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Sepsis and Septic Shock Sepsis is an infectious syndrome that results in considerable morbidity, mortality, and long-term sequelae among survivors. Sepsis, derived from the Greek word sipsi, “to make rotten,” was first described by Hippocrates in the 400s b.c. In the 1800s, Sir William Osler opined on sepsis by saying, “except on few occasions, the patient appears to die from the body’s response to infection rather than from it.” The first consensus definition of sepsis, published in 1992, recognized sepsis as the body’s systemic response to infection. To operationalize this defini tion, systemic inflammatory response syndrome (SIRS) clinical criteria were established, which included temperature <36°C or >38°C, heart rate >90 beats/min, respiratory rate >20 breaths/min or partial pres sure of CO2 <32 mmHg, and leukocyte count <4000/μL or >12,000/μL or >10% bands. Suspected infection with two or more SIRS criteria was classified as sepsis, while the term severe sepsis required evidence of hypoperfusion or end-organ dysfunction including oliguria, acute alteration in mental status, or lactic acidosis. Septic shock was defined as sepsis-induced hypotension, determined by systolic blood pressure <90 mmHg or reduced ≥40 mmHg from baseline, absent other causes, despite adequate volume resuscitation. Sepsis-2, the second consen sus definition established in 2003, acknowledged clinical complexity beyond existing SIRS criteria and expanded the list of clinical and laboratory criteria to diagnose sepsis. Sepsis-3, established in 2016 as the current consensus definition, abandoned SIRS criteria, given

Percent (%)

Sepsis mortality Sepsis incidence FIGURE 315-1 Sepsis incidence and mortality. Sepsis incidence and mortality. Sepsis incidence is expressed as a proportion of sepsis cases among 7,801,624 adult hospitalizations across 409 U.S. hospitals from 2009–2014. Mortality is the proportion of sepsis

deaths among sepsis cases.

poor specificity for distinguishing sepsis from other noninfectious inflammatory processes, and eliminated the term severe sepsis. Sepsis was redefined as life-threatening organ dysfunction caused by a dys regulated host response to infection, and septic shock was defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities increase mortality risk beyond sepsis alone. EPIDEMIOLOGY Each year, an estimated 48.9 million sepsis cases occur globally, and 1.7 million cases occur in the United States. Data from >400 U.S. academic, community, and federal hospitals indicate that sepsis occurs in ~6% of hospitalized adults, with stable incidence over time (Fig. 315-1). Approximately 11 million sepsis deaths occur globally each year, accounting for one in five total global deaths, with 85% occurring in low- and middle-income countries. An estimated 350,000 sepsis deaths or discharges to hospice occur annually in the United States, with an estimated 15% overall mortality among U.S. hospital ized adults with sepsis (Fig. 315-1) and up to 40% mortality in patients with septic shock. Data from the U.S. Centers for Medicare and Med icaid Services indicate the aggregate cost for inpatient hospital and skilled nursing facility sepsis admissions was an estimated $13.4 billion dollars in 2018. A retrospective evaluation of sepsis costs in U.S. hospi tals during 2010–2016 suggests a cost of $16,324 and $38,298 per sepsis and septic shock admission, respectively. ■ ■PATHOGENS AND SITES OF INFECTION Approximately 88% of sepsis cases are community onset, defined as being detected within 48 h of hospitalization, whereas an estimated 12% are hospital onset, detected after 48 h of hospitalization. While viruses, fungi, and other pathogens may induce sepsis, the role of bacterial infection is best described. An estimated 53% of sepsis cases in the United States are bacterial culture positive, with a relatively even split between gram-positive and gram-negative organisms. A retrospective cohort study of 17,430 adult community-onset culture-positive sepsis cases from 104 U.S. hospitals during 2009 to 2015 identified Staphylococcus aureus, Streptococcus spp., and Entero coccus spp. as the most prevalent gram-positive organisms isolated, of which 13.6% were antibiotic-resistant, including methicillin-resistant S. aureus (MRSA) and vancomycin-resistant enterococci (VRE). Escherichia coli, Klebsiella spp., and Pseudomonas aeruginosa were the most frequently isolated gram-negative organisms, of which 13.2% were resistant to ceftriaxone, extended-spectrum β-lactams, or car bapenems. The most frequently reported anatomic site of primary infection was the urinary tract (48.9%), followed by the respiratory tract (32.9%), an intraabdominal site (13.6%), and skin or soft tissue (10.3%). Bacteria were most frequently isolated from urine (52.1%), blood (40.0%), and the respiratory tract (16.7%). Year

Patients with hospital-onset sepsis differ from community-onset sepsis patients in that they more often have comorbidities and expe rience intraabdominal infections and bacteremia with Enterococcus, Candida, and Pseudomonas. Patients with hospital-onset sepsis also experience higher intensive care unit (ICU) admission rates, longer hospital length of stay, and increased mortality. ■ ■RISK AND PROGNOSTIC FACTORS U.S. Centers for Disease Control and Prevention (CDC) data from 2021 show that sepsis mortality increases with age and is higher among men than women in all age groups: 232.7 versus 173.0 (65–74 years), 477.3 versus 349.8 (75–84 years), and 1037.8 versus 755.5 (≥85 years) deaths per 100,000 population, respectively. Preexisting medical condi tions including diabetes and obesity; neurologic, respiratory, or cardiac conditions; renal or hepatic insufficiency; and cancer or other immu nosuppressing conditions increase sepsis mortality risk. Recent hos pital admission for any reason has also been associated with threefold increased risk of developing sepsis in the following 90 days. Multiple composite illness severity scoring

