Diagnosis and Management of Sepsis

Faculty

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The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher dis-

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Disclosure Statement

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Course Objective

The purpose of this course is to provide healthcare professionals with a current review and updated, evidence-based guidance for the diagnosis and management of sepsis and septic shock. The objective is to address knowledge gaps, enhance clinical skill, and enable effective strategies of collaborative care to improve patient outcomes.

Learning Objectives

Upon completion of this course, you should be able to:

1. Define the various stages of sepsis, and describe the history and incidence of sepsis relative to mortality.

2. Identify risk factors associated with the development and progression of sepsis.

3. Describe the pathogenesis of SIRS, including the five phases of development, and the pathophysiology of sepsis.

4. Anticipate and assess emerging organ dysfunction associated with septic shock.

5. Recognize clinical and laboratory parameters of sepsis, and implement a strategy for antimicrobial therapy and incremental resuscitation that incorporates fluids, inotrope-vasopressors, and the selective use of corticosteroids.

6. List the diagnostic criteria of suspected SIRS in the pediatric patient.

E B
EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION AND DEFINITIONS

Sepsis is a systemic pathophysiologic and clinical syndrome caused by infection and manifest by signs of inflammation, host immune response, and organ dysfunction. The causes of sepsis are myriad, and the scope of illness is broad. Most cases of sepsis syndrome arise from bacterial infection, but certain viral (e.g., Ebola and other hemorrhagic fevers) and fungal (e.g., candidiasis, histoplasmosis) infections induce a sepsis syndrome as well.

Infection may be defined as invasion of normally sterile host tissue by a micro-organism. Clinically, infection is recognized by the constellation of symptoms and signs that result from the host's immune response to an invading micro-organism. Bacteremia is defined as demonstrable evidence (e.g., by culture) of viable bacteria within the general circulation.

Historically, there has been some confusion and a lack of consensus with respect to the various stages of systemic infection and how best to manage patients along the spectrum of illness and complications induced by sepsis. This lack of consensus prompted the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) to convene a conference for the purpose of agreeing on definitions for sepsis and its sequelae. The ACCP/SCCM published their definitions in 1992 [1].

A second task force, international in scope, was convened in 2001. The purpose of this conference (sponsored by the ACCP, SCCM, the European Society of Intensive Care Medicine, the American Thoracic Society, and the Surgical Infection Society) was to modify, where appropriate, the original ACCP/SCCM definitions to reflect current understanding of the pathophysiology of sepsis. Although the signs and symptoms of sepsis were expanded to reflect clinical bedside experience, the task force found insufficient evidence to support alternative definitions of sepsis [2]. This international effort spawned the global Surviving Sepsis Campaign, comprised of 29 sponsoring clinical specialty societies

that convene at regular intervals to review the clinical literature and provide evidence-based guidelines for management of severe sepsis [3; 4].

Task force guidelines redefined sepsis as a systemic inflammatory response arising from known or suspected infection, leading to widespread tissue injury and manifested by two or more of the following conditions [1; 2]:

- Fever (temperature greater than 38.3°C [100.6°F])

- Hypothermia (core temperature less than 36°C [96.8°F])

- Tachycardia (heart rate greater than 90 beats per minute in adults)

- Tachypnea (respiratory rate greater than 20 breaths per minute)

- Altered mental status

- Hyperventilation (partial pressure of carbon dioxide [$PaCO_2$] less than 32 mm Hg)

- Leukocytosis (leukocyte count greater than 12,000 cells per mm^3)

- Leukopenia (leukocyte count less than 4,000 cells per mm^3)

This emphasis on the systemic signs of inflammation as the marker for sepsis requires the recognition that other, noninfectious, pathophysiologic conditions also cause tissue injury and inflammation with systemic ramifications. Systemic inflammatory response syndrome (SIRS) includes any serious, ongoing inflammatory process resulting in end-organ damage and multisystem failure. SIRS encompasses a continuum of escalating inflammatory responses to infectious or noninfectious stimuli; end-organ dysfunction and mortality increase with each stage of the advancing inflammatory process. While sepsis is a common and important form, SIRS may also develop in response to noninfectious insults, including trauma, burns, pancreatitis, anaphylaxis, adrenal insufficiency, pulmonary embolism, myocardial infarction, massive hemorrhage, and cardiopulmonary bypass [1; 5; 6].

Severe sepsis has been defined as sepsis associated with organ dysfunction and tissue hypoperfusion. Signs of tissue hypoperfusion are hypotension (systolic blood pressure <90 mm Hg or a drop in systolic pressure of >40 mm Hg), lactic acidosis, oliguria, and acute alteration in mental status. Organ dysfunction results from falling blood pressure and widespread microvascular injury caused by circulating toxic byproducts of infection and the inflammatory immune response. Common manifestations include acute lung injury, renal failure, disseminated intravascular coagulation (DIC), and laboratory signs of liver dysfunction. In clinical practice, "septic shock" (a subset of sepsis) is present when there is persistent hypotension requiring vasopressor therapy, after adequate fluid resuscitation has been administered [1; 7].

In 2014, the European and American societies of critical care medicine convened a third task force (Sepsis 3) to re-examine current concepts and definitions of sepsis and septic shock based on current understanding of the pathobiology, epidemiology, and management of sepsis. After a synthesis of evidence, the task force determined that previous definitions (as presented by the previous task forces) lacked precision because of excessive focus on inflammation. The task force also concluded that the conceptual model of sepsis invariably following a continuum through severe sepsis to shock is misleading; that the SIRS criteria have inadequate specificity and sensitivity for defining sepsis; and that the term "severe sepsis" is redundant. The Sepsis 3 report, with new consensus definitions for sepsis and septic shock, was published in 2016 [8]. The Sepsis 3 definitions are intended to provide greater clarity and specificity while emphasizing the life-threatening nature of sepsis syndrome. The goal is to achieve greater clinical recognition and consistency in diagnosis, therapy, and clinical investigation of sepsis.

The Sepsis 3 task force emphasized that sepsis is the primary cause of death from infection and thus requires early recognition, urgent attention, and prompt treatment. Following infection, the clinical characteristics of sepsis may emerge gradually over time, shaped by the interplay of pathogen factors and host factors such as genetic determinants, age, comorbidities, and environment. Sepsis is differentiated from infection by the presence of an aberrant or dysregulated host response accompanied by organ dysfunction. Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained acute-onset organ dysfunction should thus raise the possibility of underlying infection. Pre-existing illness, chronic comorbidities, medication, and medical interventions may modify signs and symptoms of sepsis. At times, systemic infection may disrupt critical organ function without generating signs of systemic inflammatory host response [8].

The definition of sepsis is a syndrome defined as life-threatening organ dysfunction caused by dysregulated host immune responses to infection [8]. This new definition emphasizes the loss of adaptive homeostasis in response to infection, the potential lethality of infection when any degree of organ dysfunction is present, and the importance of urgent assessment and prompt treatment. Because even modest organ dysfunction has been found to confer a mortality risk in excess of 10%, sepsis is inherently a serious condition and the term "severe sepsis" is no longer considered useful [8].

The presence and extent of organ dysfunction can be assessed with various scoring systems that rely on clinical and laboratory parameters, such as the following [3; 8; 9]:

- Acute lung injury: A ratio of arterial oxygen tension to fraction of inspired oxygen of 280 or less
- The presence of a metabolic acidosis (e.g., lactate >2 mmol/L)

- Oliguria: Urinary output of less than 0.5 mL/kg body weight/hour for at least two hours in a patient with a urinary catheter in place
- Coagulation abnormalities: International normalized ratio (INR) >1.5
- Thrombocytopenia: Platelet count <100,000 cells/mcL
- Elevated bilirubin: >2 mg/dL
- Acute alteration in mental status

The scoring system currently used in most critical care units is the Sequential Organ Failure Assessment (SOFA) score, which grades abnormality by organ system and accounts for clinical interventions [9]. A higher SOFA score is associated with an increased probability of mortality. Organ dysfunction can be identified by an acute change in SOFA score ≥2 points consequent to the infection [8].

Working from a model derived from a large data base, the task force was able to identify and validate a simple "bedside" clinical measure that can be used to identify which patients with suspected infection are at risk for developing sepsis, referred to as the quick SOFA (qSOFA). This measure consists of three elements [8]:

- Respiratory rate ≥22 per minute
- Altered mentation
- Systolic blood pressure ≤100 mm Hg

Data analysis has demonstrated that patients with infection who are positive for two or more of these elements are likely to have a prolonged intensive care unit (ICU) stay (i.e., three or more days) or die in the hospital. Physicians and nurses can employ the qSOFA in the office, emergency department, or hospital ward to quickly identify which patients with an infection are on the clinical threshold of sepsis and thus at risk of further clinical deterioration. The task force suggests that positive qSOFA criteria be used to prompt clinicians to further investigate for organ dysfunction, to initiate or escalate therapy as appropriate, and to consider referral to critical care [8].

