Management of Sepsis: The Surviving Sepsis Guidelines for Early Therapy

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Sepsis is a common condition that is associated with poor patient outcomes and high financial costs. An estimated 750,000 cases of sepsis occur each year. Because sepsis is more common in elderly patients, its incidence is expected to rise as the US population ages.[1] Despite recent advances in management and therapy, the mortality rate from severe sepsis remains high at approximately 28%.[1] The average treatment cost per case of sepsis is approximately $22,000, and the cost of treatment increases significantly with the number of dysfunctional organs.[1] Given the substantial clinical burden of sepsis, physicians should be knowledgeable about evidence-based interventions for acute management of septic patients.

Sepsis can be viewed as a heterogeneous syndrome with widely differing pathophysiologic mechanisms and outcomes.[2] The pathogenesis of severe sepsis and septic shock is remarkably complex.[3] The syndrome starts with an inciting event, usually microorganism proliferation at a nidus of infection, that leads to a complex inflammatory reaction and the release of a large number of host-derived immune mediators (eg, interleukins, tumor necrosis factor-α). These mediators in turn have a profound physiologic effect on the vasculature and organ systems. Septic shock can produce cardiovascular, respiratory, renal, hematologic, metabolic, hepatic, and neurologic dysfunction. Death generally results from progressive hypotension or the failure of at least 1 organ system.[4]

For nearly a century, sepsis had been defined as the systemic response to an infection.[5] In a 1992 consensus conference, the American College of Chest Physicians and the Society of Critical Care Medicine first delineated criteria for defining disease states in the sepsis continuum and introduced the term systemic inflammatory response syndrome (SIRS), which does not require the presence of infection (**Table 1**).[6] The 2001 International Sepsis Definition Conference attempted to improve on the specificity of these definitions by elaborating common clinical and laboratory manifestations of the disorder (**Table 2**).[7]

TAKE HOME POINTS

- Early treatment is essential in the management of sepsis, and therapy should be started as soon as the syndrome is recognized.
- Adequate fluid resuscitation, antibiotic therapy, intubation and mechanical ventilation, and source control are key components of early sepsis therapy.
- Intravenous (IV) antibiotic therapy should be administered within 1 hour of identifying sepsis.
- Vasopressors are indicated when fluid challenges do not restore blood pressure and achieve organ perfusion goals.
- Low-dose IV corticosteroids are recommended in patients with vasopressor-dependent septic shock.
- Recombinant human activated protein C (drotrecogin alfa [activated]) should be considered in appropriately selected patients.

One of the goals of creating these definitions was to help physicians recognize patients at risk for severe sepsis and intiate therapy promptly. In order to reflect the many prognostic factors in sepsis and provide a hypothesis-generating model for future research, the PIRO (Predisposing factors, nature of Insult, intensity of Response, number of Organ dysfunction) grading system was also proposed.[7]

Another step in the evolution of sepsis management occurred in 2004 when the guidelines from the Surviving Sepsis Campaign (SSC) were published.[8]

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Table 1. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Definitions of Sepsis Disease States

Systemic Inflammatory Response Syndrome (SIRS). The systemic inflammatory response to a wide variety of severe clinical insults, manifested by 2 or more of the following conditions:

1. Temperature > 38°C or < 36°C
2. Heart rate > 90 bpm
3. Respiratory rate > 20 breaths/min or $Paco_2$ < 32 mm Hg
4. White blood cell count > 12 × 10^3/μL or < 4 × 10^3/μL, or > 10% immature (band) forms

Sepsis. The systemic inflammatory response to infection. In association with infection, manifestations of sepsis are the same as those previously defined for SIRS. It should be determined whether they are a direct systemic response to the presence of an infectious process and represent an acute alteration from baseline in the absence of other known causes for such abnormalities. The clinical manifestations would include 2 or more of the following conditions as a result of a documented infection:

1. Temperature > 38°C or < 36°C
2. Heart rate > 90 bpm
3. Respiratory rate > 20 breaths/min or $Paco_2$ < 32 mm Hg
4. White blood cell count > 12 × 10^3/μL or < 4 × 10^3/μL or > 10% immature (band) forms

Severe sepsis/SIRS. Sepsis (SIRS) associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

Sepsis (SIRS)-induced hypotension. A systolic blood pressure < 90 mm Hg or a reduction of ≥ 40 mm Hg from baseline in the absence of other causes of hypotension.