systems have been applied to hospitalized septic patients to predict outcome or guide stratification or post-hoc analyses in clinical trials or observational studies of sepsis. For example, the Sequential Organ Failure Assess ment (SOFA) score quantifies dysfunction in six organ systems includ ing neurologic, using the Glasgow Coma Scale score; cardiovascular, using mean arterial blood pressure or use of vasoactive agents; respira tory, using the ratio of arterial blood partial pressure of oxygen (Pao2) to fraction of inspired oxygen (Fio2) or use of mechanical ventilation; hepatic, using serum bilirubin levels; renal, using serum creatinine lev els; and coagulation, using blood platelet levels. Elevated SOFA scores are associated with increased sepsis mortality at the population level but cannot accurately predict outcomes of individual patients. Improved stratification of sepsis patients based on clinical “phe notype,” determined by clustering of clinical variables using machine learning tools to better predict outcome, has been proposed. In a ret rospective analysis of >45,000 patients who met Sepsis-3 criteria, sta tistical, machine learning, and simulation tools were applied to clinical data obtained within 6 h of emergency room presentation to identify α, β, γ, and δ phenotypes, with associated 2%, 5%, 15%, and 32% mor tality rates, respectively. Beyond using immediately available clinical data to identify sepsis phenotypes, integration of transcriptional and proteomic data to define sepsis “endotypes” has also been attempted. While these approaches hold promise to guide improved clinical trial design and patient care, additional research is needed to contextualize and operationalize them across patients and pathogens. PATHOGENESIS The host-pathogen interaction during sepsis is heterogeneous, based on patient demographic and clinical factors and pathogen type and viru lence. Consequently, the pathophysiology and molecular pathogenesis of sepsis vary across hosts and pathogens. However, a working frame work for sepsis pathogenesis, with commonalities across hosts and pathogens, provides a basis for understanding which factors contribute to organ injury and dysfunction during severe infections. During local infection, a prototypical physiologic response is characterized by patho gen recognition followed by balanced inflammatory, anti-inflammatory, and repair responses resulting in pathogen clearance with minimal disruption to systemic homeostasis. During sepsis, however, pathogen components and exuberant cellular and soluble immune responses con tribute to systemic illness, resulting in end-organ injury and dysfunc tion (Fig. 315-2). Pathogen components and host responses to infection may also impair or delay adaptive immunity and tissue repair. Pathologic responses in sepsis are mediated by myeloid lineage cells (i.e., neutrophils, monocytes, macrophages, and dendritic cells), lymphoid lineage cells (i.e., natural killer [NK] cells and lymphocytes), parenchymal cells (e.g., endothelial and epithelial cells), and soluble mediators (e.g., cytokines, chemokines, nitric oxide, histamine, prosta glandin, and bradykinin). Activated leukocytes adhere to endothelium, migrate into tissue, and perform end-effector functions, including reactive oxygen species (ROS) generation, that contribute to tissue

injury. Activation of endothelial cells, platelets, the clotting cascade, and the complement system contribute to a prothrombotic state. When platelets and clotting factors are consumed, hemorrhage risk increases. Pathophysiologic manifestations of sepsis include systemic vasodila tion, capillary leakage with interstitial fluid accumulation, and micro vascular thrombosis resulting in impaired oxygen delivery, uptake, and utilization. Taken together, these factors drive cellular injury and end-organ dysfunction.

■ ■TRIGGERS OF HOST IMMUNE RESPONSES Host immune responses in sepsis are initiated by pathogen compo nents termed pathogen-associated molecular patterns (PAMPs) and propagated

by host factors termed damage-associated molecular pat terns (DAMPs). PAMPs and DAMPs interact with innate and adaptive immune cells and parenchymal cells early during sepsis, amplifying immune responses. PAMPs include bacterial lipopolysaccharide (LPS) or other bacterial cell wall or membrane components, pathogen nucleic acids, including single- or double-stranded RNA, and other pathogenrelated molecules. DAMPs include proteins, lipids, nucleic acids, and other components released from injured cells. Examples include histones, high mobility group box 1 proteins, S100 proteins, oxidized phospholipids, double-stranded DNA, and adenosine triphosphate. PAMPs and DAMPs are recognized by extra- or intracellular receptors, termed pattern recognition receptors (PRRs). Multiple PRRs, including toll-like receptors (TLR), of which 10 have been described in humans, C-type lectin receptors (CLR), receptors for advanced glycation end products (RAGE), retinoic acid–inducible gene-I-like receptors (RIG-I), and nucleotide-binding oligomerization domain-like (NOD) receptors, have been implicated in sepsis signaling. Recognition of PAMPs and DAMPs by PRRs on innate immune cells such as neutro phils, monocytes, and macrophages activates inflammatory pathways, triggers release of proinflammatory cytokines and chemokines, and increases surface expression of vascular adhesion molecules. CHAPTER 315 Sepsis and Septic Shock ■ ■MYELOID RESPONSES Neutrophils, monocytes, and macrophages provide early innate immune defenses against invading pathogens but also contribute to sepsis patho genesis by promoting inflammation and cellular injury and, in some cases, limiting adaptive immunity. Differentiated mature neutrophils are the most abundant circulating leukocytes in healthy individuals. Upon activation during sepsis, neutrophils upregulate surface adhe sion molecule expression (e.g., CD11b) to bind endothelium. Within the microvasculature, neutrophils release neutrophil extracellular traps (NETs), web-like structures of DNA decorated with antimicrobial pro teins such as cathepsin-G, myeloperoxidase, and neutrophil elastase to limit dissemination of invading pathogens. NETs interact with activated platelets, endothelial cells, and fibrin to form microvascular thrombo ses. Activated neutrophils also migrate into tissues to combat microbes through phagocytosis, degranulation, ROS generation, NET formation, and proinflammatory cytokine and chemokine release. Neutrophil granule components degrade extracellular matrix, while ROS oxidize proteins and lipids contributing to cellular injury and dysfunction. Soluble inflammatory mediators further recruit immune cells to sites of infection, exacerbating inflammation and cellular injury. Mediators such as interleukin (IL) 6, granulocyte-macrophage colony-stimulating factor, and granulocyte colony-stimulating factor trigger release of immature neutrophils from the bone marrow, a process termed emergency granu lopoiesis that is associated with poor outcomes in septic patients. Monocytes are innate myeloid cells that circulate in healthy indi viduals for up to 7 days following release from the bone marrow. Three main monocyte populations are defined by CD14 and CD16 surface expression, including classical (CD14+, CD16–), intermediate (CD14+, CD16+), and nonclassical (CD14lowCD16+) monocytes. Clas sical monocytes account for 85% of circulating monocytes in healthy individuals but rapidly migrate to infected tissues during sepsis, resulting in transient monocytopenia and an increased proportion of circulating nonclassical and intermediate monocytes. Nonclassical monocytes are more terminally differentiated blood-resident mono cytes thought to patrol the endothelium during sepsis. Monocytes

Localized Damage Systemic Damage Pathogens A Triggers of Immune system Phagocytosis Cell damage PAMPS DAMPs Chemokines Cytokines PART 8 Critical Care Medicine B PRR Damaged endothelial Monocyte TF PRR TF+VIIa vWF C Xa X Neutrophil Antithrombin Increased adhesion molecules D E Complement cascade C3 C5 C5a VE-Cadherin MAC ICAMs VCAM-1 C3a F Neutrophil

