Management of Severe Sepsis in the Surgical Patient

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Sepsis and septic shock are not uncommon conditions in the surgical intensive care unit (ICU). There are many aspects to the term sepsis; thus before focusing on therapy, the terminology needs to be clarified. Sepsis is a generalized activation of the immune system in the presence of clinically suspected or culture-proven infection. Severe sepsis is sepsis with organ system dysfunction. Septic shock is sepsis with hypotension (systolic blood pressure $<90$ mm Hg) without other causes [1].

Epidemiology

In the year 2000 the incidence of sepsis in the United States was 240 per 100,000 population, based on the National Hospital Discharge Survey, and was increasing at 9\% per year [2]. The incidence of severe sepsis is estimated at three cases per 100,000 population, based on hospital discharge data from seven states. The curve of the incidence across ages is J-shaped, with a high rate in infants, low rates in children and young adults, and steadily increasing rates thereafter (Fig. 1). More than half of the cases of sepsis are in patients 65 years of age or older. The overall incidence of severe sepsis is similar in men and women, but the age-adjusted incidence in women is lower. Overall mortality from severe sepsis is 28.6\%, with the lowest mortality (10.0\%) in children and the highest (38.4\%) in adults 85 years of age or...
older. For adults who have comorbidities, however, mortality is higher and does not vary much with age. Overall mortality is higher for males than females, but when adjusted for age, comorbidities, and site of infection, the morality rates are the same for both genders.

The burden of disease associated with severe sepsis is staggering. Total hospital cost for the care of severe sepsis in the United States in 1995 was estimated at $16.7 billion [3]. In addition to the high in-hospital mortality, patients who have severe sepsis are still at a higher risk of dying once they are discharged from the hospital. In a study by Weycker and colleagues [4], in-hospital morality for adult patients who had severe sepsis was 21.2%, and at 1 year after diagnosis it had risen to 51.4%.

Surgical patients compose 28.6% of all severe sepsis patients and have similar mortality to medical patients [3]. In a study of 1125 patients who were hospitalized for more than 48 hours after surgery, 6.5% developed severe sepsis [5]. Among patients having major oncologic surgery, 20.4% developed severe sepsis, and 36.8% of these patients died. The most common source of sepsis was the lungs. Preoperative risk factors for severe sepsis included male gender and a higher burden of coexisting disease. Intra- and postoperative factors that put patients at increased risk for severe sepsis included presence of a pronounced systemic inflammatory response and a greater degree of early postoperative organ dysfunction, evident as early as postoperative day 2 [6]. In patients who had intra-abdominal infection and who required surgery, 11%
developed severe sepsis. Organ dysfunction was most commonly limited to the respiratory and cardiovascular system. The mortality was 34% in patients who had severe sepsis, compared with 6% overall. As in the prior study, pre-existing comorbidities, specifically cardiovascular, pulmonary, hepatic, renal, or neurologic disease, increased the risk of severe sepsis. Severe sepsis was more likely to complicate peritonitis if there was a nonappendiceal source or there was evidence of recurrent infection [7].

The Surviving Sepsis Campaign

Given the availability of clinical strategies and pharmacologic agents for the treatment of severe sepsis, there has been an increased emphasis on the identification and evidence-based management of severe sepsis. The Surviving Sepsis Campaign is the result of an international effort to develop guidelines for the treatment of severe sepsis [8]. The recommendations were developed by a modified Delphi technique, with recommendations graded based on the strength of the evidence behind them. In this article, the authors focus on the Severe Sepsis guidelines and modify the recommendations where necessary, such that they might better meet the needs of the surgical patient.

Initial resuscitation

It is generally believed that earlier and aggressive resuscitation to restore tissue perfusion reduces the risk of organ dysfunction and mortality in patients who have severe sepsis. Early attempts at resuscitation initially focused on providing supraphysiologic levels of tissue oxygen delivery, a concept referred to as supranormal oxygen delivery; however, two randomized controlled trials based on interpretation of data from pulmonary artery catheters and in which the intervention arm made liberal use of inotropic support failed to show benefit, and suggested the potential for harm [9,10]. In both of these studies, this goal-directed therapy was started when patients arrived in the ICU.

Providing resuscitation at an earlier phase of care in the emergency department and limiting the resuscitation goals to relatively conservative end points might offer greater benefits. This concept of early goal-directed therapy is derived from a trial in which 263 patients presenting to the emergency department with signs of severe sepsis or septic shock were randomized to receive either standard care or goal-directed therapy for the first 6 hours of resuscitation [11]. The experimental group received central venous catheters capable of measuring superior vena caval oxygen saturation as a surrogate for mixed venous oxygen saturation (SvO₂) and arterial catheters for measuring blood pressure. Central venous pressure (CVP) was maintained at 8 to 12 mm Hg with boluses of 500 mL of crystalloid intravenous fluid. Mean arterial pressure (MAP) was kept at 65 mm Hg
or higher with intravenous fluid (Fig. 2). Patients were placed on mechanical ventilation if necessary and sedated as needed. Using this relatively simple approach, in-hospital mortality was reduced from 47% to 31%. Because these interventions (fluid, transfusions, \( \text{SvO}_2 \) monitoring) were evaluated together, it is difficult to ascertain how much each intervention contributed to the reduction in mortality. As a result, many institutions have simply emulated this protocol with the hope of reproducing these results at their institutions. Trzeciak and coworkers [12] studied their implementation of early goal-directed therapy and concluded that it could be implemented effectively without changes to the emergency department physical plant or staffing.

