MAYO CLINIC

Severe Sepsis and Septic Shock: Clinical Overview and Update on Management

Kelly A. Cawcutt, MD, and Steve G. Peters, MD

CME Activity

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Learning Objectives: On completion of reading this article, you should be able to (1) recognize patients with severe sepsis and septic shock to provide appropriate early-goal directed therapy, (2) define treatment goals within the first 6 hours for patients with severe sepsis and septic shock, and (3) describe the management strategies for patients with severe sepsis and septic shock after the completion of early-goal directed therapy (after the first 6 hours).

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Abstract

Sepsis is among the oldest themes in medicine; however, despite modern advances, it remains a leading cause of death in the United States. Every clinician should be able to recognize the signs and symptoms of sepsis, along with early management strategies, to expeditiously provide appropriate care and decrease resultant morbidity and mortality. This review addresses the definitions, pathogenesis, clinical manifestations, management, and outcomes of patients with sepsis, severe sepsis, and septic shock.

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From the College of Medicine, Mayo Clinic, Rochester, MN.

One of the oldest themes in the history of medicine is the syndrome of sepsis, with descriptions dating to Hippocrates. Despite advances in medicine, from germ theory to the advent of modern critical care medicine, sepsis continues to be a leading cause of inpatient expenditures and death in the United States, thus demanding ongoing attention and research.[1,2]

The descriptions and categories of severity of sepsis have evolved over the past 30 years, with the first international consensus panel defining sepsis in the early 1990s.[1,2] This first classification provided the framework for the current clinical practice, research, and education on sepsis, severe sepsis, and septic shock. The definition follows a continuum of variables. *Sepsis* was initially defined as findings of the systemic inflammatory response syndrome in the presence of documented or suspected infection. Features of the systemic inflammatory response syndrome include fever or hypothermia, tachycardia, tachypnea, and leukocytosis. The current definition of sepsis is less specific, defining *sepsis* as suspected or documented infection plus at least 1 systemic manifestation of infection (Table).

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Severe sepsis has been defined as sepsis plus evidence of organ dysfunction (eg, hypotension, oliguria, and metabolic acidosis), and *septic shock* has been defined as sepsis with persistent signs of hypotension despite fluid resuscitation.[1,2]

The incidence of severe sepsis in the United States has been reported as approximately 300 cases per 100,000 population and is increasing. The annual hospital cost for the care of patients with sepsis in the United States has recently been estimated at $14 billion/y.[1,2] The condition is responsible for 2% of hospital admissions, with approximately 50% of these patients requiring the intensive care unit (ICU). Severe sepsis accounts for 10% of all ICU admissions. The rising incidence is postulated to be secondary to the increases in the aging population, the number of patients who are immunocompromised from any cause, and an increasing number of patients undergoing invasive procedures.[2]

Sepsis, severe sepsis, and septic shock may be secondary to either community-acquired, health care–associated or hospital-associated infections. The most common underlying causes are pneumonia, intra-abdominal infections, and urinary tract infections. Etiologic organisms cover the spectrum of pathogens, with bacteria and fungi being predominant. However, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus* species, *Streptococcus pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, species within the *Klebsiella* family, and *Candida* species account for most of the pathogens described.[1,2]

TABLE. Definitions of Systemic Inflammatory Response Syndrome (SIRS), Sepsis, Severe Sepsis, and Septic Shock[1-3]

Term	Criteria
SIRS	Meets 2 of of the following 4: • Temperature >38°C or <36°C • Heart rate >90 beats/min • Respiratory rate >30 breaths/min or arterial CO_2 <32mm Hg White blood cell count >12,000 or <4000 cells/μL or >10% band forms
Sepsis	• 1991 definition: SIRS plus documented or suspected infection Current definition: Documented or suspected infection plus systemic manifestations of infection (any of the SIRS criteria count, in addition other possible manifestations include elevations of procalcitonin, C-reactive protein, hyperglycemia in those without diabetes, altered mental status)
Severe sepsis	Sepsis plus evidence of organ dysfunction • Arterial hypoxemia (PaO_2/FiO_2<300) • Acute oliguria (urine output <0.5 mL/kg per hour for at least 2 h despite adequate fluid resuscitation • Increase in creatinine >0.5 mg/dL • Coagulation abnormalities (INR>1.5, aPTT>60 s, platelets <100,000/μL) • Hepatic dysfunction (elevated bilirubin) • Paralytic ileus • Decreased capillary refill or skin mottling
Septic shock	Sepsis with hypotension refractory to fluid resuscitation or hyperlactatemia. • Refractory hypotension persists despite resuscitation with bolus intravenous fluid of 30 mL/kg • Hyperlactatemia >1 mmol/L

aPTT = activated partial thromboplastin time; INR = international normalized ratio.