Lymphocyte Exhausted Apoptotic ↓ Proliferation Monocyte FIGURE 315-2 Sepsis pathogenesis. (A) Invading pathogens and tissue-resident and recruited leukocyte responses induce localized cell damage. (B) Systemic damage is mediated by pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), cytokines, and chemokines that activate pattern recognition receptors (PRRs) on circulating monocytes and neutrophils. (C) Increasing tissue factor (TF) on endothelium and leukocytes triggers the clotting cascade and fibrin generation. Adherent neutrophils release extracellular traps (NETs) and microthrombi form, composed of leukocytes, fibrin, and platelet aggregates, bound together by von Willebrand factor (vWF). Antithrombin levels are decreased, promoting clot formation, and plasminogen activator inhibitor-1 (PAI-1) levels are increased, impairing clot breakdown. (D) Complement activation generates C3a and C5a, which activate platelets and myeloid cells. The C5b-9 membrane attack complex (MAC) promotes endothelial injury. (E) Activated and injured endothelium increase intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecule (VCAM)-1 expression, glycocalyx breakdown, apoptosis, and loss of intercellular vascular endothelial (VE)-cadherin and tight junctions contributing to interstitial edema, decreased oxygen diffusion, and leukocyte migration. (F) Activated neutrophils degranulate and release reactive oxygen species (ROS) and NETs, and monocytes differentiate into proinflammatory (M1) macrophages, contributing to cellular injury and dysfunction. Activated myeloid cells also suppress lymphocyte function, through exhaustion, apoptosis, and decreased proliferation. (G) Arterial vasodilation, partially mediated by excess nitric oxide, contributes to tissue hypoperfusion and ischemia. (H) With or without adequate oxygen delivery, cellular mitochondrial and metabolic functions are disrupted during sepsis.

Interstitium Vasculature G Vasodilation NO Thrombosis PAI-1 Activated platelets Thrombin Fibrinogen Fibrin NETosis Glycocalyx degredation Edema O2 diffusion Leakage due to leaky endothelial cells H Tissue Cellular injury ROS NETosis Degranulation Mitochondrial and metabolic dysfunction M1 Proinflammatory macrophage

that migrate into tissues are exposed to PAMPs, DAMPS, cytokines, and other mediators, stimulating them to differentiate into den dritic cells or macrophages. Dendritic cells are phenotypically and transcriptionally diverse professional antigen-presenting cells with a broad PRR and cytokine secretion repertoire. These cells contribute to pathogen clearance and inflammation and bridge innate and adap tive immune responses through antigen presentation and lymphocyte activation. Macrophages that originate from bone marrow–derived monocytes are distinct from tissue-resident macrophages, which derive from embryonic progenitors. Depending on environmental conditions within tissues, bone marrow–derived monocytes polarize to become proinflammatory (M1) or anti-inflammatory, reparative (M2) macrophages. M1 macrophages contribute to pathogen clearance through phagocytosis, extracellular trap formation, ROS generation, and inflammatory cytokine release (e.g., IL-1β, IL-6, and tumor necro sis factor [TNF]-α). However, these same effector functions contribute to tissue injury. Macrophages also process and present antigens on surface major histocompatibility complex (MHC) II molecules, which are required for development of antigen-specific effector and memory B- and T-cell responses. This essential link between myeloid and lym phoid cells can be disrupted by diverse pathogen-induced mechanisms including downregulation of MHC surface expression or interruption of antigen processing or presentation by pathogen proteins and other components. While myeloid cells typically contribute to inflammation in sepsis, a subset of pathologically activated myeloid cells in tissues, termed myeloid-derived suppressor cells, functionally suppress NK-cell, T-cell, and B-cell

function, contributing to immunosuppression in sepsis. ■ ■LYMPHOID RESPONSES NK cells are a heterogenous group of innate lymphocytes that migrate to sites of infection, contribute to pathogen clearance, and mediate inflam matory responses during sepsis. NK cells have activating and inhibi tory cell surface receptors that modulate their activity. NK-cell PRRs recognize PAMPs including LPS, peptidoglycan, and double-stranded RNA. NK-cell cytokine receptors recognize inflammatory cytokines including type 1 interferons (IFN) and IL-12. Activated NK cells release proinflammatory cytokines including IFN-γ and IL-32, which activate myeloid cells in a positive feedback loop. Activated NK cells also directly kill infected cells that have downregulated MHC class I surface molecule expression, through release of cytotoxic granules including perforin and granzyme. In studies of human sepsis, circulating NK cells with increased CD69 expression, indicative of activation, and increased plasma concen trations of IFN-γ and granzyme A and B support a proinflammatory role of NK cells. However, NK cells also release IL-10, known to suppress myeloid cell–mediated inflammatory responses, highlighting an antiinflammatory role of NK cells in sepsis as well. B- and T-cell responses in sepsis are essential for recognizing and clearing pathogens. B cells produce antibodies against foreign antigens and form antigen-specific memory cells. CD8+ T cells lyse infected cells that present foreign antigens in association with MHC surface molecules and form memory cells. CD4+ (TH1) cells activate CD8+ T cells and support memory T-cell formation, CD4+ (TH2) cells con tribute to B-cell class switching, and CD4+ (TH17) cells protect against extracellular fungal and bacterial infections. B- and T-cell dysfunction in sepsis impairs adaptive immunity and predisposes to subsequent infections among survivors. Contributing factors to adaptive immune dysfunction in sepsis include death of lymphocytes in the circulation and tissue, cellular exhaustion, decreased proliferation, and apoptosisrefractory regulatory T cells, all of which can inhibit inflammatory responses. Functional manifestations of T-cell exhaustion include impaired cytokine production and diminished cytotoxic activity, while diminished antibody production is observed in exhausted B cells. ■ ■ENDOTHELIAL ACTIVATION During homeostasis, endothelial cells line blood vessels and regu late vascular tone and the exchange of cells, fluid, and molecules between the bloodstream and surrounding tissues. The endothelial glycocalyx, a network of proteoglycans, glycoproteins, glycolipids,

