Treatment of Patients with Severe Sepsis and Septic Shock: Current Evidence-Based Practices

JISOO LEE, MD; MITCHELL M. LEVY, MD, MCCM, FCCP

ABSTRACT

Sepsis remains a field of active research with many unknown and unanswered questions. Over the past few decades, advancements in sepsis management have led to improved mortality and morbidity. This article will review the current evidence-based practices of the treatment of sepsis and septic shock. It will also critically appraise some of the current controversies in sepsis management, such as fluids, steroids, early vasopressors, early goal-directed therapy and immunotherapy.

KEYWORDS: sepsis, septic shock, management, controversies

INTRODUCTION

Sepsis is a common disease entity that is associated with high morbidity and mortality. Globally, it is estimated that over 30 million people are hospitalized for sepsis every year, and sepsis may contribute to up to 5.3 million deaths every year.[1] The terms systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock were initially described through a consensus statement in the early 1990s by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM).[2] Most recently, the terms SIRS and severe sepsis were eliminated, and sepsis is now defined as "life-threatening organ dysfunction due to a dysregulated host response to infection."[3]

In this review article, the concept of sepsis bundles for management of sepsis and septic shock based on evidence-based practice will be reviewed. Additionally, some of the major controversies in sepsis management will be reviewed, focusing on the roles of steroids, fluids, vasopressors, early goal-directed therapy and immunotherapy.

MANAGEMENT OF SEPSIS – THE SURVIVING SEPSIS CAMPAIGN (SSC) AND SEPSIS BUNDLE

Unfortunately, there are no specific molecular therapies that have proven to be effective in sepsis treatment. The Surviving Sepsis Campaign (SSC) was initiated in 2002 to provide guidelines for sepsis and septic shock management for clinicians with the goal to reduce mortality. The "sepsis

Table 1. Hour-3 and Hour-6 Bundles.

To be completed within 3 hours and 6 hours of time of presentation, respectively. The "time of presentation" is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements severe sepsis or septic shock ascertained through chart review.

Hour-3 Bundle	Hour-6 Bundle
1. Measure lactate level.	Hour-3 Bundle elements (as seen on the left). Plus,
2. Obtain blood cultures prior to administration of antibiotics.	5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65mmHg
3. Administer broad-spectrum antibiotics.	6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion.
4. Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L.	7. Re-measure lactate if initial lactate elevated.

bundles", which have gone through multiple iterations in the SSC Guidelines, describe a selected set of interventions that are recommended to be conducted. The hour-3 bundle and hour-6 bundle highlight interventions to be completed within 3 hours and 6 hours of time of presentation, respectively (**Table 1**). Studies have shown that increased compliance with the sepsis bundle is associated with improved survival.[4]

According to the SSC 2016 guideline recommendations, initial resuscitation should begin immediately, as sepsis and septic shock are medical emergencies.[4] Some of the highlights of the SSC 2016 guidelines include fluid resuscitation of at least 30 mL/kg of intravenous crystalloid fluid to be given in the first three hours, then guiding additional fluid administration by reassessing hemodynamic status. Further hemodynamic assessment such as assessing cardiac function is recommended to determine the type of shock, and dynamic over static variables should be used to predict fluid responsiveness. Targeting mean arterial pressure (MAP) of 65 mm Hg should be an initial target for patients with septic shock requiring vasopressors, and the resuscitation should be continued until lactate is normalized. The SSC guidelines

recommend (best practice statement) hospitals have a performance improvement program to screen for patients for sepsis. Routine microbiologic cultures including at least two sets of blood cultures should be obtained prior to starting broad-spectrum intravenous antimicrobial therapy without causing substantial delay in the therapy.

The 2018 update to the SCC guidelines describes the "hour-1 bundle" (**Table 2**).[5] This bundle consists of five bundle elements as follows: Measure lactate level; obtain blood cultures prior to administration of antibiotics; administer broad-spectrum antibiotics; rapidly administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L; and apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg. This hour-1 bundle intends to underscore the urgency to treat patients with sepsis and septic shock, combining the three-hour and six-hour bundles into a single hour to shorten the time to beginning resuscitation and management and improve outcome. Further research is warranted to assess the efficacy of hour-1 bundle implementation.

Table 2. Hour-1 Bundle.

To be completed within 1 hour of time of presentation. The "time of presentation" is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock ascertained through chart review.

