Chapter 46: Sepsis and Septic Shock

INTRODUCTION

- The older and more recent definitions of terms related to *sepsis* are given in **Table 46-1**. Sepsis-3 redefined sepsis by combining sepsis and severe sepsis from the Sepsis-2 guideline.

TABLE 46-1

Comparison of Definitions from Sepsis-2 and Sepsis-3 Guidelines

Sepsis-2 Guideline (2012)	Sepsis-3 Guideline (2016)
Systemic inflammatory response syndrome (SIRS) to infectious or noninfectious insults: Two or more of the following: • Temperature >38°C or <36°C • Heart rate >90 beats/minute • Respiratory rate >20 breaths/minute • WBC >12,000/mm^3 (12×10^9/L) or <4000 cells/mm^3 (4×10^9/L) or >10% (0.10) immature bands **Sepsis:** SIRS + probable or documented infection **Severe sepsis:** Sepsis + one or more organ dysfunction or hypoperfusion **Septic shock:** Sepsis + refractory hypotension despite fluid resuscitation (30 mL/kg) or serum lactate >1 mmol/L	**Sepsis:** Life-threatening organ dysfunction caused by a dysregulated host response to infection • Acute change in total SOFA score ≥2 points **Septic shock:** Sepsis + persistent hypotension requiring vasopressor use and serum lactate >2 mmol/L despite adequate fluid resuscitation

SOFA, sequential organ failure assessment; WBC, white blood cell.

ETIOLOGY AND PATHOPHYSIOLOGY

- Patients at risk for infection who are predisposed to sepsis include advanced or very young age; preexisting conditions including heart failure, diabetes, chronic obstructive pulmonary disease, cirrhosis, alcohol dependence, and end-stage renal disease; and other immunosuppressive diseases such as neoplasm and human immunodeficiency virus (HIV) disease.

- The most common anatomic source of infection that leads to sepsis is the lung (40%–42%), followed by intra-abdominal space (31%–34%) and genitourinary tract (11%–15%). The microorganisms isolated from blood cultures of patients with sepsis or septic shock include gram-negative organisms in 44%–59% of patients, gram-positive bacteria in 37%–52%, anaerobic organisms in 5%, and fungi in 4%–10%.

- *Escherichia coli* is by far the most commonly isolated gram-negative microorganism in sepsis (55%–60%), followed by *Klebsiella* species, *Proteus* species, *Enterobacter* species, and *Pseudomonas aeruginosa.* Mortality increases significantly with increasing severity of sepsis (3.5% for sepsis, 9.9% in severe sepsis, and 29% in septic shock), especially in presence of *P. aeruginosa.* The most common gram-positive organisms are *Staphylococcus aureus*, followed by coagulase-negative *Staphylococci*, *Enterococcus* species, and *Streptococcus pneumoniae.*

- *Candida* species (particularly *Candida albicans*) are common fungal etiologic agents of bloodstream infections. The 30-day mortality rate for

sepsis due to candidemia is 54%.

- The pathophysiologic focus of gram-negative sepsis has been on the lipopolysaccharide (endotoxin) component of the gram-negative cell wall membrane. Lipid A is a part of the endotoxin molecule from the gram-negative bacterial cell wall that is highly immunoreactive and is responsible for most of the toxic effects. In gram-positive sepsis, the exotoxin peptidoglycan on the cell wall surface appears to exhibit proinflammatory activity.
- Sepsis involves a complex interaction of proinflammatory (eg, tumor necrosis factor-α [TNF-α]; interleukin [IL]-1, IL-6, IL-12) and anti-inflammatory mediators (eg, IL-1 receptor antagonist, IL-4, and IL-10).
- TNF-α concentrations are elevated early in the inflammatory response during sepsis. TNF-α also stimulates release of cyclooxygenase-derived arachidonic acid metabolites (thromboxane A2 and prostaglandins) that contribute to vascular endothelial damage.
- A primary mechanism of injury with sepsis is through endothelial cells. With inflammation, endothelial cells allow circulating cells (eg, granulocytes) and plasma constituents to enter inflamed tissues, which may result in organ damage.
- A key endogenous substance involved in inflammation of sepsis is activated protein C, which enhances fibrinolysis and inhibits inflammation. Levels of protein C are reduced in patients with sepsis.
- Shock is the most ominous complication associated with gram-negative sepsis and causes death in about one-half of patients. Another complication is disseminated intravascular coagulation (DIC). Simultaneous widespread microvascular thrombosis and profuse bleeding from various sites characterize DIC. DIC can produce acute renal failure, hemorrhagic necrosis of the gastrointestinal (GI) mucosa, liver failure, acute pancreatitis, acute respiratory distress syndrome (ARDS), and pulmonary failure.
- ARDS and acute kidney injury are other common complications of sepsis. ARDS can result in loss of functional alveolar volume, impaired pulmonary compliance, and profound hypoxemia.
- The hallmark of the hemodynamic effect of sepsis is the hyperdynamic state characterized by low systemic vascular resistance (SVR) and high cardiac output with tachycardia and arterial hypotension.

