from 1995 to 2000. Sepsis occurs more commonly among men than women and among nonwhite than white persons. Gram-positive bacteria have been identified as predominant pathogens since 1987. The rate of sepsis due to fungal organisms has been increased by 207% [5]. In this article, we review recent guidelines for the management of severe sepsis and septic shock published in 2008 by the International Surviving Sepsis Campaign Guidelines Committee [6].

2 Updated recommendations on diagnosis

In 20%–30% of patients with sepsis, a definite source of infection is not identified [7–9]. Previous guidelines recommended obtaining appropriate cultures before starting antibiotics; however, the current recommendation is to

obtain a culture as long as it does not delay delivery of antibiotics. Two or more blood cultures should be drawn: one should be drawn percutaneously and another from each vascular access device. Prompt imaging is advised to confirm and sample any source of infection. Patients should be evaluated for a focus of infection amenable to drainage or debridement except in the case of pancreatic necrosis where surgical intervention is best delayed. Intravascular access devices should be promptly removed if potentially infected.

3 Resuscitation

In a randomized controlled trial, Rivers *et al*. compared a standard resuscitation protocol with a protocol of early goal-directed therapy during the initial 6 h after presentation with septic shock. The investigators demonstrated significantly lower in-hospital mortality rates in patients treated with early goal-directed therapy than those treated with standard resuscitation (30.5% *vs* 46.5%, $P = 0.009$) [10].

The 2008 Surviving Sepsis guidelines underscore the importance of early resuscitation in the first 6 h and recommend protocolized resuscitation with goals to maintain central venous pressure (CVP) $\geqslant$ 8–12 mmHg, mean arterial pressure $\geqslant$ 65 mmHg, urine output $\geqslant$ 0.5 mL·kg^{-1} per hour and central venous oxygen saturation $\geqslant$ 70%, or mixed venous $\geqslant$ 65%. Further fluid administration, transfusion of packed red blood cells to achieve a hematocrit of $\geqslant$ 30% and/or infusion of dobutamine (max 20 μg·kg^{-1} per minute) are advised if venous O_2 saturations remain below 70%. In patients with decreased ventricular compliance or mechanical ventilation, a target CVP of 12–15 mmHg is recommended. New guidelines also recommend slowing the rate of fluid replacement if cardiac filling pressures increase without concurrent hemodynamic improvement.

4 Antibiotic therapy

Current guidelines recommend starting intravenous antibiotics as early as possible and within 1 h of presenting with severe sepsis or septic shock. Antibiotic therapy should be reassessed daily, a reduction from previous recommendations of 48–72 h. Initial therapy should have broad-spectrum coverage with good penetration into the presumed source. Current guidelines also emphasize combination therapy for $\leqslant$ 3–5 days with de-escalations following sensitivities. Combination therapy should be considered in pseudomonas infections and in neutropenic patients; duration of therapy should be limited to 7–10 days. Longer antibiotic treatment is advisable if the response to therapy is slow, undrainable foci of infection are present or the patient has immunologic deficiencies. Antibiotics should be discontinued if a non-infectious cause of sepsis is identified.

5 Fluid therapy

In a double-blind randomized trial, the SAFE investigators [11] demonstrated that use of either 4 percent albumin or normal saline for fluid resuscitation resulted in similar outcomes at 28 days, suggesting that albumin and saline should be considered clinically equivalent treatments for intravascular volume resuscitation. Current recommendations are to fluid-resuscitate using crystalloids or colloids targeting a CVP of $\geqslant$ 8 mmHg ($>$ 12 mmHg if mechanically ventilated). A fluid challenge technique providing fluid boluses of 1000 mL of crystalloids or 300–500 mL of colloids over 30 min can be utilized. More rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion. The rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement.

6 Vasopressors

When administering vasopressors, the goal is to maintain the mean arterial pressure $\geqslant$ 65 mmHg. Initial vasopressors of choice are norepinephrine or dopamine. Vasopressin at low "physiologic doses" (0.03 U/min) may be subsequently added to norepinephrine. Epinephrine should be used as the first alternative agent when hypotension is poorly responsive to norepinephrine or dopamine. Vasopressin deficiency may contribute to refractory hypotension in established septic shock. In "physiologic doses" (0.01–0.04 U/min), vasopressin is synergistic with exogenous catecholamines and may vasodilate some vascular beds. At "pharmacologic doses" ($>$ 0.04 U/min), the pressor effect of vasopressin is associated with potentially harmful vasoconstriction of renal, mesenteric, pulmonary and coronary vasculature [12].