Hour-1 Bundle
• Measure lactate level. Remeasure if initial lactate is >2 mmol/L.
• Obtain blood cultures prior to administration of antibiotics.
• Administer broad-spectrum antibiotics.
• Rapidly administer 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L.
• Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg.

HOT CONTROVERSIES IN SEPSIS

There have been many hotly debated controversies in sepsis and septic shock management over the past few decades. While some have robust amount of trials with conflicting results over time, others are in need of more research. We will discuss some of the topics, including the use of steroids, fluid choice, vasopressor choice and timing, early goal-directed therapy, and immunotherapy for personalized medicine.

Steroids

Since the first randomized controlled trial published in JAMA in 1963, there have been over 40 randomized controlled trials to determine the use of corticosteroids in severe sepsis and septic shock. The 2016 SSC guidelines suggest against using intravenous corticosteroids to treat septic shock if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. However, it is suggested to use 200 mg of hydrocortisone per day if hemodynamic stability is not achievable.[4] The most two recent trials after these guidelines showed conflicting data regarding corticosteroid use and mortality benefit in septic shock. The ADRENAL trial by Venkatesh *et al.* compared 200 mg of hydrocortisone per day versus placebo for 7 days in patients with septic shock undergoing mechanical ventilation, which showed no difference in 90-day mortality.[6] The APROC-CHSS trial by Annane *et al.* evaluated the effect of hydrocortisone-plus-fludrocortisone therapy, drotrecogin alfa, the combination of the three drugs, or their respective placebos.[7] This study showed that the hydrocortisone-plus-fludrocortisone therapy reduced the 90-day mortality compared to the placebo (43.0% versus 49.1%, p=0.03). The drotrecogin alfa group was not completed due to the withdrawal of the drug from the market in 2011. Regardless of the difference in the primary outcomes of mortality, both trials demonstrated that corticosteroid treatment group has a shorter time to resolution of shock compared to placebo. Although there is no systematic review and meta-analysis involving these two recent trials, the BMJ Rapid Recommendations, which is a BMJ collaboration that aims to accelerate evidence into practice, incorporated these two trials and made a weak recommendation for corticosteroids with sepsis, concluding that both steroids and no steroids are reasonable management options for refractory septic shock.[8]

Fluids

Early fluid resuscitation is one of the key recommendations for sepsis and septic shock management, and there have been many controversies regarding the types of fluid. In the SSC guidelines, crystalloids have been recommended as the first line of fluids for resuscitation, and these are most widely available. More recently, a great deal of attention has been focused on balanced fluids. The most commonly used isotonic crystalloid, 0.9% normal saline, has high chloride concentration (154 mmol per liter) compared to human plasma (94 to 111 mmol per liter), and is thought to worsen kidney function due to the excess chloride. Unlike normal saline, balanced fluids such as lactated Ringer's solution and Plasma-Lyte A have electrolyte compositions that are closer to that of plasma, with chloride concentration of 109 mmol per liter and 98 mmol per liter, respectively. The SPLIT trial published in 2015 compared a buffered crystalloid solution (Plasma-Lyte 148) with saline on their effect on acute kidney injury (AKI) among patients admitted to the intensive care unit.[9] The study did not show any significant difference in the risk of AKI, the use of renal replacement therapy, or hospital mortality. However, there was a signal towards improved outcome with the buffered crystalloid solution, which prompted the need for further studies. The SMART trial published in 2018 compared balanced crystalloids

(lactated Ringer's solution or Plasma-Lyte A) with saline and looked at a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction within 30 days.[10] This study showed that the use of balanced crystalloids resulted in a lower rate of the composite outcome, favoring its use over saline. Most recently, a single center, multi-crossover trial compared balanced crystalloids with saline among adults in the emergency department who were hospitalized outside an ICU.[11] This study did not show any difference in the number of hospital-free days in the two groups; however, the balanced crystalloids group had less major adverse kidney events within 30 days compared to the saline group.

Other types of fluids have been studied as well. Colloids such as albumin have also been evaluated for its effect on fluid resuscitation. The SAFE trial looked at 4% albumin or normal saline for fluid resuscitation in a heterogenous population of ICU patients.[12] The CRISTAL trial compared colloids (gelatins, dextrans, hydroxyethyl starches, 4% or 20% albumin) to crystalloids (isotonic or hypertonic saline or Ringer lactate solution) in critically ill patients with hypovolemic shock.[13] Both the SAFE and CRISTAL trials showed no significant difference in the primary outcome of 28-day mortality.