**Fluid resuscitation**

Septic shock is a form of distributive shock, and large volumes of fluid may be required to compensate for the profound vasodilation. Hypotensive patients should receive fluid boluses of 500 to 1000 mL of crystalloid, rather than simply increasing the rate of their maintenance fluids, to more rapidly assess their fluid responsiveness. Increasing the maintenance IV fluid rate from 100 mL/hr to 200 mL/hr will take 10 hours to infuse an extra liter of fluid, compared with 1 hour or less to infuse the same amount as a bolus. These patients can require massive amounts of fluid, and the input/output ratio is not useful for monitoring fluid needs during resuscitation. Patients should be monitored for fluid tolerance by watching for signs of pulmonary edema and congestive heart failure. Peripheral edema is to be expected because of the profound capillary leak that accompanies the systemic inflammatory response, and should not be taken as a sign of fluid intolerance.

Because of this capillary leak, there has been an interest in using albumin for resuscitation, with the thought that it would remain within the intravascular space. Results of two meta-analyses comparing albumin and crystalloid suggested that mortality was higher in patients receiving albumin [13,14]. The authors also found that trials with higher methodologic quality showed a trend toward reduced mortality with albumin [14]. A subsequent randomized controlled trial of almost 7000 critically ill, hypovolemic patients, of whom 18% had sepsis, demonstrated a trend toward reduced survival in septic patients receiving albumin (31% mortality versus 35%, \( P = 0.09 \)) [15]. In light of the lack of clear benefit of albumin coupled with its increased cost, crystalloid remains the resuscitation fluid of choice at this time. Lactated Ringer’s solution should be used to prevent the hyperchloremic metabolic acidosis seen with the administration of large volumes of saline. Because lactated ringer’s contains potassium, repeat assessments of serum potassium levels should be considered, particularly in patients who have oliguria or renal dysfunction.

A CVP monitor should be placed to better guide fluid management in patients who have severe sepsis, with a target CVP of 8 to 12 cm H₂O. Fluid status can also be assessed by monitoring the respiratory variation of the arterial line tracing. When the systolic pressure varies by more than 5 to 10 mmHg with respiration, the patient remains hypovolemic [16]. This measurement is only useful in patients receiving positive pressure ventilation. A slightly more complex measurement is assessment of the pulse pressure (systolic minus diastolic blood pressure). The maximal pulse pressure (\( P_{\text{p max}} \)) is measured during inspiration and the minimal pulse pressure (\( P_{\text{p min}} \)) is measured during expiration. The percentage difference is then calculated by the formula \( \Delta P_p(\%) = 100 \times (P_{\text{p max}} - P_{\text{p min}}) / [(P_{\text{p max}} + P_{\text{p min}})/2] \). A \( \Delta P_p \) of 13% or more is indicative of a patient who will be volume responsive. This was a more reliable indicator of fluid responsiveness than systolic pressure variation in a study of 40 patients who had septic shock [17]. Although this is more difficult to calculate, it is one
of the calculations performed automatically by the lithium indicator dilution cardiac output monitor device, which provides real-time cardiac output data from the arterial line tracing [18].

In septic patients who develop acute lung injury, a more conservative approach to intravascular volume may be useful. A trial of 1000 patients who had acute lung injury, of whom about 25% had sepsis [19], showed that limited fluid administration once patients were no longer hypotensive and liberal use of diuretics shortened time on the ventilator by 1.5 days, and reduced ICU length of stay by 2.3 days. There was no difference in mortality. Of note, in this same trial, subjects were also randomized to a central venous catheter or pulmonary artery catheter (PAC). Patients randomized to a PAC had no better outcome and a higher risk of catheter-related complications [20]. The extent to which these data from either trial can be generalized to the surgical patient is unclear. Only 44% of subjects randomized were in a surgical ICU, and care was highly protocolized. Nevertheless, there is no reason to believe that patients undergoing operation for sepsis would have a significantly different risk/benefit ratio using these approaches than critically ill medical patients.

**Management of metabolic acidosis**

Metabolic acidosis, particularly lactic acidosis, commonly complicates sepsis and septic shock. Lactic acidosis is sometimes divided into type A (caused by tissue hypoxia) and type B (no clinical evidence of tissue hypoxia), but in sepsis both mechanisms may be involved. Clinicians commonly correct a low pH with bicarbonate, usually citing the negative effects of acidemia on myocardial dysfunction; however, studies of myocardial function in acidemia have found conflicting results. Moreover, as experience grows with permissive hypercapnia in acute respiratory distress syndrome (ARDS) and asthma, it has become clear that patients can often tolerate a pH as low as 7.20. There is even some evidence that acidemia is protective in critical illness, with delayed onset of cell death in acidic hepatocytes undergoing anoxia, and acidosis during reperfusion has been shown to limit the size of infarcted myocardium [21].