glycosaminoglycans, and bound plasma proteins, lines luminal endo thelium and maintains homeostatic functions. During sepsis, PAMPs and DAMPs activate endothelial cells, altering their structure and function. Glycocalyx breakdown disrupts blood flow and mediates proadhesive, procoagulant, and proinflammatory endothelial proper ties. Activated endothelial cells increase surface adhesion molecule expression, including intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecule (VCAM)-1, that coordinates leukocyte adhesion, rolling, and diapedesis. Activated endothelium promotes clotting through increased tissue factor (TF) expression and platelet adhesion and impairs fibrinolysis through increased plasminogen activator inhibitor (PAI)-1 release, among other factors. Activated endothelial cells also produce proinflammatory cytokines, including IL-1β, IL-6, and IFN-α, contributing to local and systemic inflam mation. Beyond glycocalyx breakdown, barrier function is impaired through endothelial cell apoptosis and loss of intercellular adher ence (e.g., vascular endothelial [VE]-cadherin) and tight junctions. Loss of endothelial barrier function contributes to interstitial fluid accumulation, increased interstitial pressure, and tissue hypoperfusion. Alterations in endothelial cell nitric oxide (NO) metabolism in sepsis contribute to systemic vasodilation and cellular injury.

CHAPTER 315 Sepsis and Septic Shock ■ ■COAGULOPATHY The coagulation system, composed of plasma proteins, platelets, and the endothelium, maintains vascular integrity. During sepsis, PAMPs and DAMPs interact with these components, innate immune cells, and the complement system to promote thrombus formation and impair clot breakdown. Increased TF expression on activated leukocytes and endothelium triggers the extrinsic clotting cascade, thereby driving thrombin-mediated conversion of fibrinogen to fibrin. Endothelial injury exposes von Willebrand factor (vWF) on subendothelial sur faces, which binds platelets via glycoprotein Ib receptors, and platelets bind fibrinogen via glycoprotein IIb/IIIa receptors. Activated platelets and endothelium release additional vWF from intracellular stores (i.e., Weibel-Palade bodies in endothelial cells), forming multimers that aggregate platelets at the endothelial surface. Activated monocytes and neutrophils bind to these platelet aggregates, and neutrophils release NETs, contributing to a meshwork of fibrin-rich microthrombi. The complement system, which is composed of >50 soluble or membrane bound proteins, also contributes to microthrombi formation. During sepsis all three complement pathways (classical, alternative, and lectin) become activated. Release of C3a and C5a anaphylatoxins further acti vates platelets and myeloid cells, and assembly of the membrane attack complex (MAC), composed of C5b-9, promotes endothelial injury. Counterregulatory anticoagulant molecules, including antithrombin, tissue factor pathway inhibitor, and activated protein C, are impaired in sepsis, and increased activity of antifibrinolytic molecules, including PAI and thrombin-activatable fibrinolysis inhibitor, limit clot break down. When clotting factors and platelets are consumed, spontaneous and provoked hemorrhage can occur. ■ ■CELLULAR INJURY AND DYSFUNCTION A hallmark of sepsis is multiorgan cellular injury and dysfunction. Arterial hypotension due to systemic vasodilation, myocardial depres sion, and hypovolemia; increased interstitial edema due to vascular leakage resulting in increased oxygen diffusion distance; and micro circulatory dysfunction in part due to endothelial activation, injury, and microvascular thrombosis all contribute to inadequate oxygen delivery and cellular injury and dysfunction during sepsis. Cell death or dysfunction can also result from direct interactions with PAMPs, DAMPs, activated leukocytes, and their associated mediators including cytokines, chemokines, toxic granules, ROS, and reactive nitrogen spe cies (RNS), including peroxynitrite, nitrogen dioxide, and dinitrogen trioxide. ROS and RNS contribute to protein and lipid oxidation and DNA damage of proximate cells. Even in the setting of adequate oxygen delivery, cellular mitochondrial and metabolic functions are disrupted during sepsis, including ATP generation through glycolysis and oxida tive phosphorylation, ion (i.e., Na+, K+, and Ca2+) homeostasis, and regulation of cell death pathways.

CLINICAL MANIFESTATIONS

AND MANAGEMENT Sepsis may present with nonspecific signs and symptoms including fever, tachycardia, lethargy, and myalgias with or without localizing end-organ findings such as cough, pyuria, or abdominal pain or evi dence of end-organ dysfunction such as oliguria or altered mental status. There is no gold standard diagnostic test for sepsis, so epidemio logic, demographic, clinical, laboratory, radiologic, and microbiologic parameters must be considered in diagnosing sepsis. In addition to a focused history and physical examination to elicit signs, symptoms, and physical manifestations of sepsis, an initial laboratory evaluation should include complete blood count with differential, basic metabolic panel, liver function test, serum lactate, coagulation panel, urinalysis, and point-of-care pathogen testing when available. Microbiologic testing with culture of blood and other potentially infected sites (e.g., urine, sputum, wound), ideally prior to antimicrobial

administra tion, should be performed to identify a specific infection and guide antimicrobial therapy. Focused imaging examination by x-ray, com puted tomography, or ultrasound of potentially infected sites (e.g., lung, abdomen) to support a diagnosis of sepsis and guide efforts to control the source of infection should also be pursued. Sepsis mim ics include but are not limited to noninfectious inflammatory febrile syndromes such as connective tissue diseases and vasculitides; heart failure and other noninfectious causes of pneumonitis or lung injury; noninfectious abdominal syndromes including mesenteric ischemia and inflammatory bowel disease; and hypotension due to noninfec tious causes including hypovolemia, autonomic dysfunction, and adrenal insufficiency. In a recent study of septic patients admitted to the ICU, 25% were retrospectively deemed to have sepsis mimics. The most common mimics were cardiovascular (e.g., heart failure, cardiac arrest) and respiratory (e.g., noninfectious chronic obstructive pul monary disease). In patients with suspected sepsis or septic shock in whom infection is not confirmed, continuous reevaluation for alternative diagnoses is imperative.