While the data analysis supports the use of qSOFA as a predictor of poor outcomes in patients, no analysis was performed to support the use of qSOFA as a screening tool, and numerous studies since publication of the Sepsis 3 report have yielded contradictory results as to its usefulness. For example, studies have shown that qSOFA is more specific but less sensitive than having two of four SIRS criteria for early identification of infection-induced organ dysfunction. Although the presence of a positive qSOFA can alert the clinician to the possibility of sepsis in all resource settings, the 2021 Surviving Sepsis Campaign guidelines for the management of sepsis and septic shock include a strong recommendation against using qSOFA compared with systemic inflammatory response syndrome (SIRS) criteria, national early warning score (NEWS), or modified early warning score (MEWS) as a single screening tool for sepsis or septic shock [10].

Sepsis 3 defines septic shock as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Within the clinical construct of sepsis, the patient with septic shock can be identified by the presence of the following two criteria [8]:

- Persisting hypotension requiring vasopressors to maintain mean arterial blood pressure (MAP) ≥65 mm Hg

- Blood lactate >2 mmol/L despite adequate volume resuscitation

The hospital mortality rate for patients meeting these criteria is in excess of 40%, or four times greater than for patients with sepsis [8].

EPIDEMIOLOGY AND BURDEN OF SEPSIS

The first description of multiple organ failure appeared in 1973 in a discussion of three patients who died of distal organ failure that followed ruptured aortic aneurysms. Multiple organ failure was subsequently described as multiple, progressive, or sequential systems organ failure. It was noted that shock or infection alone did not cause the distal organ dysfunction. Other severe insults could set in motion an underlying reaction that would lead to widespread endothelial damage, edema resulting from increased vascular permeability, and impaired availability of oxygen [11; 12; 13].

Sepsis, septic shock, and multiple organ failure are major causes of morbidity and mortality in the United States. The Centers for Disease Control and Prevention (CDC) estimates that each year 1.7 million adults develop sepsis, at least 350,000 die as a result of sepsis, and 1 in 3 patients who dies in a hospital has sepsis [14]. Approximately 9.3% of all deaths in the United States can be attributed to sepsis, which equals the number of deaths resulting from myocardial infarction and far exceeds the mortality rates from acquired immune deficiency syndrome (AIDS) or breast cancer. The aggregate hospital cost of care for patients with septicemia totaled nearly $23.7 billion (6.2%) in 2013 [15; 16; 17].

A study of hospital emergency department visits between 1999 and 2005 found that of the 750,000 hospitalizations, more than two-thirds may have initially presented to an emergency department. Cases of suspected sepsis account for more than 570,000 emergency department visits annually. The average length of stay in the emergency department is 4.7 hours. However, more than 20% of patients with sepsis had a length of stay that exceeded six hours, resulting in a substantial burden on facilities nationwide in providing sepsis care [18; 19].

The incidence of septicemia more than doubled between 1993 and 2009, increasing by an annual average of 6% [15]. Between 1993 and 2003, 8.4 million cases of sepsis and 2.4 million cases of severe sepsis were reported; the annual age-adjusted sepsis hospitalization and mortality rates increased from 5.6% to 8.2%, whereas the fatality rate decreased by 1.4% [20]. The percentage of severe sepsis cases among all sepsis cases increased from 25.6% to 43.8% during the same time period [20]. Sepsis is more common among men than women, and the fatality rate is greater in men and nonwhite populations [21].

Prior to 2017, national estimates of sepsis burden relied on the use of administrative codes, which demonstrated increasing incidence and decreasing mortality [22]. However, studies have demonstrated that coding for sepsis has steadily increased over the past decade, while coding for the most common underlying infections has been stable or decreasing. These analyses suggested that code-based case identification might be unreliable for surveillance purposes because of coding practice biases and changes in diagnosis over time [22]. In order to improve hospital surveillance of sepsis, the CDC developed a case definition based on objective clinical data elements conceptually analogous to Sepsis-3 and optimized for surveillance directly from electronic health records [22]. An analysis of data from 409 participating hospitals showed that sepsis was present in 6% of adult hospitalizations, and neither the incidence of sepsis nor the combined outcome of death or discharge to hospice changed significantly between 2009 and 2014 [23].

The reported incidence rates of sepsis increase with advanced age. Two-thirds of all sepsis cases occur in people 65 years of age and older, with case fatality rates as high as 40% [16]. In a study of the burden of sepsis among Medicare recipients for the period 2012 to 2018, six-month mortality rates remained high for septic shock (60%), severe sepsis (36%), sepsis attributed to a specific organism (31%), and unspecified sepsis (27%) [24]. In the same period,

the estimated annual cost of sepsis care (inpatient and subsequent skilled nursing facility) for all Medicare patients increased from $27.7 to $41.5 billion.

Mortality from sepsis of gram-negative etiology is the cause of 20% to 50% of the overall total number of septic deaths. The figures are now similar for sepsis of gram-positive etiology [25]. Mortality has been reported as high as 60% in patients with underlying medical problems. Among patients who develop the complications of shock and organ failure, mortality can reach 90% [26]. Extent of organ failure contributes to the prognosis, with a greater survival rate in patients with fewer than three failing organs. The risk of death increases as each organ fails [26].

Sepsis is among the leading causes of hospitalization and ranks as the most expensive inpatient conditions treated in U.S. hospitals [15; 27]. Hospitalized patients with sepsis include those with community-onset infection/sepsis and those with hospital-onset sepsis. Data from the 2008 National Hospital Discharge Survey show that the rate of hospitalization for sepsis increased from 11.8 to 24 per 10,000 population during the period 2000 through 2008 [27]. Compared with other conditions, the hospital stay for sepsis was 75% longer and the likelihood of dying during hospitalization was eight times higher. In a large cohort study of 2.2 million adult patients hospitalized in 2009–2015, hospital-onset sepsis complicated 1 in 200 hospitalizations and accounted for 1 in 8 sepsis cases [28]. Patients with hospital-onset sepsis had more comorbidities, longer hospital length of stay, and higher risk of death (33% vs 17%) than patients with community-onset sepsis. Among patients admitted without sepsis, hospital-onset sepsis tripled the risk of dying in the hospital. The estimated annual cost of hospitalization for sepsis and septicemia in 2013 was $14.6 billion and increasing at the rate of 11.9% each year [15; 27].

Despite immense clinical effort and high treatment expenditures, mortality rates remain high. Those who survive often sustain permanent organ damage, some degree of physical disability, and long-term cognitive impairment [29].

RISK FACTORS AND PREVENTION

The risk of sepsis complicating an infection is determined by virulence of the pathogen and host factors that increase susceptibility and/or impede host defense mechanisms. Factors considered important in the development of sepsis include: recent use of broad-spectrum antibiotics; immunosuppressive drugs, such as cancer chemotherapy; invasive procedures; organ transplantation; burns or other trauma; anatomic obstruction; intestinal ulceration; extremes of age; and progressive clinical conditions, such as malignancy, diabetes, or AIDS [30].

To the extent that a patient seeks medical care at an early stage of infection, risk factors for sepsis might also include how well the healthcare provider has recognized the nature of the clinical issue and taken into account the patient's vulnerabilities. In a retrospective cohort study involving 46,000 hospitalized patients with sepsis in two large healthcare delivery systems, half the patients had outpatient clinical encounters in the week prior to hospitalization and one-third were diagnosed with an acute infection [31]. Outpatient primary care and subspecialty providers play an important role in identifying patients who are at risk for sepsis and in need of close follow-up.

The majority of infections that progress to sepsis begin outside of hospitals; however, as noted, most patients with sepsis have had recent encounters with the healthcare system even before becoming ill. Using a data set from the CDC Emerging Infections Program, a retrospective cohort study was designed to identify patient characteristics and risk factors for sepsis. Among 1,078 adult patients hospitalized with sepsis across 10 states, the median age was 64 years and 973 (90%) were classified as community-onset sepsis [32]. Of the total, 654 patients (60.7%) had healthcare exposures before hospital admission for sepsis and 447 (41,5%) had received medical treatment (e.g., antimicrobial drugs, chemotherapy, wound care, dialysis, surgery) in the 30 days prior

to admission. An etiologic diagnosis for sepsis was established in 57% of cases; the most common pathogens identified were *Escherichia coli*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*. Controlling for other factors, the 30-day mortality was significantly higher in patients with cirrhosis, immunosuppression, and vascular disease. These findings indicate that most adult patients with sepsis have health facility exposures or medical treatment in the weeks before hospital admission for sepsis, encounters that may offer opportunities to intervene in ways that alter the disease course for patients at risk of severe outcomes [32].