The other issue is the direct effect of bicarbonate. Bicarbonate has been shown to raise PCO$_2$ (CO$_2$ being a weak acid) when given to mechanically ventilated patients who have lactic acidosis [22]. Bicarbonate has also been shown to increase lactic acid production [23]. A variety of mechanisms have been proposed for this effect, including a shift in the oxyhemoglobin saturation relationship, increased anaerobic glycolysis (mediated by pH-sensitive phosphofructokinase, the rate-limiting step), and changes in hepatic blood flow or lactate clearance. Because bicarbonate raises CO$_2$ levels, and CO$_2$ is more diffusible than bicarbonate, pH in intracellular spaces and cerebrospinal fluid may actually drop. This mechanism might explain the increase in intracranial pressure sometimes seen with bicarbonate boluses. Animal studies
have not shown a hemodynamic benefit to bicarbonate infusion over saline. Two human studies showed no changes in hemodynamics or catecholamine responsiveness, despite an increase in pH and serum bicarbonate concentrations. Both studies compared bicarbonate to saline and suggested that the commonly observed hemodynamic improvement seen with bicarbonate may in fact be due to increased preload from the volume of the infusion [22,24].

Therefore bicarbonate administration is not recommended for pH greater than 7.15 [25], and may not be necessary at even a lower pH. It is, however, still recommended for bicarbonate-losing acidoses, such as renal tubular acidosis.

**Antimicrobial therapy**

*Empiric selection of antimicrobials*

In patients who have suspected sepsis, it is critical to initiate early empiric antimicrobial therapy, because several cohort studies have demonstrated an increased incidence of adverse outcomes in patients who had bacteremia or pneumonia and who experienced a delay in receiving the appropriate antimicrobials [26,27]. Similar data exist for patients who have intra-abdominal infection, with inappropriate empiric choices associated with a twofold greater risk of death [28]. Agents should be broad-spectrum and should cover likely causative organisms, based on patient presentation and susceptibility patterns in the hospital and community. Empiric treatment of patients who have complicated skin and soft tissue infections should take into account the prevalence of community-acquired, methicillin-resistant *Staphylococcus aureus*, which might necessitate empiric therapy with vancomycin or linezolid [29]. The goal should be to initiate empiric antimicrobial therapy within 1 hour of arrival in the ICU or emergency department, after drawing blood cultures. Once the causative organism has been identified, the spectrum of antimicrobial therapy may be narrowed. This de-escalation of antimicrobial therapy offers the best balance between appropriate early coverage and prevention of the later emergence of resistant organisms [30].

Surgical patients are at significant risk for fungal infections, and their diagnosis is frequently not suspected ante mortem, a phenomenon related to the limited predictive utility of culture-based (eg, blood cultures) means of making the diagnosis [31]. Even in those patients in whom the diagnosis is suspected, delays in instituting therapy have a significant impact on outcome [32]. Given these data, early presumptive therapy in specific subgroups of surgical patients may be warranted. For example, the addition of fluconazole to an empiric antimicrobial regimen in patients who have severe sepsis and peritonitis lowers the risk of fungal infections [33]. The risk factors for yeast in the peritoneal cavity have been well studied, and include female gender, prior antimicrobials, shock, and upper gastrointestinal (GI) perforation [34]. Patients who have severe sepsis caused by intra-abdominal infection and any of these risk factors should be treated with an antifungal agent.
The agent of choice will vary with the risk of non-albicans species and the patterns of institutional antifungal resistance [35].

**Duration of antimicrobial therapy**

Duration of therapy is guided by the patient’s response to therapy. There is some evidence from a randomized trial of patients who had ventilator-associated pneumonia [36] that 8 days of therapy is as efficacious as 15 days, with the possible exception of non-lactose-fermenting, gram-negative rod infections, which had a higher pulmonary reinfection rate, but no increased mortality. For other infections, antibiotics should be stopped after 7 to 10 days, assuming the patient has improved clinically [37]. Failure to respond should mandate a careful search for either other sources of infection, superinfection, antimicrobial resistance, or inadequacy of source control.

**Source control**

Source control addresses the root cause of the sepsis by reducing or eliminating the focus of infection. There are three principles to source control: (1) drainage of infected fluid collections, (2) removal of infected or dead tissue and infected foreign bodies, and (3) correction of the abnormality that set the stage for the development of infection. Although all of these things need to be done, the patient must be resuscitated first. Investigations to determine the source of the infection can be done simultaneously if they can be done at the bedside (eg, portable ultrasound). Control should then be obtained with the least physiologic insult possible (eg, percutaneous catheter drainage of abscesses) until the patient is able to withstand a more definitive procedure if necessary. Necrotizing soft tissue infections and necrotic bowel are two surgical emergencies that necessitate rapid resuscitation and operation without delay once the patient is able to tolerate induction of general anesthesia [38].

Central lines should be removed if identified as a source of infection or if no other source can be found [39]. In the patient who has difficult or limited central venous access, the line can be exchanged over a guide wire, but this is associated with an increased risk of catheter exit site infection and failure of resolution of bacteremia. The risk of mechanical complications, however, is reduced with guide wire exchange [40]. Absence of inflammation at the site of catheter insertion should not be used to judge the presence of a catheter infection [41]. Ideally, a patient who has suspected catheter-related sepsis would have a 24 hour period without any central lines to help clear the infection and avoid seeding the new line, but this is frequently not possible in a critically ill patient. A new site of insertion should be used whenever possible.
Vasopressors

When adequate blood volume has been restored as evidenced by a central venous pressure (CVP) of 8 to 12 cmH$_2$O, persistent hypotension should be treated with vasopressors. If the patient is severely hypotensive, vasopressors may need to be started before fluid resuscitation can be completed. Target MAP is generally 60 to 65 mm Hg, but there is limited evidence for this goal. Ideally, the appropriate MAP for a given patient is determined by evaluating organ perfusion as vasopressors are titrated. Organ perfusion can be monitored by SvO$_2$, urine output, and lactate levels.