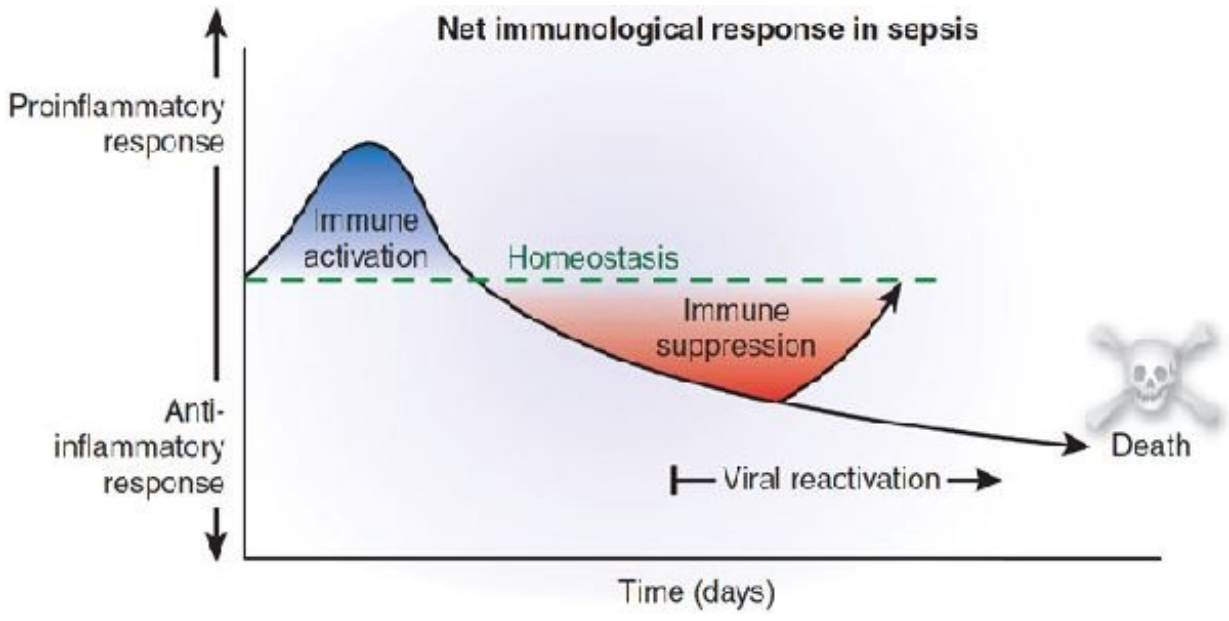
PATHOGENESIS

The pathophysiology of sepsis is complex and multifactorial. A detailed description of these mechanisms is beyond the scope of this review; however, an abbreviated overview is crucial for comprehension.

Infection triggers both proinflammatory and anti-inflammatory processes that ultimately contribute to the clearance of infection and the tissue damage that lead to organ failure.[1,4] In general, the proinflammatory processes are triggered by the infectious agent and are focused on the elimination of the pathogen, whereas the anti-inflammatory processes are triggered by the host to promote tissue repair and healing. An imbalance of these mechanisms may lead to either excess tissue damage (proinflammatory) or immunosuppression and increased susceptibility to secondary infections (anti-inflammatory). The individual patient response is dependent on characteristics of both the host (comorbidities and immunosuppression) and the pathogen (virulence and organism load).[1]

Furthermore, coagulation abnormalities, such as intravascular coagulation and fibrinolysis, result in endothelial dysfunction, microvascular thrombi, and impaired tissue oxygenation. This impairment, combined with the systemic vasodilation and hypotension, causes tissue hypoperfusion and decreased tissue oxygenation, further complicated by impaired mitochondrial oxygen utilization secondary to oxidative stress. These mechanisms result in further tissue damage and ultimately contribute to multiorgan failure.[1,4]

Septic Shock: Readmission Rates Above Average



Most patients now survive a hospital stay for septic shock, although 23 percent of these patients will return to the hospital within 30 days, according to a new study. The number is noticeably higher than the normal readmission rate at a large academic medical centre, researchers reported. The study findings have been published in *Critical Care Medicine*.