Healthcare-associated infections are a major cause of sepsis among severely ill patients. Increased risk of nosocomial infection is associated with the presence of underlying chronic disease, alteration in host defenses, prolonged hospital stay, and the presence of invasive catheters or monitoring devices [33]. Pulmonary, urinary tract, gastrointestinal, and wound infections predominate [30; 34; 35]. In hospitalized adult patients, the etiology of sepsis has shifted from being predominantly gram-negative nosocomial infections (*Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., and *Pseudomonas aeruginosa*) to gram-positive infections (*Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*). The incidence of sepsis caused by gram-positive infections has increased by 26.3% per year over the last three decades [36]. As of 2024, however, the rates of sepsis and septic shock due to gram-positive organisms are rising again because of the more frequent use of invasive procedures and lines in critically ill patients. As a result, gram-positive and gram-negative micro-organisms are now about equally likely to be causative pathogens in septic shock [30]. Multidrug-resistant pathogens, such as *S. aureus*, now account for more than half of all sepsis cases. *S. aureus* is singly responsible for 40% of ventilator-associated pneumonia episodes and most cases of nosocomial pneumonia [36; 37]. Group B streptococcus is a leading cause of neonatal sepsis in the United States [38].

Vascular and monitoring catheters and infusion sets may become contaminated and lead to the development of nosocomial infections and sepsis. The risk of catheter-related sepsis is increased when the IV catheter is placed in a central vein, particularly if the catheter remains in place longer than three to five days or if the catheter is used for blood sampling [39]. For this reason, consideration should be given to changing the catheter and possibly the insertion site after 72 hours. The risk of contamination of arterial catheters is higher than that observed with venous catheters. Contamination can occur if the system is entered frequently for blood sampling, if the infusate remains in place for more than 48 hours, or if inflammation develops near the catheterized artery [40]. Urinary catheters left in the bladder longer than two weeks often cause infection. Therefore, increased surveillance for signs of urinary tract infections when catheters remain in place beyond a few days is necessary [41].

Central venous catheters (CVCs) are increasingly used in the pediatric population, leading to an increase in CVC-related complications. Implanted ports may be the device of choice when long indwelling times are expected, with consideration given to the patient's age and need for sedation and analgesia during the insertion procedure. Radiograph following the insertion procedure is recommended to ensure correct catheter positioning. Full sterile barrier precautions, strict protocols for catheter care, and prompt removal of the catheter when it is no longer needed are recommended to prevent infectious complications [42].

Bacterial contamination of platelet units (estimated at 1 in 1,000–3,000) results in many occurrences of transfusion-associated sepsis in the United States each year. In 2004, the AABB (formerly the American Association of Blood Banks) adopted a standard requiring member blood banks and transfusion services to implement detection measures and limit bacterial contamination in all platelet components [43].

Patients who live with malignancy are commonly hospitalized due to infection. Immunosuppresive treatments (or the malignancy itself) can lead to severe infection, which is a frequent cause of death among cancer patients. One in six patients with sepsis has underlying disease [44].

PATHOGENESIS OF SIRS

The natural defense of the body to an infection, or other assault, involves a number of cellular and humoral factors. They include B and T lymphocytes, macrophages, neutrophils, platelets, tumor necrosis factor (TNF), interleukins, the coagulation factors, and probably several other products [45; 46; 47]. There are five rather distinct phases that describe how these biologic products work together to overcome the assault and, paradoxically, how they can interact to cause SIRS and potentially lead to critical organ failure [45; 48].

FIRST PHASE: THE LOCAL RESPONSE

An infection, injury, burn, or similar process can initiate a response that causes the release of various proinflammatory mediators in the immediate area of involvement. Among others, these include the cytokines, eicosanoids, and platelet-activating factors. In an attempt to limit or ameliorate the local injury, these mediators act to remove damaged tissue, stimulate new tissue growth, and combat the spread of neoplastic cells, pathogenic organisms, and antigens. To counteract the effects of these mediators and prevent them from causing damage, the body soon produces a set of anti-inflammatory substances, such as interleukins and TNF receptors [45; 48].

SECOND PHASE: THE EARLY SYSTEMIC RESPONSE

If the initial injury or insult is severe enough, the proinflammatory and anti-inflammatory mediators can appear in the systemic circulation. This may occur by direct entry into the bloodstream in the case of massive trauma, by spillover from the local site in the event of a severe infection, or by other

means. The presence of these mediators in the general circulation is a sign that the local region is incapable of handling the situation and that assistance is needed. The proinflammatory response brings additional neutrophils, platelets, lymphocytes, coagulation factors, and other materials to the local site. This should eventually lead to a compensatory anti-inflammatory response that down regulates and controls the proinflammatory actions. In the typical situation, this will occur and no significant untoward effects are seen [45].

THIRD PHASE: PROINFLAMMATORY EXCESS

In some patients, control of the proinflammatory process fails to develop, resulting in a systemic reaction that produces tachycardia, abnormal body temperature, and, in time, hypotension. These are the early signs of SIRS and are thought to be due to: increased microvascular permeability with transudation into organs; platelet sludging, causing capillary blockage and ischemia; reperfusion injury; dysregulation of vasodilatory and vasoconstrictive mechanisms; and maldistribution of blood flow. Persistent hypotension and shock may supervene unless homeostasis is restored, leading to organ dysfunction or organ failure. In an acutely ill patient, altered function in more than one major organ constitutes multiple organ dysfunction syndrome (MODS). While emphasis has been placed on the role of the proinflammatory state in SIRS, an important alternative mechanism may involve an imbalance in the amount or effectiveness of proinflammatory and anti-inflammatory mediators [45].

FOURTH PHASE: EXCESSIVE IMMUNOSUPPRESSIVE RESPONSE

In some patients who survive an initial massive infection or other inflammatory process, there may be a compensatory, but excessive, anti-inflammatory response that results in immunosuppression [49]. This may explain the increased susceptibility to infection in patients with severe burns, trauma, hemorrhage, or pancreatitis. The process is thought to involve impaired monocyte function, altered T- and B-cell activity, diminished proinflammatory cytokines, and several other factors. This process can be self-limiting, and the immunosuppression can resolve without further consequences. If it does not resolve, patients may experience the final, life-threatening complication of MODS [45].

FIFTH PHASE: TRANSITION TO MODS

This phase indicates that there has been an overwhelming, dysregulated host response to the biologic insult. It can take varied forms, depending on the character and severity of critical organ failure. The progression to MODS is common in patients with late-stage SIRS and carries a high mortality risk. If the immune system cannot recover, organ failure and death may follow. In another group of patients, there may be an oscillating effect, with periods of severe inflammation, immunosuppression, and then another proinflammatory response, resulting in increased mortality rates. This has been seen in patients with severe burns, whose levels of cytokines fluctuate widely for several weeks after injury [45; 47].

The nature of the insult can significantly affect the degree of local inflammation and tissue injury. The balance between the expression of pro- and anti-inflammatory mediators often determines the magnitude of early tissue injury and risk of subsequent infectious complications. High levels of the proinflammatory mediators can initiate remote organ injury as a result of organ cross talk. Organ failure and death will occur in patients in phase five unless homeostasis can be maintained and there is a balance between pro- and anti-inflammatory forces [45; 50; 51].

PATHOPHYSIOLOGY OF SEPSIS

A complex, dynamic, and bidirectional interaction occurs between pathogens and the body's immune defense mechanisms during the course of invasive infection. If the defenses are breached successfully, the result can be sepsis [26].

When the etiology of sepsis began to shift from a predominance of gram-negative bacteria to a predominance of gram-positive, drug-resistant bacteria, it led to a re-evaluation of basic assumptions about the pathogenesis of sepsis (e.g., there may or may not be differences in the host response to gram-negative organisms compared with the response to gram-positive organisms) [52; 53]. It is important to note that discrimination between gram-negative and gram-positive organisms is based on the recovery of specific pathogens from blood or the presumed site of infection rather than from any specific immunologic criterion. In 30% to 50% of sepsis cases, the inciting organism is not identified [25; 30; 37].

MICROBE RECOGNITION

The innate immune system recognizes invading pathogens and initiates an inflammatory or septic response. Gram-positive and gram-negative bacteria activate the immune response through unique cellular constituents referred to as pattern-associated molecular patterns (PAMPs) or microbial-associated molecular patterns (because they are also common in nonpathogenic bacteria). PAMPs bind to immune system receptors called pattern recognition receptors (PRRs), which are expressed on the surface of host cells. PRRs are essential for initiating the host's immune response and regulating the adaptive immune response to infection or tissue injury, yet PRRs can also contribute to harmful systemic inflammation and tissue damage in organs [7; 37].

Toll-like receptors (TLRs) are the most common class of PRRs. Each of the known TLRs has unique binding properties that allow for the differentiation between gram-negative and gram-positive bacteria. When the TLR system recognizes a pathogen, a response is generated that is both generalized (similar response to dissimilar stimuli) and specific (pathogen is recognized by multiple TLRs simultaneously). The result is an immune system response that is tailored to the pathogen [37; 54]. The degree to which TLRs mediate the outcome of sepsis in individual patients is not yet fully understood [7].