First-line agents for blood pressure support are norepinephrine and dopamine, with dobutamine added as needed for support of cardiac output. Dopamine is a precursor to norepinephrine and epinephrine. At low doses of dopamine the stimulation of DA1 receptors in the renal, coronary, and mesenteric beds predominates. At higher doses β-adrenergic effects start to dominate, increasing cardiac contractility and heart rate. At even higher doses α-adrenergic effects become dominant, with arterial vasoconstriction and increased blood pressure occurring. Norepinephrine is an α-adrenergic agonist with some β-adrenergic effects. Therefore it has a predominately vasoconstrictive effect, and may require the addition of dobutamine to augment cardiac output in patients who have sepsis-induced myocardial depression or pre-existing heart disease. Dobutamine is a β$_1$- and β$_2$-adrenergic agonist. It increases stroke volume and heart rate, and therefore cardiac output. Cardiac output can either be measured with a pulmonary artery catheter or other means of assessment (arterial wave form analysis, transesophageal echocardiography). Adequacy of cardiac output may also be inferred from central venous oxygen values. Because of the increase in afterload from norepinephrine, goal MAP should be as low as possible to maintain end-organ perfusion so as not to compromise cardiac output.

No large-scale clinical trials have been completed to provide recommendations as to which agents are associated with improved outcomes. A Cochrane review concluded that there was insufficient evidence to recommend one pressor strategy over another [42]; however, a large-scale observational trial conducted across multiple ICUs in Europe evaluated 1058 patients [43]. Of the patients in septic shock, 80% received norepinephrine and 35% received dopamine. Most patients received multiple agents. In a multivariate analysis, patients in shock who received any dopamine had higher 30-day mortality when compared with patients who did not receive any dopamine. Because this was an observational study, it is not sufficient to change practice, but it is an intriguing finding that warrants further study. Until a randomized controlled trial can be performed, practitioners should base choice of pressor agent on familiarity with the agent and individual patient response.

Vasopressin at 0.04 units/min without titration can be added to either dopamine or norepinephrine if high doses of the initial pressor are required to maintain MAP. Normally vasopressin has minimal effect on blood pressure.
with an intact tonic inhibitory baroreceptor input; however, this input is attenuated in septic shock, making the system much more sensitive to the vasoconstrictive effects of vasopressin [44]. In septic shock there is also a relative deficiency of vasopressin because of depletion of neurohypophyseal stores, inhibition of release by norepinephrine, and inhibition of production by nitric oxide [45]. The addition of vasopressin has been shown to reduce the dose of norepinephrine needed [46]. Higher doses of vasopressin (>0.1 – units/min) are associated with complications such as significant depression in cardiac output, myocardial ischemia, and cardiac arrest, and should not be used. Phenylephrine and epinephrine should not be used as first-line agents [47]. Phenylephrine can decrease stroke volume. Epinephrine may impair splanchnic circulation and exacerbate tachycardia.

**Corticosteroids**

Because the manifestations of sepsis are the result of a profound systemic inflammatory response, attempts to modify this response using corticosteroids have been evaluated for almost 50 years. Early studies evaluated very high, supraphysiologic doses for short durations (<72 hours). Taken together, these studies demonstrated no benefit to this approach and a significant potential for harm [48]. There are several potential reasons for the adverse effects of corticosteroids administered in this fashion. First, these higher doses typically have immunosuppressive effects and might limit the ability to clear an infection. These doses are also associated with significant hyperglycemia, which has been shown to adversely effect prognosis [49]. Lastly, this short duration is insufficient to adequately counter the more prolonged inflammatory response (Fig. 3).

![Fig. 3. The time course of cortisol concentrations in patients with septic shock (open circles) and multitrauma (closed squares). The upper limit of normal values is displayed as a dashed line. (From Beishuizen A, Thijs LG, Veres I. Patterns of corticosteroid-binding globulin and the free cortisol index during septic shock and multitrauma. Intensive Care Med 2001; 27:1584–91; with kind permission of Springer Science and Business Media.)](image-url)
More recent reassessment of the role of corticosteroids has focused on providing lower doses for longer durations and identifying patients who have relative adrenal insufficiency. This approach is derived from a large prospective cohort study in which dynamic testing of the hypothalamic-pituitary-adrenal axis was used to predict outcome in patients who had septic shock [50]. Patients who had less than a 9 μg/dL increase in serum cortisol levels after a 250 μg corticotropin challenge were identified as at high risk of death, leading to the belief that these patients suffered relative adrenal insufficiency. In this context, there is insufficient adrenal reserve to respond in the face of the significant physiologic stressor represented by critical illness. Although high baseline cortisol levels were also an adverse prognostic marker, it was recognized that this cannot be affected by intervention (Fig. 4). Thus the goal changed from providing pharmacologic doses of corticosteroid to physiologic doses in the range of 300 to 400 mg of hydrocortisol equivalents daily. A subsequent randomized controlled trial [51] of 50 mg hydrocortisone every 6 hours for 7 days (and fludrocortisone) following the onset of septic shock demonstrated a significant mortality reduction and a faster rate of shock reversal in patients randomized to receive corticosteroid. In this study, 77% of all patients were nonresponders (<9 μg/dL increase in cortisol after a stimulation test), and there was no evidence of harm in administering this dose of corticosteroid to the responders.