Septic shock/SIRS shock. A subset of severe sepsis (SIRS) and defined as sepsis (SIRS)–induced hypotension despite adequate fluid resuscitation along with presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients receiving inotropic or vasopressor agents may no longer be hypotensive by the time they manifest hypoperfusion abnormalities or organ dysfunction, yet they would still be considered to have septic (SIRS) shock.

Multiple organ dysfunction syndrome (MODS). Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Adapted with permission from Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644–55.

Developed to increase awareness around sepsis and improve outcomes in severe sepsis, these guidelines provide evidence-based recommendations regarding aspects of acute management of sepsis and septic shock. This article reviews the SSC recommendations with a focus on early interventions needed in the care of patients with sepsis.

INITIAL EVALUATION AND RESUSCITATION

Early recognition of sepsis is important because prompt initiation of therapy likely improves outcomes.[9] Shock is considered a clinical diagnosis suggested by the signs and symptoms of organ hypoperfusion, which include altered level of consciousness, decreased urine output, mottled skin, and hemodynamic instability (Table 2). Shock is frequently accompanied by hypotension, although some patients may initially be able to maintain their blood pressure due to the body's catecholamine response.[10]

The initial steps in the management of a critically ill patient in shock are as follows: assess and establish an airway, evaluate breathing (including consideration of whether mechanical ventilator support is required), and resuscitate the inadequate circulation.[10] Ensuring adequate oxygenation is essential, and the goal of hemodynamic support is to achieve an arterial oxygen saturation of 90% or greater.[11]

Early Goal-Directed Therapy

Early goal-directed therapy consists of aggressive hemodynamic support in the resuscitation of septic patients that is aimed at achieving specific physiologic targets. The goals of resuscitation during the first 6 hours after sepsis is recognized include: central venous pressure, 8 to 12 mm Hg; mean arterial pressure, greater than 65 mm Hg; urine output, greater than 0.5 mL/kg/hr; central venous oxygen saturation ($Scvo_2$; superior vena cava), greater than 70%. The goal for central venous pressure in patients who are mechanically ventilated or who have increased abdominal pressure is between 12 and 15 mm Hg. If an $Scvo_2$ of 70% is not achieved by fluid resuscitation alone, the guidelines recommend transfusion of packed red blood cells to achieve a hematocrit over 30% and/or administering dobutamine intravenously (IV) to achieve this goal.

$Scvo_2$ can be measured by performing blood gas analysis on blood drawn through the distal port of a central venous catheter in the superior vena cava. Mixed venous oxygen saturation (Svo_2) is measured using a sample of blood drawn from the distal port of a pulmonary artery catheter. (Catheters equipped with continuous oximetry are also available.) Studies evaluating the numeric correlation of $Scvo_2$ and Svo_2 have concluded that $Scvo_2$ values are (on average) approximately 5% higher than Svo_2 values. This difference is

likely due to the contribution of deoxygenated blood from the coronary sinus.[12] Thus, substituting $Scvo_2$ for Svo_2 in the calculation of oxygen consumption can make it prone to unacceptably large errors.[12] This difference between Svo_2 and $Scvo_2$ values was acknowledged by the SSC guidelines, which recommend obtaining an Svo_2 level of 65% and/or an $Scvo_2$ level of 70%.[13] Initial assessment of the plasma lactate level and serial measurements during the course of illness also may provide important prognostic information.[14]

These recommendations are mostly based on a randomized controlled trial that showed reduced in-hospital, 28-day, and 60-day mortality in septic patients who received an early aggressive resuscitation protocol (fluid therapy, vasoactive agents, and transfusions of red blood cells) to increase oxygen delivery before intensive care unit (ICU) admission compared with septic patients who received a standard resuscitation protocol.[9] Timing is key to achieving benefits with early goal-directed therapy, as the improved outcomes seen in the Rivers et al study[9] were achieved with an emergency department–based protocol. Thus, these resuscitative measures should be started as soon as the syndrome is recognized without waiting for admission in the ICU.[8]