PART 8 Critical Care Medicine ■ ■RECOGNIZING SEPSIS Early recognition and treatment of bacterial septic shock with appro priate antibiotics has been associated with reduced mortality. There fore, the 2023 CDC Hospital Sepsis Program Core Elements guidance document and the 2021 Surviving Sepsis Campaign guidelines recom mend hospitals have dedicated sepsis improvement programs that include standard operating procedures for sepsis screening and early treatment. To operationalize updated Sepsis-3 definitions, consensus criteria for sepsis include an increase of ≥2 in SOFA score from base line in patients with suspected or confirmed infection, and criteria for septic shock include septic patients requiring vasopressor therapy to maintain a mean arterial pressure >65 mmHg and lactate >2 mmol/L despite fluid resuscitation. To more rapidly screen patients for sepsis, the quick (q)SOFA score has been proposed, which includes respira tory rate ≥22 breaths/min, Glasgow Come Scale score <15, and systolic blood pressure ≤100 mmHg. A qSOFA score ≥2 is associated with poor outcome and is more specific, although less sensitive, than SIRS criteria for identifying patients with end-organ dysfunction due to infection. Multiple other sepsis screening tools have been proposed including the National Early Warning Score, the Modified Early Warning Score, and the artificial intelligence–based Targeted Real-Time Early Warning System. Given that each screening tool has advantages and limitations, none is preferentially endorsed for sepsis screening by the 2021 Surviv ing Sepsis Campaign guidelines. ■ ■INITIAL SEPSIS MANAGEMENT Initial treatment of patients with sepsis or septic shock includes timely blood pressure and end-organ support, antimicrobial therapy, and identification and elimination of the source of infection. The 2021 Surviving Sepsis Campaign treatment guidelines provide the most up-to-date and evidenced-based approach for initial and subsequent treatment of patients with sepsis and septic shock. Initial manage ment recommendations include obtaining intravenous access with peripheral or central venous catheters, administering appropriate and

timely antibiotics, treating life-threating hypotension with intravenous crystalloid and vasopressor therapy, and managing respiratory insuf ficiency or failure with supplemental oxygen, airway support, and mechanical ventilation, when indicated. Following initial stabilization in patients who are critically ill or in shock, admission to the ICU within 6 h should be targeted. Of these interventions, early appropriate antibiotic administration in patients with bacterial septic shock has been most clearly associ ated with improved survival. In patients with bacterial septic shock, there is an estimated 7–8% increase in mortality for every 1-h delay in appropriate antibiotic administration following shock recognition. Consequently, in patients with suspected or confirmed

septic shock, immediate empiric antimicrobial therapy within 1 h of shock recogni tion is recommended. The association between time to antibiotics and mortality in patients with suspected or confirmed sepsis without shock has not been established. In patients in whom a diagnosis of sepsis is less certain and shock is absent, further time-limited clinical evaluation is recommended prior to empiric antibiotic administration. If an alter native diagnosis is not identified within 3 h of clinical presentation, empiric antibiotic administration is recommended. Selection of initial empiric antibiotics should consider site of infec tion and potential etiologic organisms; community versus health care exposure; known prior infections, antibiotic usage, and local antimi crobial resistance profiles; and the patient's immune status, comor bidities, and illness severity. Recommendations for initial empiric antibiotic use based on site of infection and other pertinent factors are summarized in Table 315-1. In patients with undifferentiated sepsis, in whom the primary site of infection is unclear, use of broad-spectrum antibiotics with a high likelihood of in vitro susceptibility to all organ isms likely causing infection is recommended. In patients in whom Pseudomonas is not considered a likely pathogen, then a third-generation cephalosporin such as ceftriaxone or cefotaxime is recommended for gram-negative bacteria coverage. If Pseudomonas is likely, then cefepime, piperacillin-tazobactam, or a carbapenem such as imipenem or meropenem is recommended for gram-negative bacteria coverage. In patients at risk for highly resistant gram-negative infections (e.g., patients with prior known highly resistant infections or colonization), use of two empiric gram-negative antibiotics is recommended. Finally, in patients with undifferentiated sepsis with risk factors for MRSA (e.g., frequent health care exposure or hospital-onset sepsis), vancomycin or linezolid administration is recommended. Optimization of antibiotic delivery, such as administering β-lactam antibiotics prior to vancomycin, prolonged infusion of β-lactam anti biotics after the initial infusion, and optimization of pharmacokinetics/ pharmacodynamics, should be considered in consultation with trained pharmacy and infectious diseases experts. Routine empiric antifungal therapy use in patients with undifferentiated sepsis is not recom mended. However, in patients at increased risk of fungal infection (e.g., recent abdominal surgery, parenteral nutrition, liver failure, diabetes, colonization of multiple anatomic sites with Candida spp.), empiric echinocandin administration is recommended. While the Surviving Sepsis Campaign does not provide recommendations on antiviral use, remdesivir or neuraminidase inhibitor (e.g., oseltamivir) administra tion in septic patients with severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) and influenza infection, respectively, should be considered. In addition to providing appropriate and timely antibiotics, identify ing sources of infection amendable to control is imperative. Examples include, but are not limited to, intraabdominal abscess, bowel perfora tion, pyelonephritis, cholangitis, and necrotizing skin and soft tissue infections that are amendable to surgical or procedural source control. Source control should occur as rapidly as possible. Furthermore, removal of indwelling catheters should occur if the catheter appears infected (e.g., erythema or purulence at the catheter insertion site), if endovascular infection (e.g., endocarditis) is suspected or documented, and in critically ill patients without a clear alternate source of infection. Finally, antibiotic stewardship to limit development of resistant organ isms and other antibiotic-associated complications (e.g., Clostridioides difficile infection, hypersensitivity/allergic reaction, and acute kidney

TABLE 315-1 Site-Specific Empiric Antibiotic Recommendations SITE OF INFECTION INITIAL EMPIRIC THERAPY OTHER CONSIDERATIONS Pulmonary CAP Multidrug therapy with a β-lactam (ampicillin + sulbactam, ceftriaxone, or ceftaroline) and a macrolide (azithromycin or clarithromycin) Monotherapy with a respiratory fluoroquinolone (levofloxacin or moxifloxacin) Risk factors for MRSA