As a result of these and other compelling data, patients who require vasopressors should undergo a cortisol stimulation test and be started on physiologic cortisol replacement until the results are available. Patients who have an adequate response to a cosyntropin stimulation test may have their corticosteroid replacement stopped, whereas those with an inadequate response should continue to receive corticosteroids for a total of 7 days. There is no need to taper the dose at the end of the course.

Activated protein C

The inflammatory response to sepsis is intimately associated with the coagulation cascade. Several inflammatory cytokines activate coagulation and inhibit fibrinolysis. Endogenous activated protein C promotes fibrinolysis and inhibits thrombosis and inflammation. Recombinant activated protein C (also known as drotrecogin alpha) is recommended for patients who have severe sepsis and an APACHE II score greater than 25 without significant risk of bleeding [52]. In this group it reduced mortality from 30.8% to 24.7%. Activated protein C has not been shown to be beneficial in patients who has single organ system failure or APACHE II lower than 25 [53]. A more extensive discussion of the role of APC in surgical patients is in an article elsewhere in this issue.

Transfusion

Transfusions are common in the ICU, with 37% to 40% of ICU patients receiving at least one unit of blood [54,55]. Patients who have sepsis may
become anemic through multiple mechanisms. They may have preexisting anemia, either from medical causes or from recent surgery. Anemia may be acquired through phlebotomy for laboratory testing, with blood loss from this source averaging about 40 mL per day [56]. Additionally, normal mechanisms of red cell replacement are suppressed in critical illness. There is
a blunted increase in erythropoietin for a given hemoglobin concentration, a phenomenon attributed to the inhibitory effects of proinflammatory cytokines such as interleukin-1\(\beta\) and tumor necrosis factor-\(\alpha\), and by IL-1 and bacterial endotoxin. Acute renal failure, when present, is another contributor. Proliferation and differentiation of erythroid precursors are also inhibited. These effects are compounded by the alteration in iron metabolism, resulting in low concentrations of circulating iron [57].

Blood transfusion, however, is a double-edged sword. On one edge are the benefits of increased oxygen-carrying capacity and increased oncotic pressure from a colloid infusion that stays within the intravascular space. On the other edge are the numerous problems with transfusion: disease transmission, transfusion reactions, immunosuppression, inflammation, use of a limited resource, and cost. Traditional transfusion thresholds have been challenged by recent studies, most notably by the Transfusion Requirements in Critical Care trial [58], which demonstrated no harm from a transfusion threshold of 7 to 9 g/dL compared with a more traditional 10 to 12 g/dL and possible benefit in patients older than 55 and those who had an APACHE II of 25 or lower. Only 6% of patients in the restrictive group and only 4% in the traditional transfusion group were admitted to the ICU with a diagnosis of sepsis, however. In a post-hoc subgroup analysis there was no difference in mortality in patients who had cardiovascular disease using a restrictive transfusion threshold [59]. These results need to be viewed with caution because a significant number of patients screened for the original trial were not enrolled and the population was limited to euvoletic patients.

At this time, in light of evidence that restrictive transfusion thresholds are not harmful and may reduce mortality, transfusions should be limited to patients who have a hemoglobin of less than 7.0 g/dL. Some patients may tolerate an even lower hemoglobin level, whereas others, particularly those who have ongoing myocardial ischemia, will benefit from a higher hemoglobin level[60]. Transfusion for low SvO\(_2\) was performed as part of the study on early goal directed therapy by Rivers and colleagues [11], but this has not been well-studied as an independent intervention. In a small study of 29 patients, transfusion did not result in a statistically significant increase in SvO\(_2\) [61].

One often proposed solution to reduce transfusion needs is recombinant human erythropoietin. It has been widely used in patients who have chronic renal failure, but no studies exist of exogenous erythropoietin use in sepsis. A large trial of erythropoietin in critically ill patients [62], however, of whom 9% had sepsis or systemic inflammatory response syndrome (SIRS), showed a reduction in the likelihood of receiving a transfusion, with an odds ratio of 0.65 for the erythropoietin group. Of those who received blood, the erythropoietin group received a median of one unit, versus two units for the placebo group [62]. Because the effect required at least a week of treatment to be evident, erythropoietin should be reserved for those patients who are not only anemic, but also have an anticipated ICU length of stay of more than 7 days. Practitioners who choose to use erythropoietin should be aware
that a trial of erythropoietin in patients who had metastatic breast cancer was terminated prematurely after 28.5% of patients in the erythropoietin arm developed thrombotic events, compared with no patients in the control arm [63]; however, patients who have metastatic breast cancer have a different thrombotic risk profile than septic patients, so it is unclear how this finding applies to these patients.

**Mechanical ventilation**

The most common site of organ failure in severe sepsis is the respiratory system. Respiratory failure, defined as the need for mechanical ventilation, occurs in 46% of cases of severe sepsis [3]. Mechanical ventilation should be instituted as needed. One of the most common manifestations of organ failure in patients who have sepsis is acute lung injury (ALI). Specific ventilatory strategies have been advocated in the management of ALI and are covered in greater detail in an article elsewhere in this issue.

**Sedation and analgesia**

Patients who have sepsis frequently require analgesia and sedatives, particularly if they are intubated. There are few randomized, controlled trials that provide evidence of superiority of one agent over another. The profiles and side effects of various drugs in concert with the patient’s particular illness, and comorbidities will guide the selection.