Abdominal Compartment Syndrome

Abdominal compartment syndrome occurs when intra-abdominal pressure is abnormally raised in association with increasing organ dysfunction. Typically, it is identified in the presence of rising peak airway pressures, oliguria, and reduced cardiac output. Abdominal decompression can reverse this condition if it is initiated in time.[15]

FLUID THERAPY

Fluid resuscitation is one of the cornerstones of sepsis therapy.[8] Studies in septic patients have failed to show any apparent differences in the incidence of pulmonary edema, mortality, or length of stay in patients given isotonic crystalloid versus colloid resuscitation.[16] However, crystalloid resuscitation has been associated with lower mortality in trauma patients.[17] A recent Saline versus Albumin Fluid Evaluation (SAFE) study was one of several studies that evaluated whether the choice of resuscitation fluid affects survival for ICU patients.[18] This randomized, double-blind trial assigned patients to 4% albumin or normal saline for resuscitation and found similar outcomes at 28 days in the 2 groups, suggesting that the choice of fluids is probably less important than the quantity given. Cardiac output and systemic oxygen delivery increase in proportion to the degree of intravascular volume expansion achieved.[19] Tissue perfusion is restored to the

Table 2. Diagnostic Criteria for Sepsis

Infection (documented or suspected) and some of the following:
General variables
Fever (core temperature > 38.3°C)
Hypothermia (core temperature < 36°C)
Heart rate > 90 bpm or > 2 SD above normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)
Hyperglycemia (plasma glucose > 120 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count > 12 x 10^3/μL)
Leukopenia (WBC count < 4 x 10^3/μL)
Normal WBC count with 10% immature (band) forms
Plasma C-reactive protein > 2 SD above normal value
Plasma procalcitonin > 2 SD above normal value
Hemodynamic variables
Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or < 2 SD below normal for age)
Mixed venous oxygen saturation > 70%
Cardiac index > 3.5 L/min/m^2
Organ dysfunction variables
Arterial hypoxemia (Pao_2/Fio_2 < 300)
Acute oliguria (urine output < 0.5 mL/kg/hr or 45 mmol/L for ≥ 2 hr)
Creatinine increase > 0.5 mg/dL
Coagulation abnormalities (INR > 1.5 or aPTT > 60 sec)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100 x 10^3/μL)
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)
Tissue perfusion variables
Hyperlactatemia (> 1 μmol/L)
Decreased capillary refill or mottling

Adapted with permission from Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. SCCM/ESICM/ACCP/ATS/SIS. Crit Care Med 2003;31:1250–6.

aPTT = activated partial thromboplastin time; Fio_2 = fractional concentration of oxygen in inspired gas; INR = international normalized ratio; MAP = mean arterial pressure; Pao_2 = partial arterial oxygen tension; SBP = systolic blood pressure; SD = standard deviation; WBC = white blood cell.

same degree when crystalloids or colloids are titrated to the same filling pressures.[20] The availability, cost, and ease of administration of crystalloids generally make them the first-line therapy for fluid resuscitation.

The SSC guidelines recommend administering fluid challenges of 500 to 1000 mL of crystalloids every 30 minutes in patients with suspected hypovolemia; these should be repeated based on the patient's response (increase in blood pressure and urine output) and tolerance (evidence of intravascular volume overload). Fluid challenges are given in addition to the baseline maintenance fluid administration.[19] Precise endpoints for fluid resuscitation have not been defined. A combination of clinical variables, including mean arterial pressure, urine flow, skin perfusion, and level of consciousness, are used to determine the adequacy of fluid resuscitation.[21]

VASOPRESSORS AND INOTROPIC AGENTS

If resources permit, an arterial catheter should be placed as soon as practically possible. Vasopressors are indicated when fluid challenges do not restore blood pressure and organ perfusion. When used, the vasopressors should be titrated to maintain a mean arterial pressure of 65 mm Hg or higher.[22] Norepinephrine or dopamine are the vasopressors of choice. Norepinephrine may be more effective than dopamine at reversing hypotension in patients with septic shock,[23] and it is associated with a trend toward decreased mortality.[24] Epinephrine, phenylephrine, or vasopressin should not be used as first-line agents.