and/or Pseudomonas aeruginosa: add vancomycin or linezolid for MRSA coverage; replace standard CAP therapy with antipseudomonal coverage such as piperacillintazobactam, cefepime, meropenem, or imipenem. Recommendation based on “local validation” of risk factors for community-onset MRSA or P. aeruginosa or prior isolation of these organisms in the previous year, particularly from respiratory specimens. HAP/VAP Multidrug therapy with vancomycin or linezolid and piperacillin-tazobactam, cefepime, ceftazidime, imipenem, meropenem, or aztreonam Two antipseudomonal antibiotics from different classes (addition of fluoroquinolones, aminoglycosides, or polymyxins) if prior intravenous antibiotic use within 90 days for HAP/VAP and septic shock at time of VAP, ARDS preceding VAP, 5 or more days of hospitalization prior to VAP, or acute renal replacement therapy prior to VAP. If prior colonization with carbapenem-resistant Enterobacterales or KPC-producing organism, ceftazidime-avibactam and meropenem-vaborbactam should be considered, but further efficacy data are needed. Empiric regimens should be informed by local distribution of pathogens and their antimicrobial susceptibilities. Central Nervous System Health care–associated ventriculitis and meningitis Vancomycin and cefepime, ceftazidime, or meropenem β-Lactam choice based on local in vitro susceptibility patterns. If carbapenem-resistant Acinetobacter is suspected, addition of meropenem and colistin or polymyxin B. Meningitis Vancomycin and ceftriaxone Age >50, alcohol abuse, or immunocompromised: add ampicillin. Penetrating head trauma, CSF shunt, or postneurosurgery, vancomycin and cefepime, ceftazidime, or meropenem. Clinical presentation suggestive of Rickettsia or Ehrlichia, add doxycycline. Skin and Soft Tissue Necrotizing fasciitis including Fournier gangrene Multidrug therapy with vancomycin or linezolid and piperacillin-tazobactam, a carbapenem, or ceftriaxone and metronidazole Prompt surgical consultation is recommended for patients with aggressive infections associated with signs of systemic toxicity or suspicion of necrotizing fasciitis or gas gangrene. Nonpurulent cellulitis/ erysipelas (severe) Vancomycin and piperacillin-tazobactam Emergent surgical inspection to rule out necrotizing process. Purulent furuncle/ carbuncle/abscess (severe) Vancomycin, daptomycin, linezolid, telavancin, or ceftaroline Incision and drainage as indicated. Intraabdominal Community-onset extrabiliary (mild) Cefoxitin, ertapenem, moxifloxacin, or tigecycline Health care setting with high prevalence of ESBL-producing Enterobacterales or >20% of Pseudomonas resistant to ceftazidime, consider carbapenem or piperacillin-tazobactam. Community-onset extrabiliary (severe) Imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam Health care associated: imipenem-cilastatin, meropenem, or piperacillin-tazobactam, levofloxacin, or cefepime each along with metronidazole, vancomycin added to each regimen. Community-onset biliary (mild to moderate) Cefazolin, cefuroxime, or ceftriaxone Empiric therapy should be driven by local microbiologic data and source control performed as indicated. Community-onset biliary (severe) or cholangitis Imipenem-cilastatin, meropenem, or piperacillin-tazobactam, levofloxacin, or cefepime each in combination with metronidazole Genitourinary Acute pyelonephritis (IDSA archived) Ceftriaxone, trimethoprimsulfamethoxazole, or ciprofloxacin Requiring hospitalization: intravenous fluoroquinolone, aminoglycoside, extended-spectrum cephalosporin, extended-spectrum penicillin, or carbapenem with choice of agents based on local resistance data. Do not use fluoroquinolone if >10% resistance prevalence or trimethoprim-sulfamethoxazole in areas of high resistance. Abbreviations: ARDS acute respiratory distress syndrome; CAP, community acquired pneumonia; CSF, cerebrospinal fluid; HAP, hospital-acquired pneumonia; IDSA, Infectious Diseases Society of America; KPC, Klebsiella pneumoniae carbapenemase; ESBL, extended spectrum beta-lactamase; MRSA, methicillin-resistant Staphylococcus aureus; VAP, ventilator-associated pneumonia. injury) requires regular reassessment of the patient’s clinical course and available microbiologic data to guide narrowing

the spectrum of anti biotic therapy and using shorter rather than longer courses of therapy. ■ ■NEUROLOGIC COMPLICATIONS Encephalopathy, manifested by altered consciousness, cognition, or attention, ranging from mild delirium to coma, that is not attributable to an alternative etiology, is the most common neurologic complica tion of sepsis (Table 315–2). Sepsis-associated encephalopathy occurs in over half of septic patients and is associated with increased mortal ity and long-term functional and neuropsychiatric sequalae among

 survivors. Septic patients may also experience hyper- or hypoactive delirium, seizure, stoke, central nervous system infection, or coma, not directly attributable to sepsis. Thus, further diagnostic evalua tion is needed in septic patients with clinical findings indicative of seizures (i.e., electroencephalogram), stroke (i.e., brain imaging), or meningoencephalitis (i.e., lumbar puncture) to identify and treat these complications. Underlying factors contributing to sepsis-associated encephalopathy include decreased cerebral perfusion, microcirculatory and blood-brain barrier disruption, and exposure of brain parenchyma to circulating inflammatory mediators and oxidative stress resulting in neuronal injury, dysfunction, and death. Neuronal and glial apoptosis

TABLE 315-2 Organ-Specific Clinical Findings and Management EPIDEMIOLOGY CLINICAL FINDINGS DIAGNOSIS TREATMENT Neurologic 54% of septic patients develop encephalopathy Altered consciousness, cognition, or attention; seizure, stroke, or meningism Cardiovascular 25% of septic patients develop shock and half have myocardial dysfunction Tachycardia, hypotension, skin mottling, prolonged capillary refill, oliguria, altered mental status Respiratory 7% of septic patients develop ARDS Tachypnea, hypoxia, increased work of breathing Genitourinary 67% of septic patients have acute kidney injury Oligura or anuria Elevated serum creatinine and blood urea nitrogen, acidemia, hyperkalemia Gastrointestinal 50% of septic shock patients have liver dysfunction Right upper quadrant pain, asterixis, jaundice Hematologic 35% of septic shock patients have disseminated intravascular coagulation Clinical or subclinical thrombosis or hemorrhage Abbreviations: ARDS, acute respiratory distress syndrome; CT, computed tomography; EEG, electroencephalogram; INR, international normalized ratio; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PT, prothrombin time. are correlative findings at autopsy among fatal cases. The management of sepsis-associated encephalopathy includes early recognition, treat ment of the underlying infection, supportive care including correction of metabolic or electrolyte abnormalities, and limiting exposure to pharmacologic agents that are neurotoxic (e.g., cefepime) or have cen tral nervous system effects including opiates and benzodiazepines that might exacerbate the condition or predispose to long-term disability or neurocognitive dysfunction. ■ ■CARDIOVASCULAR DYSFUNCTION Cardiovascular comprise, manifested as hypotension or shock, occurs in ~25% of septic patients. Hypotension results from peripheral arteriolar vasodilation and decreased cardiac venous return due to venous vasodilation and intra- to extravascular fluid shifts. Clinical signs of diminished tissue perfusion include skin mottling, prolonged capillary refill time, oliguria, and altered mental status. During early compensated shock, heart rate and cardiac output increase. As septic shock progresses, loss of vascular smooth muscle contractility, despite endogenous neurohormonal stimuli and exogenous catecholamine administration, results in progressive or refractory shock. Up to half of patients with septic shock also have myocardial dys function, which is associated with increased mortality. Sepsis-induced cardiomyopathy manifests as decreased left ventricular ejection frac tion, increased end-diastolic volume index, and right ventricular impairment. Contributing factors to sepsis-

induced cardiomyopathy include global ischemia, hypoxia, and impaired myocardial metabo lism; endothelial damage, increased adhesion molecule expression, and coronary microcirculatory dysfunction; and direct cardiomyocyte suppression, mitochondrial dysfunction, or cardiomyocyte death from exposure to inflammatory mediators including cytokines (e.g., IL-1β, IL-6, and TNF-α), complement proteins, and NO.