A recent randomized, double-blind trial of low-dose vasopressin compared with norepinephrine in patients with septic shock showed no significant difference in the 28-day mortality rate (35.4% in the vasopressin group *vs* 39.3% in the norepinephrine group, $P = 0.26$) [13].

Low-dose dopamine should not be used for renal protection as it worsens splanchnic oxygenation, impairs the gastrointestinal, endocrine and immunologic systems and blunts ventilatory drive. The predominant effect of low-dose dopamine appears to be diuresis, which can be detrimental to oliguric septic patients. Furthermore, low-dose dopamine can worsen gut ischemia resulting in translocation of endotoxin into the portal circulation [14].

Dobutamine is indicated in patients with myocardial dysfunction as evidenced by elevated cardiac filling pressures and low cardiac output. It is not advisable to

raise the cardiac index to predetermined supranormal levels.

7 Steroids

Use of corticosteroids in sepsis is controversial, and adverse effects of these agents are well known, including neuromyopathy, hyperglycemia, immunosuppression and loss of intestinal epithelial cells through apoptosis. Serum total cortisol measures both free cortisol and cortisol bound to cortisol-binding globulin and albumin. Patients with sepsis often have low serum albumin and thus low serum total cortisol levels. A recent study revealed that critically ill patients with hypoalbuminemia had corticotrophin-stimulated serum total cortisol levels that were subnormal, but their serum-free cortisol levels were higher than normal [15]. Avoidance of etomidate is advisable because a single dose can inhibit the metabolism of corticosteroids for at least 24 h in patients who are critically ill [16].

Under previous guidelines, patients with septic shock and not responding to fluids were started on vasopressors regardless of vasopressor response. Current guidelines recommend considering use of hydrocortisone for adults with septic shock when hypotension remains poorly responsive to adequate fluid resuscitation and vasopressors. It is not recommended to perform an ACTH stimulation test to identify the subset of adults with septic shock who should receive hydrocortisone. Hydrocortisone is preferred to dexamethasone. Fludrocortisone at a daily dose of 50 μg orally may be included if an alternative to hydrocortisone is being used which lacks significant mineralocorticoid activity. Steroid therapy may be weaned once vasopressors are no longer required. The total daily hydrocortisone dose should be less than 300 mg. Corticosteroids should not be given to septic patients in the absence of shock unless the patient's endocrine or corticosteroid history warrants it.

The CORTICUS trial recently revealed that hydrocortisone does not improve survival in sepsis, though it does hasten the reversal of shock [17]. Two of five small randomized controlled trials have shown that low-dose hydrocortisone decreases need for vasopressor support in patients with sepsis [18]. Only one trial has reported a survival benefit in patients who did not respond to a corticotropin stimulation test [19].

8 Recombinant human activated protein C (rhAPC)

The mechanisms by which activated protein C improves clinical outcomes in sepsis are unknown. Therapy using activated protein C is approved for patients with severe sepsis and an increased risk of death (APACHE II scores > 25). The PROWESS trial documented a 6.1% absolute reduction in mortality [20]. The ADDRESS trial demonstrated that drotrecogin alfa offered no benefit and resulted in an increased incidence of bleeding in patients who were at a low risk for death (APACHE II scores < 25) [21]. For patients with a low risk of death or possessing single organ failure, human activated protein C is not recommended.

9 Blood product administration

Packed red blood cells should be administered to achieve a target hemoglobin level of 7.0–9.0 g/dL [22]. Higher hemoglobin levels may be required in special circumstances such as myocardial ischemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease or lactic acidosis. Erythropoietin should not be used to treat sepsis-related anemia [23]. Fresh frozen plasma should not be given to correct laboratory clotting abnormalities unless there is bleeding or a planned invasive procedure. Use of antithrombin therapy is not recommended. Platelets should be given when counts are $< 5000/mm^3$ regardless of bleeding, counts are 5000 to $30\,000/mm^3$ and if significant bleeding risk exists. Higher platelet counts ($\geqslant 50\,000/mm^3$) are required for surgery or invasive procedures.