Vasopressors

Vasopressors are one of the essential medications used in shock; however, the choice of vasopressor and the optimal timing of vasopressor initiation remain controversial. Norepinephrine is the most commonly used first-line vasoactive medication in shock, as it has shown to have lower mortality and lower risk of arrhythmias when compared with dopamine.[14] Vasopressin and epinephrine are reasonable second-line agents in order to lower the amount of norepinephrine, and the use of phenylephrine does not have enough data to support its use in septic shock currently.[4] The optimal timing of vasopressor initiation is unknown. Early vasopressor therapy might lead to faster achievement of the target MAP and thereby facilitate tissue perfusion. It may also prevent deleterious effects from fluid overload. However, a fine balance will need to be established as it may also be harmful to initiate vasopressor therapy when the intravascular fluid resuscitation has not been adequately achieved. This concept is currently being tested in an ongoing trial.[15] The 2018 update to the SSC bundle recommends vasopressor therapy within the first hour to achieve mean arterial pressure (MAP) of 65 mm Hg or greater if blood pressure is not restored after initial fluid resuscitation of 30 mL/kg.[5]

Early goal-directed therapy (EGDT)

EGDT involves optimizing tissue perfusion by giving crystalloid fluid boluses to achieve central venous pressure (CVP) 8-12 mm Hg, initiating vasopressors to maintain MAP of at least 65 mm Hg, and maintaining central venous oxygen saturation ($ScvO_2$) at greater than 70% with red blood cell transfusion and/or dobutamine administration. In 2001, Rivers *et al*. showed that a significant improvement in mortality by 15% when patients with severe sepsis or septic shock were treated using six-hour EGDT compared to standard therapy.[16] This study has since promoted best practice guidelines for early management of sepsis and septic shock. However, limitations of this study, including that it was a single-center trial lacking external validity, and the complexity and resourceful demand of the protocol, prompted further research. A little over a decade later, three multi-center clinical trials were published – ProCESS from the United States, ARISE from Australasia, and ProMISe from England. These trials compared protocol-based EGDT to standard therapy and all failed to show a difference in 90-day mortality.[17,18,19] It is important to acknowledge that the mortality rates were lower in the newer trials compared to the Rivers *et al*.'s study, and there has been overall improvement in the management of initial sepsis management in the past 15 years. However, it must be concluded that mandated central lines targeting CVP and $ScvO_2$ are no longer supported by the current literature.

Targeted Immunotherapy

Although decades of effort and multiple, large international RCTs have been conducted on promising immunomodulatory therapeutics, all of these trials have been negative and there is no current immunotherapy that is in clinical use for sepsis and septic shock. Various agents including anti-cytokines (e.g. anti TNF-α), anti-virulence factors (e.g. monoclonal antibody against lipopolysaccharide and gram negative endotoxins), anticoagulation agents (e.g. activated protein C, antithrombin III, heparin) and immune stimulators (e.g. G-CSF) have been studied without yielding significant results.[20] The heterogeneity of the patients with sepsis and septic shock, clinical trial design, variable pathways that lead to sepsis, as well as the complexity of sepsis pathophysiology, among other factors, may account for the failure of these trials. Overcoming these challenges will be crucial to advance to precision medicine and enable successful, targeted immunomodulatory therapy.

CONCLUSION

Management of sepsis and septic shock involves early interventions to achieve hemodynamic stability. Due to the heterogeneity and complexity of sepsis pathophysiology, there is no perfect therapy for sepsis that "fits for all." However, implementation of best-practice guidelines based on evidence-based medicine has shown to improve mortality associated with sepsis and septic shock. Many elements of the guidelines remain controversial and more research is needed to address these important unanswered questions.

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Authors

Jisoo Lee, MD, Division of Pulmonary, Critical Care and Sleep Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Mitchell M. Levy, MD, MCCM, FCCP, Division of Pulmonary, Critical Care and Sleep Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Correspondence

Jisoo Lee, MD
Fellow, Division of Pulmonary
Critical Care and Sleep Medicine
593 Eddy Street
Providence, Rhode Island 02903
401-444-8410
Fax 401-444-8447
jisoo_lee@brown.edu