EEG, brain imaging (MRI or CT), lumbar puncture Early recognition and supportive care; treat underlying cause; correct metabolic and electrolyte abnormalities; limit neurotoxic agents and sedatives Invasive blood pressure monitoring, dynamic assessment of volume status, echocardiogram Intravenous fluid resuscitation with balanced crystalloid, ~30 mL/kg; vasopressors for persistent hypotension, norepinephrine (first agent), vasopressin (second agent), epinephrine (third agent); hydrocortisone 200 mg/d if ongoing vasopressor requirement; consider adding dobutamine to norepinephrine or switch to epinephrine in septic shock patients with decreased LVEF; consider use of pulmonary artery catheter in patients with mixed septic and cardiogenic shock Chest x-ray or ultrasound with noncardiogenic bilateral infiltrates and Pao2/Fio2 <300 mmHg or Spo2/Fio2 ≤315 Maintain Spo2 90–96%; use high-flow nasal canula in patients with adequate neurologic status; target plateau pressure <30 cmH2O and tidal volume of 6–8 mL; consider rescue therapies in patients with refractory hypoxia Treat underlying infection, maintain renal perfusion, avoid nephrotoxic agents; start renal replacement therapy for progressive acidemia, hyperkalemia, uremia, or volume overload; infuse sodium bicarbonate if renal failure and pH ≤7.2. Elevated bilirubin, alkaline phosphatase, and transaminases; right upper quadrant ultrasound Treat underlying infection, avoid hypotension and hepatoxic agents; stress ulcer prophylaxis for highrisk patients; enteral feeding if shock controlled within 48 h; parenteral feeding if nutrition goal not met within 7 days; insulin if blood glucose ≥180 g/dL Thrombocytopenia, increased fibrin split products, decreased fibrinogen, prolonged PT/INR Administer cryoprecipitate for fibrinogen <150 mg/dL, platelets for platelet count ≤50 × 109/L and evidence of bleeding, and fresh frozen plasma for prolongated PT/INR and evidence of bleeding; transfuse packed red blood cells for hemoglobin <7.0 g/dL Intravenously administered fluids and vasopressors are used to restore and maintain blood pressure and tissue perfusion in the setting of septic shock. An indwelling arterial catheter should be placed as soon as feasible to continuously monitor blood pressure invasively. Crystalloid solutions are preferred over colloid for ini tial volume resuscitation, although colloid such as albumin can be considered in patients who have already received large volumes of crystalloid. Balanced crystalloid solution, such as lactated Ringer’s, may be preferrable to 0.9% normal saline, which is more likely to induce hyperchloremic metabolic acidosis associated with renal vasoconstriction and kidney injury. Use of pentastarch or hydroxy ethyl starch is associated with severe kidney injury and death and should be avoided. Crystalloid should be administered as a bolus over 5–10 min at a volume of ~30 mL/kg. However, 30 mL/kg may not be appropri ate for all patients, including those with end-stage renal disease and systolic heart failure. Protocolized fluid resuscitation targets including central venous pressure (CVP) of 8–12 mmHg, central venous oxygen saturation >70%, and urine output ≥0.5 mL/kg per h have not been associated with improved mortality and so are not recommended to guide total fluid replacement. Instead, dynamic assessment of volume responsiveness using capillary refill time, passive leg raise maneuver, and point-of-care ultrasound, with iterative reevaluation, should guide total volume administered and is preferred over static measurements of volume responsiveness such as CVP. Notably, a 2017–2018 clinical trial conducted in 28 ICUs in five countries found that resuscitation guided by capillary refill time compared with lactate level–targeted resuscita tion did not reduce all-cause 28-day mortality,

an important finding for sepsis care in resource-limited settings. In patients who have received adequate fluid resuscitation yet remain hypotensive, a continuous norepinephrine drip should be initiated as