Septic shock, the most severe form of sepsis, is the body's response to a severe bacterial bloodstream infection that is often systemic. It can lead to multisystem organ failure and death. "Half of patients diagnosed with sepsis are treated outside of the Intensive Care Unit at their initial admission," said senior author Mark Mikkelsen, MD, MSCE, associate director of the Medical Intensive Care Unit and assistant professor of Pulmonary, Allergy and Critical Care Medicine at the Perelman School of Medicine at the University of Pennsylvania.

Septic shock most often affects patients whose immune systems are already compromised by illnesses such as cardiovascular disease, cancer or advanced age. These patients' immune systems are unable to fight off such a severe infection.

For this study, Mikkelsen and colleagues analysed retrospective data on 269 patients admitted to one of three University of Pennsylvania Health System hospitals with a diagnosis of septic shock who were discharged to a non-hospice setting between 2007 and 2010. Their investigation yielded the following results:

- In 78 percent of cases, the reason for readmission was related to the initial/unresolved sepsis hospitalisation, accounting for 46 percent of all 30-day readmissions.
- Other common complications included new conditions such as cardiovascular illnesses or blood clots.
- One out of six readmissions resulted in death or a transition to hospice.

"Part of what makes these findings so troubling is that so many of these patients return to the hospital after discharge and that frequently these hospitalisations are due to another life-threatening condition," Dr. Mikkelsen said. "We have come so far in understanding how to tame the initial infection that we have minimal understanding of what life is like for these patients once they leave the hospital."

Patients who were readmitted, the researchers observed, were more likely to have been hospitalised within the prior 30 days or to have cancer, cirrhosis, or to have had a prolonged hospital stay. Further examination of these trends and potential prevention strategies, the authors noted, is especially important in light of the potential for Centers for Medicare and Medicaid Services to expand readmission penalties for patients with sepsis in addition to those with heart failure, heart attacks and pneumonia.

"Our hope is that these findings will give a new urgency to the need for better patient education regarding the signs of a recurrent infection and common reasons for readmission in addition to improved discharge planning to keep these patients healthy and from returning to the hospital," Dr. Mikkelsen said.

Penn Medicine, one of the world's leading academic medical centres, consists of the Raymond and Ruth Perelman School of Medicine at the University of Pennsylvania (founded in 1765 as the nation's first medical school) and the University of Pennsylvania Health System.

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CLINICAL FEATURES

The clinical features of severe sepsis vary significantly, depending on multiple factors including host characteristics, site and severity of infection, and time course of sepsis before therapy. Organ dysfunction commonly includes hypotension, acute respiratory distress syndrome, altered mental status, acute kidney injury, ileus, hepatic dysfunction, disseminated intravascular coagulation, adrenal dysfunction, and euthyroid sick syndrome.[1] The cumulative effect of organ dysfunction is the strongest predictor of mortality.[2] For patients surviving beyond early sepsis, immunosuppression increases the risk for secondary infections.[1]

MANAGEMENT

The management of patients with severe sepsis and septic shock has transitioned to protocols, with utilization of "bundles" reported to improve timeliness and quality of care and decrease mortality. The Surviving Sepsis Campaign provided the first consensus on a bundled care process for the management of patients with severe sepsis and septic shock. This has been revised and updated recently.[2,3,5-7] Two main "bundles" are recognized: an early-goal-directed therapy (EGDT) bundle for the first 6 hours and a management protocol used after the first 6 hours of therapy, usually in an ICU.[1,8]

EARLY-GOAL-DIRECTED THERAPY BUNDLE

The goals of the first bundle target resuscitation and mitigating the effects of uncontrolled infection. The landmark study by Rivers et al[8] demonstrated multiple benefits, most notably a survival benefit, with a protocol designed to guide the management of severe sepsis and septic shock. The protocol included specific target values for central venous pressure (CVP), mean arterial pressure (MAP), urine output, central venous oxygen saturation, arterial oxygen saturation, hematocrit, cardiac index, and systemic oxygen consumption.[8] Subsequently, multiple studies analyzed each component of the bundle with a resultant evolution of practice that is represented in the Surviving Sepsis Campaign guidelines.[3,4,7]

Of note, a recently published multicenter study, the Protocolized Care for Early Septic Shock trial, prospectively randomized patients in a 1:1:1 ratio into 1 of 3 groups: a protocol-based EGDT arm; a protocol-based standard therapy (requiring rapid resuscitation but no requirement for initial central line placement, mixed venous oxygen saturation [SvO_2] monitoring, or blood transfusions for a hematocrit <30); and a "usual care" arm in which care was directed by the bedside clinician. In this study, the protocol-based EGDT arm did not show any improvement in short (2-3 months) or long-term (1 year) mortality or need for organ support as compared with the other 2 arms.[9]

One should note that the mortality in all the 3 arms ranged from 18.2% to 21% and this is much lower than historically reported figures for severe sepsis and septic shock. It is very likely that "standard" care has improved and evolved to a great extent since the original publication of the EGDT study. The focus should remain on early fluid resuscitation, timely antibiotic administration, and appropriate use of vasopressors.