Vasopressin deficiency is common in septic shock.[25] Vasopressin is currently indicated in patients with refractory shock despite adequate fluid resuscitation and administration of high-dose conventional vasopressors.[8] Intravenous infusion of low-dose vasopressin (0.03–0.04 U/min) has been reported to increase blood pressure, urinary output, and creatinine clearance and to allow dramatic decreases in vasopressor therapy.[26] Low-dose dopamine for renal protection is not recommended based on the results of a clinical trial that showed no significant benefit from this intervention in critically ill patients at risk of renal failure.[27] Dobutamine remains the agent of choice to increase cardiac output, but it should not be used to increase cardiac output above physiologic levels.[28]

DIAGNOSIS OF INFECTION AND ANTIBIOTIC THERAPY

Following initial stabilization, efforts should be directed toward determining the nature of infection and identifying any organ dysfunction.[29] Careful evaluation for any high-risk predisposing conditions (eg, trauma, surgery, organ transplantation, immunosuppression) also should be undertaken.[11] Samples for culture studies should be obtained before initiation of antibiotic therapy. The guidelines recommend obtaining at least 2 blood cultures with 1 drawn percutaneously and 1 drawn from each vascular access device in place for more than 48 hours. Cultures from other sites should be obtained as dictated by clinical suspicion.

Intravenous antibiotic therapy should be administered within 1 hour of identifying the presence of sepsis. The choice of empiric antibiotic therapy depends on the patient's history, including drug allergies, underlying disease, the clinical syndrome (including involved organs and likely pathogens), and susceptibility patterns in the patient's community and health care facility.[8] The chosen antibiotic therapy should include one or more drugs that have activity against the likely pathogens (bacterial or fungal) and that can penetrate into the presumed source of the sepsis.[30] The index of suspicion for methicillin-resistant *Staphylococcus aureus* (MRSA) infection should be increased in patients with a history of MRSA infection or close contact with an MRSA-infected person or in communities where MRSA infections have been identified. If MRSA infection is suspected, clinicians should add vancomycin or linezolid to the empiric regimen.[31] Inappropriate empiric antimicrobial therapy has been independently associated with increased mortality in septic patients.[32]

Empiric monotherapy with a third- or fourth-generation cephalosporin or carbapenems or combination therapy with extended-spectrum carboxypenicillins or ureidopenicillins and β-lactamase inhibitors is as efficacious as combination therapy with a β-lactam antibiotic and an aminoglycoside.[33–37] Thus, combination therapy with an aminoglycoside and a β-lactam is unnecessary. Most experts still recommend using combination therapy for neutropenic patients with severe sepsis or septic shock.[38] Use of combination therapy for pseudomonal infections, although somewhat controversial, is still widely practiced.[39–41] Routine empiric antifungal therapy is not recommended except in selected subsets of septic patients at high risk for invasive candidiasis.[30]

The antimicrobial regimen should be reassessed after 48 to 72 hours, which includes reviewing the microbiologic and clinical data and narrowing the antibiotic spectrum, if possible.[8] The key is to cover broadly initially and then narrow coverage based on culture results.

SOURCE CONTROL

Source control is an important component of successful sepsis therapy. Appropriate steps should be

undertaken to drain infected fluids and abscesses, débride infected soft tissues, and remove infected devices or foreign bodies as well as to correct anatomic derangements that result in ongoing microbial contamination.[42] Appropriate subspecialty consultations to help in sampling, drainage, and removal of the source of infection should be obtained.

CORTICOSTEROIDS

Because an intense inflammatory response is a component of the pathogenesis of sepsis, corticosteroids have been explored as a possible therapeutic agent. However, the use of corticosteroids in sepsis remains controversial. The SSC guidelines recommend intravenous low-dose corticosteroids (hydrocortisone 200–300 mg/day) only in patients with vasopressor-dependent septic shock.[43,44] Administration of higher doses of corticosteroids in septic shock has been shown to be harmful.[45]