the first-line vasopressor to maintain a mean arterial pressure target of ≥65 mmHg. Vasopressin should be added as a second agent, and epinephrine as a third agent, if needed, to achieve the blood pressure target. A contemporary randomized clinical trial tested the efficacy of early restrictive (i.e., prioritizing vasopressors and lower intravenous fluid volumes) versus liberal (i.e., prioritizing higher volumes of intra venous fluids before vasopressors use) fluid management in the first 4 h of presentation in patients with septic shock. Across 1563 patients at 60 U.S. medical centers, there was no difference in 90-day mortality. In septic patients with evidence of myocardial dysfunction (e.g., low cardiac output, elevated filling pressures) and evidence of persistent hypoperfusion following adequate volume resuscitation, consideration should be given to adding dobutamine to norepinephrine or using epinephrine alone to increase inotropy. While routine use of pulmo nary artery catheters to guide fluid management in sepsis has not been associated with improved outcomes, use may be considered in patients with mixed septic and cardiogenic shock. In patients with septic shock and ongoing requirement for vasopres sor therapy, it is recommended to start intravenous corticosteroids with hydrocortisone at a dose of 200 mg/d often provided as 50 mg every 6 h. ■ ■ACUTE LUNG INJURY Lung injury, manifesting as acute hypoxic respiratory insufficiency or failure, and termed acute respiratory distress syndrome (ARDS), com plicates ~7% of sepsis cases. ARDS is a syndrome that is classified by noncardiogenic diffuse pulmonary infiltrates and hypoxemia, in which infiltrates can be determined by x-ray or ultrasound imaging, and hypoxemia can be determined by Pao2/Fio2 <300 mmHg or percent oxygen saturation (Spo2)/Fio2 ≤315. The pathogenesis of ARDS over laps with that of sepsis, in which activated myeloid cells and soluble inflammatory mediators disrupt pneumocytes' and endothelial cells' structure and function, resulting in leakage of plasma components and further recruitment of immune cells into lung alveolar and interstitial spaces. The histopathologic correlate of ARDS is diffuse alveolar dam age, which progresses through early exudative, then proliferative, and finally fibrotic stages. Initial management of acute lung injury in sepsis requires admin istration of oxygen to meet cellular metabolic demand while limiting cellular injury from oxidative stress, with a reasonable Spo2 target being 90–96%. In patients with adequate neurologic status, and absent other specific contraindications, high-flow nasal canula is preferred over noninvasive ventilation to improve hypoxia in patients without hypercapnia. For patients with ARDS who require invasive mechani cal ventilation, targeting a plateau pressure of <30 cmH2O and a tidal volume of 6–8 mL/kg, based on ideal body weight, has been associated with reduced mortality and is recommended. In patients with refrac tory hypoxia despite low tidal volume ventilation, rescue measures including prone positioning, neuromuscular blockade, and venove nous extracorporeal membrane oxygenation should be considered. ■ ■ACUTE KIDNEY INJURY Acute kidney injury (AKI) occurs in up to two-thirds of patients with sepsis or septic shock and is associated with increased mortal ity and risk of chronic kidney disease and disability among survivors. Sepsis-associated AKI presents with oliguria or anuria and elevated serum creatinine and blood urea nitrogen and accounts for all AKI cases occurring within 7 days of sepsis onset. Sepsis-associated AKI may be attributed to sepsis, associated complications (e.g., abdominal compartment syndrome), and clinical management including admin istration of nephrotoxic substances such as antibiotics and intravenous contrast dye. Factors that contribute to pathogenesis of AKI due to sepsis alone, termed sepsis-induced AKI, include renal hypoperfu sion, microvascular injury and dysfunction,

inflammatory cellular and soluble mediators, and altered renal tubular metabolic and mitochon drial function. Many serum and urine biomarkers have been evaluated to improve early recognition and treatment of sepsis-associated AKI. However, to date, none have been shown to improve outcomes. Management of sepsis-associated AKI includes treating underlying infection, maintaining renal perfusion with fluid resuscitation and

vasopressors to achieve blood pressure goals, avoiding nephrotoxic agents when possible, and identifying and treating reversible causes. Initiating early renal replacement therapy (RRT), including intermit tent hemodialysis or continuous renal replacement therapy (CRRT), during sepsis-associated AKI is not associated with improved out comes, and so RRT should be started for standard definitive indica tions including progressive acidemia, hyperkalemia, uremia, or volume overload. CRRT is better tolerated than intermittent hemodialysis in patients with septic shock, allowing for less dynamic intravascular vol ume shifts and so is preferred in these patients when available. Sodium bicarbonate infusion should be considered only in patients with AKI and severe metabolic acidemia (pH ≤7.2) to maintain vasopressor effectiveness and mitigate fatal ventricular arrythmia risk.

■ ■GASTROINTESTINAL COMPLICATIONS Approximately 50% of patients with septic shock develop liver dysfunc tion, which is associated with increased mortality. Clinical findings may include right upper quadrant pain, jaundice, and asterixis depend ing on severity. Common laboratory findings include elevated serum bilirubin and alkaline phosphatase levels and elevated transaminases if marked hypotension occurs. Sepsis-induced cholestasis is attributed to impaired bile formation and decreased flow in a nonobstructive pat tern. The liver plays an essential role in microbial clearance, in which the Kupffer cells phagocytose bacteria, release proinflammatory cyto kines and chemokines, and bind platelets. Neutrophils are recruited to liver sinusoids, release NETs to trap pathogens, and contribute to a proinflammatory and prothrombotic environment. In autopsy stud ies of fatal sepsis, hepatitis and steatosis are detected in most patients, while portal inflammation, centrilobular necrosis, hepatocellular apop tosis, and cholangitis may also be detected. Management of liver injury and dysfunction during sepsis includes treating the underlying infec tion and avoiding hypotension and hepatoxic medications. In septic patients with elevated serum bilirubin, abdominal ultrasound should be performed to evaluate for biliary obstruction, cholecystitis, and cholangitis. CHAPTER 315 Sepsis and Septic Shock Sepsis has also been associated with alteration of the intestinal mucosa including increased epithelial permeability, changes in gut microbiota, and translocation of enteric microbes into circulation. In patients with sepsis and septic shock and risk factors for gastrointes tinal bleeding (e.g., mechanical ventilation, coagulopathy, preexisting liver disease, high organ failure score, and need for RRT), stress ulcer prophylaxis is recommended. Decreased splanchnic perfusion and increased interstitial edema contribute to impaired intestinal absorp tion, which in combination with the catabolism of sepsis contributes to nutritional deficiencies. The route and timing of supplemental nutrition administration in patients with sepsis and septic shock are debated. Current recommendations are to initiate enteral nutrition early, within 48 h of diagnosis, in patients in whom shock is controlled with fluids and vasopressors and absent contraindications like bowel ischemia. The rationale for early enteral feeding is to maintain enteric epithelial integrity while limiting negative nitrogen and caloric balance. Supplemental use of parenteral nutrition is suggested if nutritional goals are unmet within 7 days by enteric feeding and supplemental glucose infusion. Insulin therapy is recommended for patients with blood glucose levels >180 mg/dL. ■ ■HEMATOLOGIC COMPLICATIONS Coagulation abnormalities in sepsis are common, ranging from isolated

thrombocytopenia to disseminated intravascular coagulation (DIC), and can manifest with clinical or subclinical thrombosis and hemor rhage. Up to 35% of septic shock patients meet DIC criteria, including thrombocytopenia, increased fibrin split products, decreased fibrino gen, and prolonged prothrombin time (PT)/international normalized ratio (INR), which is associated with increased mortality. Given that DIC is a late manifestation of coagulation abnormalities in sepsis, a scoring system for earlier detection of sepsis-induced coagulopathy (SIC) has been proposed. SIC scoring, which considers platelet counts, PT, and SOFA score, is more sensitive than DIC criteria for recognizing coagulation abnormalities in sepsis. However, the clinical utility of SIC

Revision #1
Created 2026-01-06 16:34:16 UTC by Omar Ayman
Updated 2026-01-06 16:34:16 UTC by Omar Ayman