Sedation is most often achieved with either propofol or benzodiazepines. Propofol has the benefit of a short duration of action, and is thus a good choice for patients who require short-term sedation or frequent neurological examinations; however, propofol can cause or worsen hypotension because of its myocardial depressant and vasodilatory properties. Among the benzodiazepines, midazolam and lorazepam have shorter half-lives than diazepam, and lorazepam does not have active metabolites. In a randomized, double-blind trial of 64 patients, Swart and coworkers [64] found no difference in the duration of sedation, but cost was lower and patients were sedated at the appropriate level for a higher percentage of time in the lorazepam group compared with the midazolam group. The authors also noted a large interpatient variability in the half-life of midazolam. They postulated this might be caused by variable hepatic function in critically ill patients and part of the mechanism behind the more appropriate sedation levels with lorazepam [64]. Another alternative for sedation is dexmedetomidine, a selective α₂ agonist approved for short-term sedation in adults. It generally does not cause hypotension, but no studies have been published on its use in septic patients.

Analgesia is generally provided by opioids. Fentanyl has a rapid onset and short half-life, although prolonged use may lead to a longer duration of action
because of accumulation of the parent compound. It is useful for short-term use such as painful procedures. Morphine is longer-acting, but may cause hypotension because of histamine release and venodilation. Its metabolites can accumulate in renal failure. Despite these limitations, it is commonly used as a first-line agent and generally works well. Hydromorphone does not have the same hemodynamic effects as morphine, nor does it have active metabolites; therefore it may be beneficial in patients who cannot tolerate morphine. Merperidine has active metabolites that can lead to seizure if they accumulate, and is therefore generally avoided in critically ill patients needing analgesia. Side effects of opioids include depressed levels of consciousness and respiration, and inhibition of gastric and intestinal motility. Acetaminophen has an opioid-sparing effect [65] in addition to its antipyretic effect, and may be given as long as there is no hepatic insufficiency.

Sedation and analgesia should not be given continuously, but rather as boluses, unless large doses are required. In a prospective cohort trial, Kollef and colleagues [66] demonstrated that patients who received bolus sedation or analgesia had significantly shorter duration of mechanical ventilation and ICU and hospital lengths of stay compared with those who received continuous infusions. Patients should have a daily “sedation vacation”; that is, withdrawal of sedative and opiate infusions until the patient is awake or agitated enough to require resumption of the infusions. At this point patient sedation needs should be reassessed, commonly by starting the infusions back at half their previous rate. Kress and coworkers [67] performed a randomized controlled trial of 128 intubated patients, and showed that daily sedation vacations resulted in a decrease in ventilator days from 7.3 to 4.9 and a reduction in ICU length of stay from 9.9 to 6.4 days. In a retrospective blinded chart review of the same study population, Schweickert and colleagues [68] found that overall complications were reduced from 6.2 to 2.8%, likely directly related to the reduction in ventilator and ICU days.

Neuromuscular blockade is occasionally needed in critically ill patients, although indications for its use are not well-defined. It is often used with profound patient-ventilator dyssynchrony or when the patient is unable to oxygenate satisfactorily; however, multiple studies have shown an association between neuromuscular blockade and long-term neuromuscular dysfunction, referred to as critical illness polyneuropathy [69]. Therefore neuromuscular blockade should only be used when there are no other alternatives and maximal use of sedation has been unsuccessful. Sedation and analgesia should be continued and train-of-four monitoring should be used to monitor the degree of blockade. Patients should be maintained with one or two twitches, and patients whose twitches disappear entirely should have the paralytics stopped until twitches return.

**Glycemic control**

Hyperglycemia, defined as a blood sugar more than 110 mg/dL, is seen in over 95% of mechanically ventilated patients in the surgical ICU [49]. This
rise in glucose has been attributed to increased amounts of circulating stress hormones, peripheral insulin resistance, drugs, including steroids, and exogenous dextrose administration. Elevated glucose levels have a number of detrimental effects, including increased leukocyte adhesion to vascular endothelium, and impaired neutrophil chemotaxis and phagocytosis. Hyperglycemia also enhances the procoagulant state of critically ill patients [70].

Tight glycemic control has become an integral part of critical care. It has been shown to improve mortality in a randomized, controlled trial of 1548 surgical patients, the majority of whom were patients admitted following cardiac surgery [49]. ICU mortality was significantly lower (4.3% versus 8.0%) in patients randomized to tight glycemic control (80–110 mg/dL) compared with those who only received insulin after their blood glucose rose above 200 mg/dL. The beneficial effect appeared to be caused by a reduction in the risk of deaths caused by sepsis-induced multiple organ failure. In addition to the mortality benefit, patients randomized to tight glycemic control also had a shorter ICU length of stay (LOS), decreased rate of mechanical ventilatory support lasting longer than 14 days, an attenuated inflammatory response, less antibiotic use, and decreased incidence and duration of critical illness polyneuropathy. Benefits from intensive insulin therapy appear to be related to control of glucose levels and not to the dose of insulin used [71]. In a later study [72], the same investigators found that the effects of tight glycemic control in a medical ICU population were not as profound. This may relate to the higher attributable mortality of sepsis in surgical patients.

Renal failure

Acute renal failure (ARF) occurs in 19% to 50% of patients who have sepsis, and is associated with a mortality of almost 70% [73]. Conversely, almost half of all cases of ARF (defined as urine output less than 200 mL in 12 hours or blood urea nitrogen greater than 84 mg/dL) are associated with septic shock, making it the leading etiology of ARF in the ICU [74]. Estimates of the true incidence are complicated by the lack of a standard definition. In a large epidemiologic study of severe sepsis [75], renal failure was the acute organ system failure most strongly associated with death, with an odds ratio of 3.1.