The host response to the stress of critical illness includes increased serum cortisol levels, but an inappropriate cortisol response is not uncommon in patients with septic shock.[46] The use of adrenal function tests to detect relative adrenal insufficiency has been proposed as an approach to determining which patients might benefit from corticosteroid therapy.[47] An absolute incremental increase of 9 µg/dL 30 or 60 minutes after administration of 250 µg of corticotropin was found to be the best cut-off value to distinguish between adequate adrenal response (responders) and relative adrenal insufficiency (nonresponders).[48] Corticosteroids should not be withheld while awaiting the results of the adrenal function test. Dexamethasone 4 mg IV every 6 hours may be given until a low-dose corticotropin stimulation test can be performed as this agent does not interfere with the cortisol assay but suppresses the pituitary-adrenal axis response. Corticosteroids may be continued in patients with relative adrenal insufficiency and can be discontinued in responders.[49]

Some authors have recommended using a baseline random cortisol level of less than 25 µg/dL (in a highly stressed patient) as this finding is highly suggestive of adrenal insufficiency.[50] A recent study, however, showed that nearly 40% of critically ill patients with hypoproteinemia had below normal serum total cortisol concentrations even though their adrenal function was normal. Measuring serum free cortisol concentrations in this subset of patients can prevent the unnecessary use of glucocorticoid therapy.[51] Corticosteroids should be continued regardless of the baseline level if the cortisol response to administration of corticotropin is blunted.

The decision of whether to treat with corticosteroids should balance the benefits of these agents with their important adverse effects in patients with sepsis. Adverse effects include neuromyopathy and hyperglycemia as well as decreased numbers of lymphocytes, immunosuppression, and loss of intestinal epithelial cells through apoptosis. Corticosteroids have also been associated with increased risk of nosocomial infection and impaired wound healing.[52]

The use of corticosteroids in the treatment of acute respiratory distress syndrome (ARDS) also remains controversial. Some earlier trials showed a mortality benefit among patients treated with methylprednisolone compared with those given placebo.[53] A recent National Heart, Lung, and Blood Institute trial involving 180 patients with ARDS of at least 7 days' duration found that starting methylprednisolone therapy more than 2 weeks after the onset of ARDS was associated with an increased risk of death at 60 days and 180 days.[54] Although methylprednisone was associated with improvement in cardiopulmonary physiology, this study did not support the routine use of methylprednisolone for persistent ARDS.[54]

A large clinical trial called Corticosteroid Therapy of Septic Shock (CORTICUS) is currently underway to answer the remaining questions about the use of corticosteroids in septic shock. This double-blind, randomized, placebo-controlled multicenter trial is comparing hydrocortisone (50 mg IV every 6 hours for 5 days followed by tapering to 50 mg every 12 hours for 3 days and then 50 mg once daily for the last 3 days) with placebo in patients with septic shock. A total of 800 patients are being enrolled. It will compare 28-day all-cause mortality in the 2 groups in patients with less than a 9 µg/dL increase in cortisol level in response to corticotropin stimulation. The results of this trial hopefully will set the standard for the use of corticosteroids in septic shock.[55,56]

RECOMBINANT HUMAN ACTIVATED PROTEIN C

Recombinant human activated protein C (drotrecogin alfa [activated]) is the first anti-inflammatory agent that has shown promise in the treatment of sepsis.[57] Activated protein C, a component of the natural anticoagulant system, is a potent antithrombotic serine protease with substantial anti-inflammatory properties. The efficacy of drotrecogin alfa (activated) in treating severe sepsis was supported by the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, which was a phase 3, randomized, double-blind, placebo-controlled trial. PROWESS enrolled patients with severe sepsis (systemic infection and organ failure) and randomly assigned

them to receive placebo or intravenous drotrecogin alfa (activated).[58,59] Treatment with drotrecogin alfa (activated) was associated with a 6.1% absolute risk reduction and a 19.4% relative risk reduction in 28-day all-cause mortality. The Extended Evaluation of Recombinant Human Activated Protein C (ENHANCE) trial was conducted to gather additional 28-day all-cause mortality and safety data among adults with severe sepsis treated with drotrecogin alfa (activated).[60] In this prospective, single-arm, multicenter clinical trial, the drotrecogin alfa (activated) group had a lower 28-day all-cause mortality rate (26.4%) than the placebo groups in the PROWESS US trial (32.9%) and the Secretory Phospholipase A2 Inhibitor (sPLA2I) in Severe Sepsis trial (33.2%), thus confirming the favorable benefit/risk profile of drotrecogin alfa (activated) in selected patients. The recent ADDRESS trial evaluated the use of drotrecogin alfa (activated) in patients with severe sepsis and a low risk of death (single organ dysfunction or Acute Physiology and Chronic Health Evaluation [APACHE II] score < 25).[61] This trial showed a statistically nonsignificant increase in mortality in the treatment group (17% in placebo versus 18% in treatment group) and was halted early because an interim analysis suggested that the trial would not likely meet its objective of demonstrating a significant reduction in 28-day mortality in patients treated with drotrecogin alfa (activated). It is important to note that in the PROWESS, ENHANCE, and ADDRESS trials, the risk of serious bleeding events was increased in patients who received drotrecogin alfa (activated).