Current recommendations and guidelines for the management of sepsis are discussed in the sections that follow. Once a diagnosis of severe sepsis or septic shock is recognized, typically in the emergency department or hospital ward, treatment should start immediately and transfer to an ICU should be considered.

Critical Care Ultrasound

A detailed discussion regarding the utilization and value of critical care ultrasound is beyond the scope of this review. However, it should be noted that bedside ultrasound assessment of critically ill patients allows trained clinicians to rapidly assess volume status and cardiac function; in addition, further evaluations may include assessment of intra-abdominal fluid, pleural effusions, pulmonary edema, and deep vein thrombosis.

Fluid Management

Early administration of intravenous fluids remains the primary focus of the first minutes of therapy for severe sepsis. There has been long-standing debate regarding the choice and appropriate volume of intravenous fluid, with the primary controversy surrounding the use of crystalloids versus colloids. The current guidelines recommend crystalloids as the initial fluid choice, with a minimum initial

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fluid challenge of 30 mL/kg, of which a portion could be albumin.[3]

The Saline versus Albumin Fluid Evaluation study compared resuscitation strategies using 4% albumin and normal saline, with the overall results demonstrating similar outcomes.[10] A recent multicenter randomized study revisited the use of albumin in combination with crystalloids, compared with crystalloids alone, and found no difference in 28- and 90-day survival among patients with severe sepsis.[11] Crystalloids include saline solutions, lactated Ringer's solution, and newer balanced salt solutions. Normal saline, the most commonly used crystalloid, is actually mildly hypertonic and its excessive use has been associated with hyperchloremic (nonanion gap) metabolic acidosis and a tendency toward higher rates of acute kidney injury. The use of lactated Ringer's solution alternating with normal saline is one way to balance these concerns. Other crystalloids, particularly balanced salt solutions, have gained favor in the attempt to decrease adverse effects associated with normal saline.[12] Semisynthetic colloids, such as hydroxyethyl starch, are not recommended for resuscitation because of adverse events including renal failure, coagulopathy, and increased mortality in some studies.[12,13]

Resuscitation utilizing blood transfusions has been stressed in previous studies because of the expectation that increasing erythrocytes and hemoglobin will result in increased oxygen-carrying capacity and improved oxygen delivery. The Rivers EGDT protocol included a hematocrit goal of 30% or more if, after improvement in blood pressure, the SvO_2 remained less than 70%.[8] This recommendation remained in the initial Surviving Sepsis guidelines, but in the absence of evidence that transfusions were truly beneficial, and with increasing evidence for harm secondary to arbitrary transfusion thresholds in other settings, the recommendations have been modified to transfusion for hemoglobin less than 7.0 g/dL (with a goal range of 7.0-9.0 g/dL) unless myocardial ischemia, coronary artery disease, acute hemorrhage, or severe hypoxemia are present.[3,7,14,15]

In summary, there does not appear to be any mortality benefit for colloids over crystalloids in early resuscitation of patients with severe sepsis and septic shock. There is, however, a substantial cost advantage to using crystalloids and these should be the preferred initial resuscitation fluid in most patients. A quantitative and aggressive approach to early fluid resuscitation with a goal of achieving hemodynamic targets and tissue perfusion goals should be the standard of care.

Hemodynamics, Oxygenation, and Tissue Perfusion

Targets of early resuscitation for sepsis include CVP, MAP, SvO_2, and serum lactate. Although measuring the CVP may not be the ideal method for monitoring fluid responsiveness compared with other dynamic variables, it remains a common and useful initial target, with a goal of 8 to 12 mm Hg for nonventilated patients and 12 to 15 mm Hg for those requiring mechanical ventilation.