TLRs can detect danger signals both inside and outside the cell [37]. TLRs induce the production of inflammasomes (multiprotein complexes) in response to the products of bacteria and damaged cells. This in turn activates caspase-1, which is important in the process of inflammation and apoptosis (a counter-regulator of the initial inflammatory response in sepsis). Caspase-1 activation is considered to be a prerequisite for an adequate immune response. Like other proinflammatory products, caspase-1 can have both positive and negative effects on the course and outcome of sepsis [7].

Nod-like receptors (NLRs) are a less well understood class of PRRs. NLRs can detect danger elements (e.g., microbial motifs, live bacteria, host-derived molecules) inside the cell [37].

ENDOTOXINS AND OTHER BACTERIAL TOXINS

Endotoxin was identified more than 100 years ago, but its potential role in the development of sepsis was not identified until 1951. Experimental studies using endotoxin reproduced some of the features of septic shock in animals, but they did not represent the features of septic shock characteristic to humans. Evidence that endotoxin might play a pathogenic role in humans was discovered accidentally in 1991. It is now understood that lipopolysaccharide (LPS) or endotoxin plays a pivotal role in the pathogenesis of sepsis [55]. LPS is the major cell wall component of gram-negative bacteria. LPS is able to activate the host defense system through interaction with TLR4, thus triggering pro-inflammatory mechanisms. A large amount of LPS induces inappropriate activation of the immune system, triggering an exaggerated inflammatory response and consequent extensive organ injury, providing the basis of sepsis damage [55]. Endotoxin is often found in the blood of critically ill patients, making its measurement of limited diagnostic value. In addition, other bacterial toxins (e.g., gram-positive peptidoglycans) can induce the production of mediators associated with sepsis [25].

COAGULATION SYSTEM

The coagulation system plays an important role in the sepsis-induced inflammatory cascade. Coagulation is the inflammatory reaction to tissue injury and is activated independent of the type of microbe (e.g., gram-positive and gram-negative bacteria, viruses, fungi, or parasites). Coagulation contributes to the outcome in sepsis by down-regulating fibrinolysis and the anticoagulant systems. The collaboration between clotting and inflammation, which works to wall off damaged and infected tissues, is an important host survival strategy. Coagulation induced by inflammation can in turn contribute to further inflammation. A key to determining survival in sepsis is to limit the damage while retaining the benefits of localized clotting and controlled clearance of pathogens [7; 56; 57].

A continuum of coagulopathy in sepsis has been suggested, extending from the appearance of coagulation abnormalities prior to the onset of any clinical signs of sepsis to consumption of anticoagulant proteins and suppression of the fibrinolytic system. Depletion of anticoagulant and fibrinolytic factors contributes to the microvascular deposition of fibrin that is associated with organ dysfunction. Coagulation abnormalities in sepsis contribute significantly to organ dysfunction and death [7; 56; 58].

MANIFESTATIONS OF SEPSIS

Any patient with sepsis who has evidence of dysfunction in one organ in the absence of an obvious cause such as traumatic injury may have incipient dysfunction of other organs. The manifestations of sepsis may be seen in the cardiovascular, pulmonary, central nervous, renal, gastrointestinal, and hematologic systems of the body (most frequently in the lungs and circulatory system) [26].

The following signs and symptoms should not be thought of merely as the manifestations of sepsis but as clear evidence that MODS may be developing. The host response may be more important in the genesis of MODS than the specific bacterium, virus, or traumatic injury. In most patients, the extent of systemic changes corresponds to the extent of shock [26; 59; 60].

CARDIOVASCULAR

In addition to hypotension, a variety of other cardiovascular manifestations may be seen. Tachycardia is common. In addition, the left and right ventricles are dilated, ejection fractions are often depressed, and the Frank-Starling and diastolic pressure-volume relationships are altered [30].

Before the onset of shock, the patient's condition is usually hyperdynamic. The skin is warm and flushed, pulse volume is increased, and pulse pressure is wide. Cardiac output is typically elevated, and systemic vascular resistance (SVR) is usually decreased. Despite the increase in cardiac output, serum lactate levels are often elevated. Anaerobic metabolism occurs because of inadequate nutrient blood flow [30].

As shock sets in, SVR drops precipitously, although cardiac output continues to increase. In the later phases of shock cardiac output declines, which exacerbates the effects of hypoperfusion and allows lactate to accumulate. The decrease in cardiac output can result in a subsequent elevation of the SVR [30].

PULMONARY

Tachypnea, with a respiratory rate of more than 20 breaths per minute, is often the earliest pulmonary sign of sepsis, occurring before hypoxemia. Hypoxemia is usually present, although it may be masked by hyperventilation. The cause of hypoxemia is usually ventilation-perfusion mismatch.

As sepsis continues, marked respiratory alkalosis often ensues; $PaCO_2$ may be 30 mm Hg or less. The hypoxemia progresses rapidly. The result is often pulmonary edema and respiratory failure. Other pulmonary manifestations of sepsis include respiratory muscle dysfunction and bronchoconstriction. The onset of either acute respiratory distress syndrome (ARDS) or persistent pulmonary hypertension is an ominous sign [59; 60; 61].

CENTRAL NERVOUS SYSTEM

Altered mental status may be the most common and most overlooked manifestation of sepsis. This causes elderly patients to be at particularly high risk. Early changes include withdrawal, confusion, irritability, or agitation. In patients with severe infection, one may see disorientation, lethargy, seizures, or frank obtundation [61; 62].

Eventually, symptoms and signs of encephalopathy, including nonfocal neurologic manifestations, may be seen, and some patients may become comatose. In addition, evidence of polyneuropathy, including impaired deep tendon reflexes, muscle weakness, and wasting, may be present [59; 60; 61].

Patients with sepsis and encephalopathy are more likely to be bacteremic and have concomitant renal and hepatic dysfunction than are patients with sepsis and normal mental status. Furthermore, the risk of death increases as the encephalopathy worsens [62].

RENAL

The renal manifestations of sepsis include oliguria and azotemia. Urinary sediment may contain red blood cells, casts, and protein. The urinary excretion of sodium may be markedly reduced (less than 20 mEq/L), and urinary osmolality may be increased (greater than 450 mOsm/kg). Protracted oliguria may reflect acute tubular necrosis, often reversible, or diffuse microvascular injury, often resulting in fixed renal failure [59; 60].

GASTROINTESTINAL

Impaired motility is the most common gastrointestinal problem. Often, this manifests as abnormal gastric emptying or as a dynamic ileus. Stress ulceration is another common problem, although it may be seen less often now than in the past. There is some evidence that stress ulcers are less likely to develop when patients are given adequate fluid resuscitation, although this has not been proven conclusively [30; 63].

HEPATIC

Large but transient elevations in serum transaminase levels may follow an episode of severe shock or hypoxemia. Less severe increases, often in association with mild-to-moderate hyperbilirubinemia, suggest focal hepatic necrosis. Acute kidney injury often accompanies sepsis [30]. In the final states of sepsis, patients may have evidence of frank hepatic insufficiency, including hypoprothrombinemia, jaundice, lactic acidosis, and hypoglycemia [2; 60; 61].

HEMATOLOGIC

Leukocytosis, usually accompanied by a shift to the left (>10% immature cells), is the most common hematologic manifestation of sepsis. Multifactorial anemia is common in late-stage sepsis. Decreased maturity and/or survival of red blood cells may contribute to anemia. Thrombocytopenia and coagulation abnormalities (elevated prothrombin or partial thromboplastin times) are often seen in sepsis. Thrombocytopenia is more common than overt DIC in sepsis. DIC is a manifestation of advanced-stage sepsis and carries a poor prognosis [2; 36; 60; 64; 65].

DIAGNOSIS AND MANAGEMENT

Methods to identify critically ill patients who are likely to die as a result of sepsis have become clearer, and increased awareness that sepsis is more common and lethal than previously understood has helped to promote the development of an organized approach to care. While the early diagnosis of sepsis continues to be a challenge (primarily because a rapid, sensitive, and specific diagnostic test is lacking), research indicates that improvements in outcomes are possible when treatment protocols are applied in a timely manner [58].

As discussed, an international consortium of critical care specialty societies has worked to standardize the definition and clinical parameters of sepsis and to develop evidence-based guidelines for optimal management of sepsis and septic shock. This is an

ongoing effort, the goal of which is to improve care and reduce mortality worldwide. Clinical care guidelines have been developed by the Surviving Sepsis Campaign and published by the Society of Critical Care Medicine (SCCM) in 2008, 2013, 2016, and 2021. Detailed management strategies are provided for rapid diagnostic evaluation and antimicrobial treatment, fluid resuscitation, and the use of vasopressors in septic shock [3; 4; 10]. Initial funding of the Surviving Sepsis Campaign was provided by the SCCM. The ongoing work and the campaign's guidelines have no direct or indirect connection to industry support. The 2021 international guideline for the management of sepsis and septic shock are available online at https://www.sccm.org/Surviving-SepsisCampaign/Home [10]. The 2021 guideline recommendations are graded for strength ("strong" or "weak") and for quality of evidence.