At this time, patients who fulfill the following criteria are most likely to benefit from treatment with drotrecogin alfa: (1) those who have severe sepsis with vasopressor dependence and/or require mechanical ventilation with an APACHE II score greater than 25; (2) those who have no active bleeding, have a platelet count greater than $30 \times 10^3/\mu L$ and an international normalized ratio below 3.0, and have no identifiable risk factors for central nervous system bleeding; and (3) both the patient and medical team approve of taking an aggressive approach to care of sepsis in a patient with a reasonable baseline quality of life to return to once they survive their ICU stay.[62]

Use of drotrecogin alfa (activated) is contraindicated in patients with known sensitivity to the drug and patients at high risk for death or significant morbidity associated with bleeding. This group would include patients with active internal bleeding, recent (< 3 months) hemorrhagic stroke, recent (< 2 months) intracranial or intraspinal surgery or severe head trauma, trauma with increased risk for life-threatening bleeding, presence of an epidural catheter, intracranial neoplasm or mass lesion, or evidence of cerebral herniation.[4] The use of prophylactic heparin in patients with severe sepsis undergoing treatment with drotrecogin alfa (activated) appears to be safe.[63]

Treatment with drotrecogin alpha (activated) consists of infusion of the drug at a rate of 24 μg/kg/hr for a total infusion duration of 96 hours. The dose is based on actual body weight. The infusion should be stopped 2 hours before patients undergo surgical procedures associated with a risk of bleeding. The infusion can be restarted immediately after minor procedures (eg, arterial line placement, tracheotomy tube changing) if there is no sign of bleeding. However, waiting approximately 2 hours before restarting the drug after procedures with slightly increased chance of bleeding (eg, chest tube placement, pulmonary artery catheter placement) is recommended. With major surgical procedures, a wait time of approximately 12 hours before restarting the infusion is recommended. Once the infusion is restarted, it should be administered so that the total infusion time (preprocedure + postprocedure) is 96 hours. "Catch up" or bolus infusions are contraindicated.[4]

GLUCOSE CONTROL

Hyperglycemia associated with insulin resistance is common in critically ill patients, including patients who have not previously been diagnosed with diabetes.[64] Hyperglycemia in critically ill patients is associated with decreased immune function, poor wound healing, postoperative infections, and worse overall outcomes.[65] A randomized controlled trial that used intensive insulin therapy in critically ill surgical patients to achieve tight glucose control (blood glucose level, 80–110 mg/dL) demonstrated a significant decrease in mortality compared with patients maintained at previously accepted levels of hyperglycemia.[66] Intensive insulin therapy also decreased rates of blood stream infections, prolonged inflammation, acute renal failure requiring dialysis or hemofiltration, critical illness polyneuropathy, and transfusion requirements.[66] A recent trial of intensive insulin therapy in medical ICU patients failed to show a reduction in mortality.[67] However, the study showed decreased morbidity in the intensive insulin therapy group via prevention of newly acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital.[67] Further studies are required to define the exact role of tight glucose control in sepsis.