Given that the CVP may not accurately define volume status, particularly in mechanically ventilated patients with high airway pressures, alternative noninvasive methods of assessing intravascular volume should be considered. A simple method of assessing intravascular volume and fluid responsiveness is with a passive leg raise. Passive leg raise is completed with the patient moved to a supine position with the legs raised to 45° for several minutes while monitoring hemodynamic response for improvement with the increased venous return.[16] Alternatively, clinicians may use dynamic variables such as pulse pressure variation or ultrasound evaluation of the inferior vena cava (IVC). Pulse pressure variation is calculated via arterial line measurements of maximum and minimum pulse pressure during a single respiratory cycle, with increasing variation predicting fluid responsiveness.[17,18] Finally, ultrasound may be used to examine the IVC for collapsibility. A minimally collapsible IVC is associated with euvolemia or hypervolemia, whereas a highly collapsible IVC is associated with hypovolemia.[19]

The typical MAP goal is 65 mmg Hg or more with or without the use of vasopressors. Especially in patients with chronic hypertension or relatively low blood pressure, the MAP should be interpreted in context of other signs of tissue perfusion. Mixed venous oxygen saturation reflects the net balance between oxygen delivery (dependent on arterial oxygen saturation, hemoglobin, and cardiac output) and oxygen consumption by the tissues. A true mixed venous sample is obtained from the right atrium; samples from the subclavian or vena cava typically

show slightly higher saturation. The published targets for adequate venous oxygen saturation are 70% or more for superior vena cava and 65% for right atrial measurements. Mixed venous oxygen saturation can be measured by intermittent samples, or continuously by the use of an oximetric central venous catheter. Pulmonary arterial catheterization and monitoring have not been shown to improve outcomes and may confer some risk.[20] Elevated lactate levels are part of the diagnostic criteria for severe sepsis, and lactate clearance, as a marker of improving tissue perfusion, is another target of early therapy. The ideal is normalization of lactate; however, early improvement of 10% or more to 20% from baseline lactate is associated with mortality benefit similar to an SvO_2 value of 70% or more.[3,21] In light of the mortality benefit of lactate clearance and results of the above-mentioned Protocolized Care for Early Septic Shock trial, the insertion of central venous catheters and rigorous following of serial SvO_2 measurements may not be essential for the early management of severe sepsis. Importantly, strategies to optimize both SvO_2 and lactate clearance may be complementary. Currently, no single measure is clearly superior.

Vasopressors

Norepinephrine is recommended as the first choice for vasopressor use in patients with septic shock.[3] Dopamine had been used widely as a first-line agent, but compared with norepinephrine, it is associated with a higher rate of dysrhythmia. Furthermore, low-dose dopamine for renal protection is not recommended.[3,4,22] If a second vasopressor is needed to maintain MAP, epinephrine or vasopressin would be appropriate. Vasopressin can be added to norepinephrine, but it is not recommended as a single agent. Finally, inotropic agents such as dobutamine may be used if there is evidence for myocardial dysfunction or ongoing hypoperfusion despite fluid resuscitation and initiation of vasopressors.[3]

Treatment of Infection

Rapid treatment of the infection leading to severe sepsis or septic shock is of paramount importance. To target appropriate therapy, clinicians must quickly assess the patient and determine a potential source for the sepsis syndrome. Initial intravenous antimicrobial therapy should have activity (and adequate target tissue penetration) against all likely pathogens and should be given within the first hour after the recognition of severe sepsis or septic shock. Mortality increases for each hour that the patient does not receive adequate antimicrobial therapy.[3,4] Ideally, 2 sets of blood cultures combined with cultures from other potential sources, such as urine, tracheal secretions, or other body fluids, if applicable, should be obtained before the initiation of antimicrobial agents, but only if this can be done without a significant time delay. Furthermore, the source of infection (eg, drainage of abscess) should be controlled aggressively.[1,3]

Corticosteroids

Corticosteroid use for the treatment of sepsis has been a source of great controversy. Early studies of short-course high-dose methylprednisolone showed no evidence of benefit and frequent adverse effects. Other studies have yielded conflicting results, including those utilizing adrenocorticotropic hormone, stimulation testing, and identifying subgroups with "relative adrenal insufficiency." Current guidelines recommend against stimulation testing and advise initiating intravenous corticosteroids (eg, hydrocortisone 200 mg/d) for patients in refractory shock who have remained hemodynamically unstable even after adequate fluid resuscitation and vasopressor use.[3,4,23,24]

Bicarbonate Therapy

There is no strong evidence to support the use of sodium bicarbonate for improving hemodynamics or decreasing vasopressor use in patients with a pH of 7.15 or more; therefore, this therapy is not recommended.[3] Furthermore, temporary and partial correction of metabolic acidosis by bicarbonate might mask the important monitoring of improving acidemia as a sign of improved tissue oxygen delivery.