MANAGEMENT OF SEPSIS

Fluid Resuscitation and Diagnosis

The SCCM guideline emphasizes that sepsis and septic shock are medical emergencies; treatment and resuscitation should begin immediately upon recognition. Intravenous fluid resuscitation of a patient with sepsis-induced shock (defined as tissue hypoperfusion) should be initiated as soon as the hypoperfusion is recognized (i.e., not delayed pending admission to an ICU).

The principal recommendations for fluid resuscitation are [10]:

- Crystalloids should be used as first-line fluid for resuscitation for adults with sepsis or septic shock (grade strong, moderate-quality evidence).

- In the setting of sepsis-induced hypoperfusion, at least 30 mL/kg of intravenous crystalloid fluid should be given within the first three hours (grade weak, low-quality evidence).

- It is suggested that albumin be added when patients require substantial amounts of crystalloids (grade weak, moderate-quality evidence).

- Fluid resuscitation should initially target a MAP of 65 mm Hg in patients with septic shock requiring vasopressors (grade strong, moderate-quality evidence).

E B

EVIDENCE-BASED
PRACTICE
RECOMMENDATION

The Society for Critical Care Medicine recommends that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first three hours.

(https://journals.lww.com/ccmjournal/Fulltext/2017/03000/Surviving_Sepsis_Campaign___International.15.aspx. Last accessed May 20, 2024.)

Strength of Recommendation/Level of Evidence: Strong recommendation, low quality of evidence

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It is recommended that, following initial fluid resuscitation, additional fluid administration be guided by frequent reassessment of hemodynamic status. A reasonable set of treatment goals suggested for the first six hours of resuscitation are [4; 10]:

- Central venous pressure of at least 8 mm Hg (12 mm Hg in mechanically ventilated patients)

- MAP of 65 mm Hg or greater

- Urine output of 0.5 mL/kg/hour or greater

- Central venous or mixed venous oxygen saturation of at least 70% or 65%, respectively

Antibiotic Therapy and Source Control

The SCCM recommends obtaining appropriate cultures before beginning antimicrobial therapy, but the process of doing so should not delay antibiotic administration. At least two sets (aerobic and anaerobic) of blood cultures should be obtained, including one drawn through any indwelling vascular catheter or device in place prior to onset of infection. Cultures from other suspected sites should be obtained as well. The guideline committee also recommends that imaging studies be performed to confirm the source of infection, assuming the patient's condition allows it [3; 4; 10].

Intravenous antimicrobial therapy should be started as early as possible, ideally within the first hour of recognition of sepsis or septic shock (grade strong, moderate-quality evidence). Clinical studies have shown that delay in antimicrobial therapy for serious infection and sepsis prolongs morbidity, lengthens hospital stay, and increases mortality [66]. A retrospective cohort study involving 2,731 patients with sepsis showed that initiation of antimicrobial therapy within the first hour of documented hypotension was associated with increased survival to discharge. Moreover, each hour of delay conferred an approximately 12% decreased probability of survival [67].

The initial choice of antibiotics will depend on the most likely pathogens associated with the source of infection as well as the prevalent micro-organisms in the local community and hospitals. The clinician should assess risk factors for multidrug-resistant pathogens, including prior hospitalization, health facility residence, recent antimicrobial use, and evidence of prior infection with resistant organism. The anticipated susceptibility profile of prevalent local pathogens and the ability of the antibiotic to penetrate to the source of the infection must also be considered. A combination of drugs with activity against all likely pathogens should be administered initially, but the regimen should be reassessed in light of culture results, the goal being to identify a single, narrow-spectrum antibiotic that will best control the infection [63; 68]. It has been found that combining an extended-spectrum beta-lactam antibiotic (e.g., penicillins, cephalosporins) with an aminoglycoside (e.g., gentamicin) was no more effective in reducing mortality than using the beta-lactam agent alone. In addition, the combination carries an increased risk of renal damage [63; 68]. A common approach is to initiate empiric therapy with a carbapenem or extended-spectrum penicillin/beta-lactamase inhibitor (e.g., ticarcillin/tazobactam) to cover gram-negative enteric bacilli and *Pseudomonas*, often in combination with vancomycin to cover *S. aureus* pending culture results.

The empirical antimicrobial regimen should be narrowed as soon as the pathogen has been identified and sensitivities are known. The duration of therapy will depend on the nature of the infection and other considerations specific to a given case. As a general rule, a 5- to 8-day course of bactericidal antimicrobial therapy is considered adequate for most serious infections associated with sepsis [10]. In the event that the syndrome is due to something other than an infectious cause, such as trauma, antibiotics should be discontinued as soon as possible.

Source control requires that a specific anatomic diagnosis of infection (e.g., skin/soft tissue infection, pyelonephritis, cholangitis, peritonitis) be identified, or excluded, as soon as possible and preferably within the first six hours after presentation. Radiographic imaging is often necessary and should be undertaken promptly as soon as the patient's condition permits and antimicrobial therapy has been administered. Source control may be achieved by percutaneous drainage of an infected cyst or abscess, debridement of infected tissue, or removal of an infected device or catheter (removal should be prompt after other vascular access has been established) [10; 63]. If necessary, surgical exploration and drainage should be undertaken within 12 hours of diagnosis (grade strong, low-quality evidence) [4].

Vasopressors and Inotropic Therapy

If hypotension persists after intravascular volume repletion, then vasopressors may be required to restore and maintain adequate blood pressure and tissue perfusion (goal MAP ≥65 mg Hg). Such patients are considered to have the combination of vasodilation and reduced cardiac contractility, a condition best managed with a combined inotrope-vasopressor agent. In order to monitor arterial pressure accurately, it is suggested that all patients requiring vasopressors have an arterial catheter placed as soon as practical, if resources are available [10].

Historically, norepinephrine, dopamine, and epinephrine were three inotrope-vasopressor used to correct hypotension in septic shock [63]. Based on comparison studies and a meta-analysis of six randomized trials, norepinephrine is considered superior to dopamine and is now the recommended first choice for vasopressor therapy in septic shock (grade strong, high-quality evidence) [4; 10; 69]. In settings where norepinephrine is not available, epinephrine or dopamine can be used as an alternative. Special attention should be given to patients at risk for arrhythmias when using dopamine and epinephrine [10]. For adults with septic shock on norepinephrine with inadequate MAP levels, vasopressin should be added instead of escalating the dose of norepinephrine (grade weak, moderate-quality evidence) [10]. If combination therapy is not effective, epinephrine may be added. For patient safety and effectiveness, intravenous vasopressor therapy should be administered via a central venous catheter.

As an alternative second drug, or to decrease the required effective dose of norepinephrine, vasopressin (up to 0.03 units/minute) may be added to norepinephrine [3; 4; 10]. Vasopressin should not be administered as the initial agent in septic shock.

Phenylephrine is a pure vasopressor that may be used in very select cases of septic shock [3; 4]. It reduces cardiac stroke volume, which can have deleterious effects in the patient with low cardiac output, and thus is not recommended as initial or additive therapy. Phenylephrine is reserved for the unusual case in which tachyarrhythmia limits norepinephrine use or the patient has known high cardiac output. Intravenous phenylephrine should be administered only by properly trained individuals familiar with its use [63; 70; 71].

Inotropic therapy may involve the use of dobutamine if the cardiac output remains low. If dobutamine is used, it should be combined with the vasopressors (grade weak, low-quality evidence) [10]. All patients requiring vasopressors should have an arterial line placed for monitoring blood pressure [63; 70].

Monitoring Serum Lactate

If elevated, serum lactate provides a marker of tissue hypoperfusion, and serial measurements (of lactate clearance) can be used to monitor progress in resuscitation of the patient with sepsis or early septic shock. In cases in which elevated lactate levels are used as a marker of tissue hypoperfusion, it is recommended that resuscitation efforts target serum lactate with the goal to achieve normalization as rapidly as possible (grade weak) [3; 4; 10].

Corticosteroids

Prior to the 1990s, there was evidence that the overall 28-day mortality was not impacted by the use of corticosteroids; consequently, their use was not advised. A review of studies conducted between 1992 and 2003 concluded that corticosteroids did not change the 28-day mortality in patients with sepsis and septic shock, but that the use of low-dose corticosteroids did reduce the all-cause mortality [72]. A 2019 update of this review concluded with moderate-certainty evidence that corticosteroids probably reduce 28-day and hospital mortality among patients with sepsis [73]. According to the 2021 guideline, corticosteroids are not recommended in adult patients with sepsis if hemodynamic stability has been achieved with fluid resuscitation and vasopressor therapy.