The etiology of renal failure in sepsis is multifactorial. Tumor necrosis factor appears to cause direct injury [76], but hypovolemia, nephrotoxic drugs, and iodinated contrast for radiographic studies also play roles. Adequate hydration and avoidance of hypotension are the mainstays of prevention of ARF. Low-dose dopamine was long thought to be beneficial to preserving renal function; however, a randomized, double-blind study of 328 patients who had SIRS and early renal dysfunction [77] found no difference in peak serum creatinine, need for renal replacement therapy, or mortality. Although not truly a preventative trial because patients were already
showing signs of renal dysfunction, it does strongly suggest that low-dose dopamine is not beneficial. Norepinephrine and vasopressin have both been shown in small-scale studies to improve urine output and glomerular filtration rate [78].

It is critical to avoid nephrotoxic agents, such as aminoglycosides and intravenous iodicated contrast media. Most nephrotoxic medications have satisfactory alternatives, but there is often no satisfactory alternative for iodicated contrast in septic patients, who often need studies for source identification or evaluation for pulmonary embolism. Iodinated contrast is thought to induce renal failure through direct tubular toxicity, generation of oxygen free radicals, and a reduction of renal blood flow. Patients who have pre-existing renal impairment and those who have diabetes are at highest risk. Hydration is the first line of defense against contrast-induced nephropathy (CIN). Trevedi and colleagues [79] showed that patients randomized to IV normal saline at 1 mg/kg/hr beginning 12 hours before contrast administration for angiography and continuing for 24 hours had a lower rate of CIN than patients randomized to unrestricted oral fluids. The relative risk for the saline group was 0.11. Mueller and coworkers [80] demonstrated that patients randomized to normal saline hydration had lower rates of CIN than those who were hydrated with half normal saline with 5% dextrose (0.9% versus 2%), with an odds ratio of 0.3.

N-acetylcysteine (NAC) has been proposed as a pharmacologic means of preventing CIN because of its free radical scavenging properties, yet trials of NAC in this context have yielded conflicting results. Further, most of the trials enroll patients receiving radiocontrast for angiography (cardiac catheterization). There is a paucity of data addressing the prevention of ARF in patients who have sepsis. In a meta-analysis of 9 trials [81], the relative risk for CIN was 0.51 (95% CI, 0.35 to 0.74) with NAC. NAC is inexpensive, nontoxic, and possibly beneficial; however, the study authors note that renal failure requiring dialysis was rare (0.2%) and that emergent studies requiring IV contrast should not be delayed for administration of NAC [81].

Because free radical formation is enhanced in an acidic environment, bicarbonate infusion has been proposed as protection from CIN. A study of 137 patients who had chronic renal insufficiency [82] randomized to hydration with sodium chloride or sodium bicarbonate before receiving iodicated intravenous contrast demonstrated significant benefit with this approach. Glomerular filtration increased by 8.5% in the bicarbonate group, yet declined by 0.1% in the sodium chloride group. Absolute risk reduction of CIN (defined as >25% increase in creatinine) was 11.9%, yielding a need to treat 8.4 patients to prevent one case of CIN. The study had several methodologic limitations, however, and was not adequately blinded [82].

A full discussion of the advantages and disadvantages of various renal replacement therapies is beyond the scope of this article. Intermittent hemodialysis (IHD) is thought to induce hemodynamic instability because of the large amount of fluid removed in a short time period. Therefore continuous
renal replacement therapy (CRRT), which removes fluid and toxins at a slower rate, is traditionally used in unstable, critically ill patients. A small trial of 27 patients did not show a difference in blood pressure changes or vasopressor requirements for patients on IHD compared to those on CRRT [83], however. Studies comparing outcomes of CRRT and IHD have been limited by methodologic issues and have yielded conflicting results [78]. At this time there is no evidence to suggest that there is a difference in outcomes among the various methods of extracorporeal renal replacement; however, there is a report suggesting that daily hemodialysis results in earlier recovery of renal function in ICU patients when compared with every-other-day hemodialysis [84].

**Stress ulcer prophylaxis**

Clinically significant gastrointestinal bleeding occurs in about 2% of critically ill patients. Risk factors include mechanical ventilation for more than 48 hours and coagulopathy [85], both of which can complicate sepsis. The relative effectiveness of various classes of pharmacologic prophylaxis (H₂ receptor antagonists, proton pump inhibitors, and sucralfate) is controversial. The clinical trials designed to address efficacy have been hampered by varying definitions of end points (any bleeding; clinically significant bleeding) and the use of a placebo or active treatment groups. The largest trial (1200 patients) by Cook and colleagues [86] compared ranitidine and sucralfate in a double-blinded fashion and examined clinically significant GI bleeding as the end point. The risk of bleeding was significantly lower in the ranitidine group (1.7%) versus the sucralfate group (3.8%). The number of critically ill, mechanically ventilated patients who would need to receive ranitidine instead of sucralfate to prevent one gastrointestinal bleed was 48 [86]. A meta-analysis published 2 years later [87] looked at the effectiveness of ranitidine and sucralfate in placebo-controlled trials. Ranitidine was statistically indistinguishable from placebo for the prevention of GI bleeding. There was only one study looking at sucralfate versus placebo for GI bleeding and it did not show a difference [87]. Recently two small trials, one comparing ranitidine to sucralfate to placebo [88], and one comparing famotidine to omeprazole to sucralfate to placebo, found no difference in the rates of gastrointestinal hemorrhage [89]. Also, a historical observational study of over 1400 patients [90] found no difference in clinically significant gastrointestinal hemorrhage before and after the institution of stress ulcer prophylaxis, largely using sucralfate. These studies suggest that the issue of overall efficacy of stress ulcer prophylaxis is not completely resolved, and that a large, placebo-controlled trial with multiple intervention groups is needed. The incidence of clinically significant stress ulcer bleeding is so low, however, that a study to definitively settle the issue is no longer practical.
H₂ receptor antagonists and proton pump inhibitors raise the gastric pH, thus defeating one of the natural mechanisms against bacteria colonization in the upper GI tract. There is concern that using these agents might result in a greater risk of ventilator-associated pneumonia as a result of microaspiration of heavily colonized gastric secretions. The study by Cook and colleagues [86] was adequately powered to detect a 25% reduction in ventilator-associated pneumonia in the sucralfate group, yet no significant difference was identified. The meta-analysis mentioned above [87] examined the risk of pneumonia with ranitidine versus placebo, sucralfate versus placebo, and ranitidine versus sucralfate. In the placebo-controlled studies, neither ranitidine nor sucralfate had an effect on ventilator-associated pneumonia rates, but in head-to-head studies, ranitidine had a higher risk of ventilator-associated pneumonia [87].