SUPPLEMENTAL MANAGEMENT

Prophylactic measures to prevent ventilator-associated pneumonia, venous thromboembolism, and stress ulcers have become a standard bundle for critically ill and intubated patients and are appropriately applied to severe sepsis. Components of these bundles are recommended in the Surviving Sepsis guidelines and include elevation of the head of the bed, ventilator-

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weaning protocols, prophylactic anticoagulants and intermittent pneumatic compression devices when possible to prevent venous thromboembolism, and H_2 blocker or proton-pump inhibitor prophylaxis for stress ulcers.[3]

Ventilator Management

Lung-protective ventilation is recommended for patients with severe sepsis or septic shock regardless of whether they have been diagnosed with acute respiratory distress syndrome. A tidal volume of 6 mL/kg ideal body weight should be utilized combined with a goal plateau pressure of <30 cm H_2O and application of positive end-expiratory pressure.[3,4,25]

Antimicrobial Stewardship

The initiation of broad-spectrum, empiric, antimicrobial agents has become a common and appropriate practice given the mortality risk of delay in effective therapy. However, the cost of this practice may be increasing antimicrobial resistance. Infection by resistant organisms prolongs hospital stays and duration of mechanical ventilation, with a less well-defined effect on mortality.[2] Daily assessment is necessary for potential de-escalation or modification of therapy.[3,26,27]

Glycemic Control, Nutrition, and Goals of Care

Glucose control in critically ill patients has evolved significantly as clinical trials produced seemingly discordant results. Early studies showed improved outcomes and fewer complications (especially in surgical patients), with glucose maintained at approximately 80 to 108 mg/dL. The large scale NICE-SUGAR trial found that tight glycemic control was associated with higher 90-day mortality. Current guidelines call for a protocol for glucose monitoring and management with insulin after 2 consecutive blood glucose values of more than 180 mg/dL, with a target level to remain 180 mg/dL or less.[3,28,29]

Early in the course of severe sepsis, consideration of enteral or parenteral nutrition is typically deferred because there is little evidence of benefit, but potential harm, of attempting feeding. After initial resuscitation, enteral feeding may be initiated, if tolerated. Parenteral nutrition should not be provided within the first week and should be avoided if enteral nutrition is possible. Hypocaloric feeding, or underfeeding, is recommended within the first week because there may be an association with improved outcomes, including mortality.[3,30]

Finally, management of any critically ill patient, including those with severe sepsis and septic shock, should include a discussion surrounding the goals of care for the individual patient. Ideally, this conversation should occur as early as possible, but no more than 72 hours into treatment.[3]

OUTCOMES

In recent decades, advances in the management of patients with severe sepsis and septic shock have demonstrated a great reduction in mortality from greater than 80% to approximately 20% to 30%.[1,2] The mortality of patients with septic shock remains the highest, with mortality approaching 50% in some studies.[2] There are many factors affecting outcomes, including the site of infection and the underlying pathogen. Gram-negative organisms and fungal infections are generally associated with a higher mortality than are gram-positive organisms.[2] Despite the improvement in early mortality rates, patients with sepsis remain at an increased risk of death for months to years after hospital discharge. Furthermore, as survival improves, long-term outcomes gain increasing importance and interest. Primary care providers will see sepsis survivors in follow-up and must recognize long-term health outcomes of such patients. Sepsis survivors have demonstrated impaired physical states, neurocognitive dysfunction, and overall lower quality of life. In addition, chronic conditions may worsen, or the patients may present in follow-up with new chronic medical problems such as chronic kidney disease or cardiovascular disease.[1]

CONCLUSION

Sepsis, in all its manifestations, has plagued physicians since the advent of medicine. Despite remarkable advances in the management of such patients, the recognition and timely, appropriate treatment of sepsis, severe sepsis, and septic shock remains of utmost importance. Every clinician should have a basic understanding of the incidence, clinical features, and treatment of sepsis, particularly given the rising incidence and the mortality

benefit of early treatment. Finally, all clinicians need to recognize that the effects of sepsis endure far beyond hospital discharge and therefore, no physician is exempt from understanding sepsis and the subsequent implications it portends for ongoing patient care.

Abbreviations and Acronyms: **CVP** = central venous pressure; **EGDT** = early-goal-directed therapy; **ICU** = intensive care unit; **IVC** = inferior vena cava; **MAP** = mean arterial pressure; **SvO_2** = mixed venous oxygen saturation

Correspondence: Steve G. Peters, MD, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (peters.steve@mayo.edu).

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