The patient with persistent hypotension despite fluids and vasopressors should be assessed for adrenal responsiveness and may benefit from corticosteroid therapy. The 2021 SCCM guideline suggests using IV corticosteroids for adults with septic shock and an ongoing requirement for vasopressor therapy (grade weak, moderate-quality evidence) [10]. The typical corticosteroid used in adults with septic shock is IV hydrocortisone at a dose of 200 mg/day given as 50 mg intravenously every six hours or as a continuous infusion [10; 74]. It is suggested that this is commenced at a dose of norepinephrine or epinephrine ≥0.25 mcg/kg/min at least four hours after initiation.

Recombinant Human Activated Protein C

Drotrecogin alpha (activated), or recombinant human activated protein C (rhAPC), has been studied in patients with sepsis due to its antithrombotic, anti-inflammatory, and profibrinolytic properties. It was voluntarily withdrawn from the market in 2011 due to studies showing no improvement in mortality with treatment [75].

Blood Product Administration

In some cases, blood product administration may be required. The 2021 guideline recommends RBC transfusion if the hemoglobin level falls below 70 g/L; however, RBC transfusion should not be guided by hemoglobin concentration alone. Assessment of the patient's overall clinical status and consideration of extenuating circumstances (e.g., acute myocardial ischemia, severe hypoxemia) is required [10]. The routine use of erythropoietin is not recommended for treatment of anemia in patients with sepsis unless other conditions are present, such as the compromise of red blood cell production induced by renal failure.

Patients who require invasive procedures or surgery typically require a platelet count that is in excess of 50,000/mm^3 [63]. The routine use of fresh frozen plasma is not recommended unless there is active bleeding or planned surgery. Direct administration of antithrombin agents for the treatment of sepsis or septic shock is not advised [63].

SUPPORTIVE THERAPY FOR SEPSIS AND SEPTIC SHOCK

Mechanical Ventilation

Patients who develop sepsis-induced acute lung injury (ALI) or ARDS may require assisted ventilation. The routine use of pulmonary artery catheters for patients with ALI/ARDS is not recommended, and it is important to remember to avoid high pressures and volumes.

The SCCM guideline committee recommends a target goal for maximum end-inspiratory plateau pressures of 30 cm H_2O and a target tidal volume of 6 mL/kg predicted body weight in adult patients with sepsis-induced ARDS (grade strong, high-quality evidence). In addition, the use of lower tidal volumes over higher tidal volumes is suggested for adult patients with sepsis-induced respiratory failure without ARDS [10].

Unless contraindicated, it is recommended that mechanically ventilated patients be kept with the head of the bed elevated (30–45 degrees is suggested) to limit aspiration and prevent the development of ventilator-associated pneumonia. In hospitals with advanced experience and equipment, it may be advantageous to treat patients with ARDS in a prone position if higher pressures are required and the patient's condition allows for the positional change [10; 63].

A protocol for weaning patients from the ventilator should be developed for use following a successful spontaneous breathing trial. Extubation should be considered if the breathing trial is successful. A successful breathing trial is characterized by the following criteria [63]:

- Patient is arousable.
- Patient is hemodynamically stable (without vasopressor agents).
- Patient has developed no new potentially serious conditions.
- Ventilatory and end-expiratory pressure requirements are low.
- Fraction of inspired oxygen requirements are able to be safely delivered with a face mask or nasal cannula.

The SCCM recommends a conservative fluid strategy for patients with established ARDS and no evidence of tissue hypoperfusion in order to minimize fluid retention and weight gain (which have been shown to prolong mechanical ventilation and lengthen ICU stay) [10].

Sedation, Analgesia, and Neuromuscular Blockade

Sedation, whether intermittent or by continuous infusion, may be required for patients who are mechanically ventilated. In such cases, the practice of daily interruption or lightening of the sedation, preferably by established protocol, will serve to maintain the minimum degree of necessary sedation.

Neuromuscular blockade agents are sometimes used in the ICU to improve chest compliance, reduce airway pressures, and facilitate mechanical ventilation. Neuromuscular blockade agents should be used with caution in the patient with sepsis and only for brief periods, so as to avoid the risk of prolonged blockade when the drug is discontinued. The SCCM 2021 guideline suggests using intermittent neuromuscular blockade agents (grade weak, moderate-quality evidence). If these agents are used, clinicians should ensure adequate patient sedation and analgesia [10].

Glucose Control

Glucose control includes a regimen of appropriate nutrition, beginning with IV glucose and advancing early to enteral feeding for the first seven days in critically ill patients with sepsis [10]. Following initial stabilization, patients with hyperglycemia should receive IV insulin therapy to reduce blood glucose levels. SCCM guidance strongly recommends that blood glucose management in ICU patients with sepsis be done by protocol [10]:

- Target an upper blood glucose ≤180 mg/dL rather than an upper blood glucose ≤110 mg/dL (grade strong, high-quality evidence)
- Following initiation of insulin therapy, a typical target blood glucose range is 144–180 mg/dL

Note: A 2009 study demonstrated more frequent episodes of hypoglycemia and higher mortality when tight glucose control was attempted in critically ill patients [76].

Bicarbonate Therapy and Deep Vein Thrombosis Prophylaxis

Bicarbonate therapy to improve hemodynamics or reduce vasopressor requirements in patients with sepsis-induced lactic acidemia is not recommended for those patients with a pH equal to or greater than 7.15 [10]. The use of bicarbonates in SIRS requires additional study.

The use of anticoagulants to prevent deep vein thrombosis (DVT) has been well studied. For patients with sepsis, the SCCM guideline committee recommends the administration of low-dose unfractionated heparin (UFH), two to three times per day, or low-molecular-weight heparin (LMWH), once daily, unless there are contraindications, such as active bleeding, thrombocytopenia, or severe coagulopathy. LMWH has been found to be superior to UFH and is preferred in high-risk patients if there are no contraindications [10; 63].

When contraindications exist, other preventive measures, such as graduated compression stockings or an intermittent compression device, are recommended. In very high-risk patients, such as those who have sepsis and a history of DVT, trauma, or orthopedic surgery, a combination of both therapies is suggested [63; 70].

Stress Ulcer Prophylaxis

The SCCM guideline suggests stress ulcer prophylaxis for patients with sepsis who have risk factors for gastrointestinal bleeding, using either a proton pump inhibitor or a histamine-2 antagonist. It is recommended that stress ulcer prophylaxis not be used for patients without risk factors for gastrointestinal bleeding [10].

Communication

Also included in the supportive therapy points of care is the SCCM recommendation that advance care planning, including the communication of likely outcomes and realistic goals of treatment, be discussed with patients and families [10; 63]. As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because communication with patients and families is considered an essential aspect of care, it is each practitioner's responsibility to ensure that information regarding goals and potential outcomes are explained in such a way that allows for patient understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

SEPSIS BUNDLE

Reducing mortality due to sepsis requires an organized process that guarantees early recognition and consistent application of evidence-based practice. To this end, carefully designed protocols and measurable quality indicators should be incorporated into hospital practice. Beginning in 2005, the Surviving Sepsis Campaign converted its guideline into protocols, with sets of quality indicators that could be implemented by hospitals working to improve outcomes. The Sepsis Bundles are a series of therapies that, when implemented together, have been proven to achieve better outcomes than when implemented individually [3]. In conjunction with the 2013 guideline, two bundles (resuscitation and management) were released.

In order to reflect the changes in the 2016 guideline, in 2018 the Surviving Sepsis Campaign published the Hour-1 Bundle, taking the place of the previously separate resuscitation and management bundles [3]. This new bundle emphasizes the importance of beginning resuscitation and management immediately, then escalating care seamlessly (e.g., by adding vasopressor therapy) on the basis of ongoing clinical parameters rather than waiting or extending resuscitation measures over a longer period. The Hour-1 Bundle consists of five elements that are intended to be initiated within the first hour after the time of triage in the emergency department or, if referred from another care location, from the earliest chart annotation consistent with all elements of sepsis or septic shock. The five elements are [3]:

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

More than one hour may be required for resuscitation to be completed, but initiation of resuscitation and treatment should begin immediately [3]. The Hour-1 Bundle, based on the 2016 guideline, is evidence-based and intended for use by emergency department, hospital, and ICU staff as a tool for improving the care of patients with sepsis and septic shock. As of May 2024, the bundles have not been updated to reflect the 2021 guidelines.

MANAGEMENT OF SEVERE CORONAVIRUS DISEASE 2019 (COVID-19) IN THE ICU

In response to the ongoing COVID-19 pandemic, a Surviving Sepsis Campaign Coronavirus Disease 2019 panel of international experts was formed to provide guidance for managing patients with severe or critical COVID-19 [77]. The panel issues updated recommendations as new evidence becomes available. COVID-19 is defined as severe when the patient has clinical signs of pneumonia (e.g., fever, cough, dyspnea, tachypnea) combined with one or more of the following: respiratory rate >30 breaths/min, severe respiratory distress, or oxygen saturation <90% on room air [77]. COVID-19 is classified as critical when the patient has acute respiratory failure requiring ventilation and/or signs of sepsis or septic shock.