Given the available evidence, H₂ receptor antagonist therapy is recommended over sulcalfate in patients meeting high risk criteria for stress ulcer bleeding. If neither is available or can be used, a proton pump inhibitor should be considered. Stress ulcer prophylaxis should be discontinued once patients are receiving enteral feeds, unless they are also receiving steroids.

Long-term outcomes after severe sepsis

There are very few studies of long-term outcomes after sepsis. One study by Granja and colleagues [91] compared 104 patients admitted to the ICU with severe sepsis to 133 ICU patients who did not have sepsis. The study authors looked at health-related quality of life 6 months after ICU discharge. The patients’ health-related quality of life was similar, with the exception of anxiety and depression, which were less prevalent in the patients who had sepsis; however, about half of both groups of patients reported that they had trouble with or were unable to perform their usual activities, suggesting that illness resulting in an ICU stay results in prolonged decline in health status [91].

Other evaluations of long-term outcome following critical illness suggest that older age and increased severity of illness are associated with decreased general health perception and poorer physical functioning [92]. Post-traumatic stress disorder might occur after an episode of critical care, and might be related to the depth of sedation. Specifically, less sedation may be protective because it mitigates the need to fill in a memory void with delusional thoughts [93]. Physical weakness is also a problem. A study by Herridge and coworkers [94] of survivors from ARDS found that patients had proximal muscle weakness and poor physical status at 3 months after discharge. This weakness improved over the first year after discharge but did not return to baseline. Most of the decline in physical status was nonpulmonary. Factors associated with poor physical function were illness acquired during the ICU stay, any corticosteroid treatment during the ICU stay, rate of resolution of the lung injury, and multiorgan dysfunction [94].
As we learn more about how to keep critically ill patients alive, we also need to learn how to maintain the quality of that life in the months and years after they leave our ICUs. Despite the poorer prognosis of elderly patients, many of them are able to return to functional lives, and age should not be used as a reason to withhold treatment [93].

Summary

The incidence of sepsis is increasing, but the case fatality rate is decreasing. Several aspects of care likely contribute to these better outcomes, including:

- Early care
- Provide large amounts of crystalloid intravenous fluids.
- Culture and then start broad-spectrum antibiotics quickly.
- Use pressors as needed to maintain blood pressure. This should be either dopamine or norepinephrine with vasopressin at a fixed dose of 0.04 units/min if high doses are needed. Dobutamine can be added for inotropic support.
- Monitor CVP and administer fluids to maintain a pressure of 8–12 cm H₂O. Monitor superior vena caval oxygen content and transfuse as needed to keep it at 70%.
- Treatment with bicarbonate is not necessary for pH > 7.15.
- Determine the source of infection and obtain source control with the least physiologic stress possible. If no source can be found, assume central lines are the source and remove or replace them at new sites.
- Begin antimicrobial therapy with broad-spectrum antibiotics and narrow coverage once the organisms and sensitivities are determined. Duration of therapy should be 8 days for VAP and 7–10 days for other conditions, with the exact duration determined by the patient’s clinical response. Antifungal therapy should be added if the patient fails to respond or there is clinical suspicion of fungal infection.
- Patients who have hypotension should receive a cosyntropin stimulation test, and if the rise is \( \leq 9 \mu g/dL \), then physiologic stress doses of hydrocortisone should be administered for 7 days.
- Activated protein C should be considered in appropriate patients.
- Red cell transfusions can be withheld until the hemoglobin concentration drops to 7 g/dL, unless the patient has an \( \text{SvO}_2 < 70\% \) (during acute resuscitation) or is experiencing an acute coronary syndrome.
- Sedation and analgesia should be provided through boluses if possible, and a daily sedation vacation should be performed. Neuromuscular blockage should be avoided unless absolutely necessary.
- Maintain blood sugars in the range of 80–110 mg/dL.
- Reduce the risk of renal failure through aggressive hydration and minimization of hypotension. Hydrate patients when they receive iodinated contrast and consider NAC and bicarbonate.
• Stress ulcer prophylaxis should be provided to high-risk patients using H₂-receptor blocking medications or proton pump inhibitors, and should be discontinued once enteral feeds are started.

References