10 Mechanical ventilation of sepsis-induced acute lung injury (ALI)/ARDS

The results of the ARDSNET Trial [24] suggested that tidal volumes of 6 mL/kg predicted body weight and recommended maintaining plateau pressures below 30 cm H_2O. $PaCO_2$ should be allowed to increase above normal to minimize plateau pressures and tidal volumes. Positive end expiratory pressure (PEEP) should be set to avoid extensive lung collapse at end expiration. Use of prone positioning can be considered for patients requiring potentially injurious levels of fraction of inspired oxygen (FiO_2). Mechanically ventilated patients should be positioned with head of the bed raised between 30° and 45°. Non-invasive ventilation may be considered in patients with mild to moderate hypoxemic respiratory failure.

A weaning protocol and a spontaneous breathing trial should be employed to evaluate the potential for discontinuing mechanical ventilation. Spontaneous breathing trial (SBT) options include a low level of pressure support with continuous positive airway pressure of 5 cm H_2O or a T-piece. Before the trial, patients should be arousable and hemodynamically stable without vasopressors, possess no new potentially serious conditions, demonstrate low ventilatory and end-expiratory pressure, and show FiO_2 levels that can be safely delivered non-invasively. Use of a pulmonary artery catheter for the routine monitoring of patients with acute lung injury

(ALI)/acute respiratory distress syndrome (ARDS) is not recommended. A conservative fluid strategy should be implemented for patients with established ALI who do not have evidence of tissue hypoperfusion. A conservative strategy of fluid management shortened duration of mechanical ventilation in a randomized study [25].

11 Sedation, analgesia, and neuromuscular blockade in sepsis

Protocols with sedation goals should be employed for critically ill and mechanically ventilated patients. Daily interruption of sedation to produce awakening is recommended. Neuromuscular blockers should be avoided if possible.

12 Glucose control

Intravenous insulin should be used to control hyperglycemia in patients with severe sepsis following stabilization in the intensive care unit (ICU). Blood glucose should be maintained at < 150 mg/dL using a validated protocol for insulin dose adjustment. Blood glucose values should also be monitored every 1–2 h (4 h when stable) in patients receiving intravenous insulin. Low glucose levels obtained with point of care testing should be interpreted with caution, as these techniques may overestimate arterial blood or plasma glucose values.

13 Renal replacement

Intermittent hemodialysis and continuous veno-venous hemofiltration (CVVH) are considered equivalent. CVVH offers easier management in hemodynamically unstable patients.

14 Bicarbonate therapy

Bicarbonate therapy is discouraged for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidemia with pH $\geqslant$ 7.15.

15 Deep vein thrombosis (DVT) prophylaxis

Either low-dose unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) should be used unless contraindicated. A mechanical prophylactic device, such as compression stockings or an intermittent compression device, can be used when heparin is contraindicated. A combination of pharmacologic and mechanical therapy should be considered for patients who are at very high risk for DVT. Patients at very high risks should receive LMWH instead of UFH.

16 Stress ulcer prophylaxis

Stress ulcer prophylaxis using an H_2 blocker or proton pump inhibitor is recommended. Benefits of preventing of upper gastrointestinal bleeding must be weighed against the potential for developing ventilator-associated pneumonia.

17 Consideration for limitation of support

Family-centered care is the ideal model for managing end-of-life care in the ICU. Clinicians should be skilled in the practical and ethical aspects of withdrawing different modalities of life support and the use of sedatives and analgesics to ease the suffering of the dying process [26].

18 Summary

The current guidelines provide updated messages for the diagnosis and therapy of sepsis shock. Initial resuscitation and antibiotic application are significant measures which demonstrate close relationships with mortality from sepsis shock. The guidelines also detail treatments of sepsis shock complications. Nevertheless, as Antonelli and Mercurio [27] showed in their review, the guidelines are not comprehensive. They provide only the basic for clinic therapy; the specific treatment should be determined by evaluating the condition of patients. Additional scientific inquiry into those therapies should be explored in future to provide more evidence for clinical therapy.

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