In March 2021, the Surviving Sepsis Campaign COVID-19 panel issued nine new or updated statements/recommendations for management of patients with COVID-19 in the ICU [78]. For severe or critical COVID-19, the panel recommends the use of systemic corticosteroids (preferably dexamethasone) and venous thromboprophylaxis but recommends against the use of hydroxychloroquine. In addition, the panel suggests against the use of convalescent plasma and therapeutic anticoagulation outside clinical trials. The use of remdesivir, an antiviral drug, is suggested for adults with severe COVID-19 who do not require mechanical ventilation; however, the panel suggests against starting remdesivir in patients with critical COVID-19 outside clinical trials. Because of insufficient evidence, no recommendation has been issued on the use of awake prone positioning [78].

EB EVIDENCE-BASED PRACTICE RECOMMENDATION

For adults with COVID-19 and shock, the Society for Critical Care Medicine suggests using norepinephrine as the first-line vasoactive agent over other agents.

(https://journals.lww.com/ccmjournal/Fulltext/2021/03000/Surviving_Sepsis_Campaign_Guidelines_on_the.21.aspx. Last accessed May 20, 2024.)

Strength of Recommendation: Weak

PEDIATRIC CONSIDERATIONS

Sepsis is a common and frequently fatal condition affecting children worldwide. The global burden and mortality of sepsis in neonates and children was assessed in a systemic review and meta-analysis of epidemiologic studies published between 1979 and 2016 [79]. The analysis demonstrated an aggregate estimate of 48 cases of childhood sepsis and 22 cases of severe sepsis per 100,000 person-years. Childhood mortality ranged from 1% to 5% for sepsis and 9% to 20% for severe sepsis. The population-level estimate for neonatal sepsis was 2,202 per 100,000 live births, with mortality between 11% and 19%.

Extrapolating data on a global scale yielded an estimated annual incidence of 3.0 million cases of sepsis in neonates and 1.2 million cases in children [79]. In the United States alone there are 72,000 children hospitalized for sepsis annually, with a reported mortality rate of 25% [80].

In 2002, an international panel of experts met to revise the definitions of sepsis and septic shock to include and reflect the developmental stages of children and age-specific norms of vital sign and laboratory data. The panel also modified the adult criteria for SIRS and proposed dividing the pediatric population into the following six distinct age groups to account for age-specific risks [81]:

- Newborn: 0 days to 1 week of age
- Neonate: 1 week to 1 month of age
- Infant: 1 month to 1 year of age
- Toddler and preschool: 2 to 5 years of age
- School-age child: 6 to 12 years of age
- Adolescent and young adult: 13 to 17 years of age

The panel's definition of SIRS for children includes the presence of at least two of the following criteria (one of which must be abnormal temperature or leukocyte count) [81]:

- Core temperature greater than 38.5°C or less than 36°C (measured by rectal, bladder, oral, or central catheter probe). Hypothermia may indicate serious infection (especially in infants).
- Tachycardia greater than two standard deviations above normal for the child's age in the absence of external stimulus; or unexplained persistent elevation over a four-hour time period; or, for children younger than 1 year of age, bradycardia (as defined by the panel); or unexplained persistent depression over a 30-minute time period. Bradycardia is not a sign of SIRS in older children but may be a sign in the newborn.

- Mean respiratory rate greater than two standard deviations above normal for the child's age or mechanical ventilation

- Leukocyte count that is either elevated or depressed for the child's age; or greater than 10% immature neutrophils

Because many pediatric disease processes present with symptoms of tachycardia and tachypnea, a diagnosis of SIRS should not be based solely on elevated heart and respiratory rates; abnormalities in temperature or leukocyte count must be present. Biomechanical markers of inflammation (e.g., elevated sedimentation rate, C-reactive protein, interleukin-6) have not been proven specific enough to be included in the diagnostic criteria [81].

The following definitions have also been proposed for use in the pediatric population [81]:

- Sepsis: SIRS in the presence of or as a result of suspected or proven infection

- Severe sepsis: Sepsis plus cardiovascular organ dysfunction, ARDS, or two or more other organ dysfunctions (as defined by specific criteria)

- Septic shock: Sepsis plus cardiovascular organ dysfunction

The diagnosis of sepsis and impending septic shock in neonates and children should be suspected when the usual inflammatory triad of fever, tachycardia, and vasodilation is accompanied by changes in mentation. Altered mentation may manifest as inability to be aroused, inconsolable irritability, or lack of interaction with parents. Children may present with hyper- or hypothermia, signs of decreased perfusion, and/or decreased urinary output. Because children often maintain their blood pressure until they are severely ill, hypotension is not necessary for the diagnosis (as in adults), but if present, it helps confirm a suspected case of septic shock. It is also important to note that shock in children may occur long before hypotension occurs [81].

Neonatal ICU (NICU) nurses play a key role in the early recognition and prompt treatment of infection/sepsis in the newborn. A published critical care nursing guide for understanding issues of sepsis in the NICU emphasizes the following goals [82]:

- A high index of suspicion for risk of infection

- An ability to recognize signs of infection and sepsis in infants

- A low threshold for reporting related concerns to the physician or advanced practice nurse

- Being an advocate on behalf of the infant to ensure a timely assessment and prompt therapeutic intervention

Prior to 2020, the most widely utilized guidance for management of sepsis in the pediatric age group was the Surviving Sepsis Campaign guidelines, reviewed and updated every four years [4; 80]. Following the 2016 edition, SCCM formed a separate task force dedicated to developing guidelines for managing sepsis in children. Published in 2020, the objective of the SCCM *Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children* is to provide guidance for clinicians caring for infants, children, and adolescents with sepsis and septic shock [83]. Resources related to these guidelines can be found on the SCCM Surviving Sepsis Campaign website at https://www.sccm.org/SurvivingSepsisCampaign/ Guidelines/Pediatric-Patients [84].

Systematic screening for sepsis is recommended in children who present as acutely unwell. Upon clinical suspicion of sepsis, an expedited diagnostic evaluation should be performed within three hours, including an assessment for sepsis-associated organ dysfunction and blood cultures [84]. If signs of shock develop, or clinical evaluation supports sepsis-associated organ dysfunction, management is escalated to a one-hour time frame with the following goals: obtain IV access, collect blood culture, start empiric broad-spectrum antibiotics, measure

lactate, and administer fluid bolus(es) if the patient is hypotensive. Vasoactive agents should be added when hypotension persists despite completion of initial fluid resuscitation protocol. Continuous clinical reassessment is recommended for early recognition of ARDS, infectious source control, and titration of vasoactive drugs [84]. Patients refractory to hemodynamic support should be evaluated and treated for adrenal insufficiency. About 25% of children with septic shock have adrenal insufficiency and will benefit from corticosteroid therapy [80].

Clinically, pediatric septic shock takes two forms. In hyperdynamic shock, the child has rapid capillary refill and bounding pulses. In hypodynamic shock, there is prolonged capillary refill, mottled cool extremities, and diminished pulses. In both types, immediate resuscitation involves maintaining necessary circulation with fluid replacement, assuring proper ventilation, and maintaining threshold heart rates. Suggested therapeutic end points include a capillary refill of less than two seconds, warm extremities, urine output greater than 1 mL/kg/hr, normal blood pressure, normal mental status, and normal pulses with no differential between peripheral and central pulses. Frequent monitoring is required as rapid changes may occur in the status of a child with sepsis [63; 85].

The international consensus panel also developed criteria for MODS in the pediatric population based on scoring systems previously described in the literature. These systems include the Pediatric Logistic Organ Dysfunction score, Pediatric-MODS score, and Multiple Organ System Failure score. The panel also considered the criteria used in the open-label rhAPC study in their development of criteria for pediatric MODS [81].

The panel's goal was to identify criteria that would optimize the enrollment of children with severe sepsis in clinical studies. To that end, they specified the following [81]:

- Cardiovascular and respiratory organ dysfunction must be present (and mechanical ventilator support for respiratory failure, if used).
- Other organ dysfunctions should be monitored during clinical studies.
- The usefulness of organ dysfunction-free days as a primary end point should be confirmed.
- Documenting organ dysfunction should be achieved with a pediatric MODS scoring system.

Experts generally agree that additional evidence-based studies are needed to understand and accurately define pediatric sepsis by accounting for the physiologic variables, age-specific norms, and risk factors of this population [80; 86; 87].

RECOVERY FROM SEPSIS

There is limited information on the long-term complications of sepsis in those who survive. One systematic review of hospitalized patients who recover from sepsis found that about 40% are re-hospitalized within 90 days, one-third die within the following year, and one-sixth experience persistent physical or cognitive impairments [88]. The most prevalent of reported residual impairments are functional limitations (e.g., inability to bathe and dress independently), cognitive deficits, anxiety, depression, and post-traumatic stress disorder. Factors associated with late sequelae included poor pre-sepsis health status, severity of the acute sepsis episode, and timeliness and quality of initial sepsis care [88]. This review discusses inpatient practices for reducing long-term morbidity and provides a framework for evaluating and treating patients in the 90 days after hospitalization for sepsis [88].