Current recommendations suggest maintaining blood glucose levels below 150 mg/dL after initial

stabilization.[8] Continuous infusion of insulin should be used if needed. Frequent monitoring of glucose may be required, and use of tight glucose control/insulin drip protocols is advisable.[64]

MECHANICAL VENTILATION

Early intubation and mechanical ventilation is suggested for patients with sepsis, who are at increased risk for developing acute respiratory failure due to increased work of breathing.[68] In the largest trial of a pressure- and volume-limited ventilation strategy, use of a lower initial tidal volume (6 mL/kg of estimated lean body weight) and plateau pressure (< 30 cm of H_2O) resulted in a significantly lower all-cause mortality rate (31%) compared with use of a tidal volume of 12 mL/kg (39.8%).[69] Based on the results of this trial, a strategy of using low tidal volume and high positive end expiratory pressure is recommended for mechanical ventilation of patients with acute lung injury (ALI)/ARDS. Daily spontaneous breathing trials are recommended for all clinically stable intubated patients.[67] Multiple studies have confirmed the efficacy of daily spontaneous breathing trials in reducing the duration of mechanical ventilation.[70,71]

Noninvasive positive pressure ventilation (NIPPV) can be considered in carefully selected patients with sepsis.[72] NIPPV has a number of potential advantages, particularly the avoidance of tracheal intubation with its associated mortality and morbidity from problems such as pneumonia. Intermittent ventilatory assistance is also possible with noninvasive ventilation, allowing gradual weaning as well as normal eating, drinking, and communication. In addition, breaks from ventilatory support can be used for administering nebulized medication, physiotherapy, and expectoration.[73] Important contraindications to the use of NIPPV include shock, altered mental status, or increased airway secretions.[74] Few studies have evaluated the use of NIPPV in patients with sepsis-induced ALI/ARDS. In our experience, patients who have normal mental status and are likely to recover within 48 to 72 hours seem to be good candidates for NIPPV.

SUPPORTIVE THERAPIES

Patients in the ICU are at high risk for developing thromboembolic phenomena.[75] All patients with sepsis should receive unfractionated heparin or low-molecular-weight heparin for deep venous thrombosis prophylaxis. Three times daily dosing of unfractionated heparin is recommended over twice daily dosing.[76] Lower-extremity graduated compression devices and intermittent pneumatic compression devices can be used in septic patients who have contraindications to the use of heparin, or these interventions can be combined with heparin in very high-risk patients.[77]

Prolonged (> 48 hr) mechanical ventilation, coagulopathy, and hypotension can predispose patients with sepsis to the development of stress gastric ulcers.[78–80] Therefore, stress ulcer prophylaxis should be given to all patients with severe sepsis. Treatment options include antacids, sucralfate, histamine$_2$ (H_2) receptor antagonists, and proton pump inhibitors (PPIs). H_2-receptor antagonists are more effective than sucralfate in decreasing the risk for clinically significant bleeding.[81,82] Although continuous administration of H_2-receptor antagonists may provide more effective acid inhibition as compared with intermittent dosing, the relevance and impact on clinical outcomes of this practice is not known.[83] A review of published studies that evaluated PPIs for stress ulcer prophylaxis concluded that PPIs are equivalent to H_2-receptor antagonists in ability to increase gastric pH.[84,85] Enteral nutrition is also an important adjunct to stress ulcer prophylaxis.[80,86]

CHALLENGES IN IMPLEMENTING THE GUIDELINES

Implementing the SSC guideline recommendations, especially early goal-directed therapy, can present challenges. Initial studies that evaluated the application of the guidelines showed underutilization,[87] which potentially was due to insufficient education of staff, logistic obstacles, cost concerns, lack of physician buy in, and failure to diagnose appropriately.[88] Recent studies, however, have demonstrated their applicability in the real world setting without need for allocation of any extra clinical staffing or special critical care capability beyond what could be found in a conventional emergency department.[89,90] A close collaboration between emergency medicine and critical care clinicians is required to facilitate change. Educating all involved personnel and making standardized protocols available are also helpful strategies in implementing the recommendations.[91,92]

CONCLUSION

Sepsis is a clinical disorder with high mortality. The SSC guidelines provide evidence-based recommendations for the management of septic patients. These guidelines recommend a well-coordinated effort that starts with early diagnosis and aggressive initial resuscitation. Successful treatment requires great attention to detail in the management of all aspects of the disease, including antibiotic therapy, choice of vasopressors, ventilator management, tight glucose control, and

deep venous thrombosis and stress ulcer prophylaxis. Appropriate use of newer therapies like drotrecogin alfa (activated) also should be considered. It is only with a well-rounded approach that we may be able to improve the outcome of this deadly disease. **HP**

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