A recommended hospital- and ICU-based approach to improving clinical outcomes centers on three strategies: attention to 2021 SCCM guidelines for sepsis care; protocol management of pain, agitation, and delirium; and early mobilization to prevent or minimize muscle atrophy [88]. Adherence to guidelines for the early identification and treatment of sepsis, including rapid administration of antibiotics, has been shown to decrease in-hospital mortality [89]. Critical care specialists have published the ABCDEF bundle, an evidence-based clinical care guide to optimize ICU patient recovery and outcomes [90]. This guide addresses issues such as pain prevention, spontaneous awakening and breathing trials, choice of sedation, management of delirium, early mobility, and family engagement and empowerment. The ABCDEF bundle helps assure more interactive ICU patients who can participate in higher-order physical and cognitive activities at the earliest in recovery from critical illness [90].

A recommended post-discharge management strategy for patients who recover from sepsis includes the following: identify new physical, mental, and cognitive problems that could benefit from appropriate treatment; review long-term medications and adjust dosage if indicated; and screen for treatable conditions that impact risk of rehospitalization, such as recurrent infection, heart failure, and aspiration [88].

CONCLUSION

Sepsis and septic shock present the clinician with a difficult management situation. Patients are usually unstable and may rapidly progress to ARDS, MODS, and death. There are several possible causes of sepsis, including traumatic injury, infections, and burns. Gram-negative and gram-positive organisms associated with nosocomial infections account for many cases. Other bacteria, viruses, fungi, and non-infectious etiologies account for the remaining [36; 59]. The mortality rate from sepsis is approximately 30%, and it was the 14th leading cause of death in the United States in 2023 [21; 91].

The pathophysiology of sepsis involves multiple organ systems and is often related to an abnormal proinflammatory and/or anti-inflammatory response to infection. Effective management requires early empiric antimicrobial therapy, hemodynamic monitoring, appropriate respiratory support, and maintenance of physiologic homeostasis.

Evidence-based practice guidelines are available to assist in the diagnosis and treatment of these disorders. This course outlines some of the current recommendations and suggestions provided by the SCCM and other experts experienced in treating patients with these disorders.

CASE STUDY

Patient A is a woman, 50 years of age, who was admitted to the emergency department after a motor vehicle accident. She incurred massive abdominal injuries and was transported to the emergency department unconscious and hypotensive upon arrival. She was receiving 35% O_2 via oxygen mask. Her respiratory rate was 28 breaths per minute, and lung sounds were clear bilaterally. She had a sinus tachycardia with a heart rate of 150 beats per minute. Her blood pressure was 80/45 mm Hg. The patient had a 40 pack-year history of cigarette smoking and had been taking medications to control hypertension.

She was transported via stretcher to radiology for a computed tomography scan, which revealed bleeding in the peritoneum. She was taken immediately to surgery. Following surgery, she was taken to the ICU. Three liters of lactated Ringer's solution had been infused in surgery. Estimated blood loss was 2,500 cc, and she received 6 units of whole blood in surgery. Despite fluid resuscitation, the patient was hypotensive during much of the surgical procedure. To assess fluid management, a pulmonary artery catheter was placed while in surgery. A variety of data was obtained upon arrival to the surgical ICU.

Vital Signs	Hemodynamic Parameters	Arterial Blood Gases (ABGs)	Laboratory Values	Ventilator Settings
BP: 100/50 mm Hg Pulse: 120 beats per minute Respirations: 14 breaths per minute on ventilator Temperature: 96.5°F	CVP: 5 mm Hg PAP: 25/15 mm Hg PAWP: 13 mm Hg CO: 3.2 SVR: 1,100 SvO_2: 72%	pH: 7.45 $PaCO_2$: 36 PO_2: 80 HCO_3: 28 SaO_2: 95%	Sodium: 130 Potassium: 4.5 Chloride: 95 Glucose: 140 Hemoglobin: 11.5 Hemocrit: 35 WBC: 11,000	Rate: 14 on assist control FiO_2: 40% Tidal Volume: 800
BP: blood pressure; CI: cardiac index; CO: cardiac output; CVP: central venous pressure; HCO_3: bicarbonate; FiO_2: fraction of inspired oxygen; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PO_2: partial pressure of oxygen; SaO_2: oxygen saturation; SvO_2: venous oxygen saturation; SVR: systemic vascular resistance; WBC: white blood cells.				

Patient A was hemodynamically stable following surgery. She awakened slowly and was able to be extubated and put on a 40% O_2 mask.

POST-OPERATIVE DAY 3

Three days after surgery, the patient's level of consciousness began to deteriorate. She was obtunded and only awoke when her name was called. Her skin was warm to touch and appeared flushed, and she had 4+ bounding pulses.

Vital Signs	Hemodynamic Parameters	ABGs on 40% O_2 Mask	Laboratory Values
BP: 110/72 mm Hg Pulse: 118 beats per minute Respirations: 28 breaths per minute Temperature: 104°F	CVP: 6 mm Hg PAP: 20/12 mm Hg PAWP: 10 mm Hg CO: 6.0 CI: 4.2 SVR: 850 SvO_2: 85%	pH: 7.48 $PaCO_2$: 30 PO_2: 85 SvO_2: 85%	Hemoglobin: 9.8 Hemocrit: 28.8 WBC: 25,000 Platelets: 168,000

Urine output was 15 cc per hour for the last three hours. Cultures of sputum, urine, and blood were obtained. Antibiotic therapy was initiated.

Analysis

1. Identify the term that best describes Patient A's condition at the present moment.

    Sepsis is caused by bacteria, viruses, or fungi in the blood. It is a clinical continuum ranging from bacteremia through septicemia to septic shock. Patient A is presently displaying signs of septicemia. Her blood pressure and cardiac output are within an acceptable range. Chemical mediators are being released and causing the physiologic changes.

POST-OPERATIVE DAY 5

On the 5th post-operative day, Patient A's blood pressure dropped to 84/58 mm Hg; her respirations were 32 breaths per minute, heart rate was 130 beats per minute, and temperature was 97°F. Despite 3000 cc fluid resuscitation, Patient A's condition continued to deteriorate. She was re-intubated and connected to a ventilator.

Hemodynamic Parameters
CVP: 3 mm Hg
PAP: 15/7 mm Hg
PAWP: 5 mm Hg
CO: 3.0
CI: 1.6
SVR: 1,597
SvO_2: 68%

Analysis

1. List the risk factors applicable to Patient A's case.

   Trauma

   Cigarette smoking

   Hypertension

   Abdominal injuries

   Multiple invasive lines

   Surgery

2. Patient A is in what stage of septic shock? Describe the symptoms to support your answer.

   Patient A is in the hypodynamic (cold) phase of septic shock. This phase is characterized by decreased cardiac output, increased SVR, hypotension, and inadequate tissue perfusion.

3. What are some of the causative organisms associated with sepsis in a post-operative, hospitalized patient?

   Escherichia coli

   Klebsiella

   Enterobacter

   Pseudomonas aeruginosa

   Staphylococcus aureus

POST-OPERATIVE DAY 8

On post-operative day 8, Patient A's skin was cool and cyanotic, and mottling was noted in the extremities. She responded only to painful stimuli.

Vital Signs	Hemodynamic Parameters	ABGs	Laboratory Values
BP: 38/40 mm Hg Pulse: 170 beats per minute Respirations: 14 breaths per minute on ventilator. She is not assisting. Temperature: 95.6°F	CVP: 6 mm Hg PAP: 38/20 mm Hg PAWP: 18 mm Hg CO: 2.0 SVR: 1746 SvO_2: 48%	pH: 7.28 $PaCO_2$: 48 PO_2: 40 SvO_2: 52% SaO_2: 80%	Sodium: 160 Potassium: 6.8 BUN: 48 Creatinine: 3.0 Platelets: 72,000 PT: 21 PTT: 100.5
BUN: blood urea nitrogen; PT: prothrombin time; PTT: partial thromboplastin time.			

Analysis

1. Patient A's temperature is 95.6°F. Is this to be expected in the hypodynamic phase and why?

   Yes. Hypothermia is common during the hypodynamic phase. Metabolic and myocardial activity are greatly reduced.

2. What is the physiologic cause of increased SVR in the hypodynamic phase?

   In the hypodynamic phase, SVR is caused by decreased cardiac output and elevated serum lactate levels.

3. What management would be appropriate in this phase?

   Afterload reduction and myocardial support are of great importance at this point. Before the use of vasodilators, cautious fluid administration with hemodynamic monitoring is essential to provide normovolemia as the vascular capacitance increases. If fluid resuscitation proves unsuccessful, the use of vasodilators in combination with a positive inotrope may be attempted.

POST-OPERATIVE DAY 10

Patient A died on the 10th post-operative day due to the complications of septic shock: renal failure and hepatic failure complicated by DIC and ARDS.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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