CLINICAL PRESENTATION

- The clinical presentation of sepsis varies significantly depending on the site of the infection (ie, pulmonary versus urinary tract), host response to the infection based on the patient's underlying health status and risk factors, and organ dysfunction. The initial presentations may include general malaise or myalgia and nonspecific signs such as fever (or hypothermia), chills, tachycardia, tachypnea, or change in mental status.
- Progression of uncontrolled sepsis leads to evidence of organ dysfunction, which may include oliguria, hemodynamic instability with hypotension or shock, lactic acidosis, hyperglycemia or hypoglycemia, possibly leukopenia, DIC, thrombocytopenia, ARDS, GI hemorrhage, or coma.
- Sepsis-3 redefined sepsis to "life-threatening organ dysfunction caused by a dysregulated host response to infection." Early recognition using a formal screening tool is critical, such as the SOFA scoring system. SOFA encompasses various organ systems such as pulmonary, hepatic, cardiovascular, renal, and neurological and gives a score ranging from 0 to 4 for each system. A SOFA score of 2 or more is associated with an increased risk of mortality by 10% in hospitalized patients with presumed infection.

TREATMENT

- Goals of Treatment: The primary goals include: timely diagnosis and identification of the pathogen, prompt hemodynamic support, rapid identification of the pathogen and source control either medically and/or surgically, early initiation of appropriate broad-spectrum antimicrobial therapy, and avoidance complications such as organ failure and septic shock.
- Evidence-based treatment recommendations for sepsis and septic shock from the *Surviving Sepsis* campaign are presented in **Table 46-2**.

TABLE 46-2

Evidence-Based Treatment Recommendations and Best Practice Statements

Recommendations	Recommendation Grades
Fluid therapy	
Initial resuscitation from sepsis-associated hypotension with at least 30 mL/kg of IV crystalloid fluid within 1 hour	Strong recommendation, low evidence
Either balanced crystalloids or saline for additional fluids guided by frequent assessment of dynamic variables	Weak recommendation, low evidence
Antimicrobial therapy	
IV broad-spectrum antibiotic within 1 hour of diagnosis of sepsis and septic shock against likely bacterial/fungal pathogens	Strong recommendation, moderate evidence
Reassess antibiotic therapy daily with microbiology and clinical data to narrow coverage (de-escalation)	BPS
Optimize dosing strategies based on pharmacokinetics/pharmacodynamics parameters in patients with sepsis or septic shock	BPS
Empiric combination therapy for patients with multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* species or septic shock	Weak recommendation, low evidence
Treatment duration of 7–10 days for most serious infections	Weak recommendation, low evidence
Vasopressors	
Initiate vasopressor therapy to maintain MAP ≥65 mm Hg	Strong recommendation, moderate evidence
Norepinephrine as the first-choice vasopressor	Strong recommendation, moderate evidence
Add vasopressin or epinephrine to norepinephrine to maintain adequate blood pressure	Weak recommendation, moderate evidence
Add vasopressin to norepinephrine to decrease norepinephrine dosage	Weak recommendation, moderate evidence
Corticosteroids	
Hydrocortisone 200 mg IV per day for septic shock only when hemodynamically unstable after adequate fluid resuscitation and vasopressors	Weak recommendation, low evidence
Hydrocortisone should be tapered when vasopressors are no longer required	Weak recommendation, low evidence
Glucose control	

Use insulin dosing protocol when two consecutive blood glucose levels are >180 mg/dL (10 mmol/L), targeting an upper blood glucose <180 mg/dL (10 mmol/L)	Strong recommendation, high-level evidence
Monitor blood glucose every 1–2 hours until insulin infusion rates are stable, then every 4 hours thereafter	BPS
Venous thomboembolism prophylaxis	
Use daily low-molecular-weight heparin (LMWH) over unfractionated heparin	Strong recommendation, moderate evidence
Combination of LMWH and intermittent pneumatic compression, whenever possible	Weak recommendation, low evidence
If creatinine clearance is <30 mL/min (0.5 mL/sec), use unfractionated heparin or dalteparin	Weak recommendation, low evidence
Stress ulcer prophylaxis	
Stress ulcer prophylaxis should be given to patients who have bleeding risk factors	Strong recommendation, low evidence
Either proton pump inhibitors or H2 receptor blockers	Weak recommendation, low evidence

BPS, best practice statement; MAP, mean arterial pressure.

Antimicrobial Therapy

- Once the source of infection is identified, prompt efforts to eradicate that source should be made as progression of sepsis can occur despite rapid initial resuscitation including fluid and appropriate antimicrobials in the absence of adequate source control.
- The Sepsis-3 guidelines recommend administration of empiric broad-spectrum therapy with one or more IV antimicrobials within 1 hour of recognition of sepsis or septic shock to treat most likely pathogens. Rapid identification of candidemia is critical in prompt initiation of appropriate therapy.
- The regimen selected should be based on the type or anatomic site of infection, the most likely pathogens, acquisition of the organism from the community or healthcare institution, and the usual antibiotic susceptibility and resistance profile of the prevalent pathogens at the institution.
- The antibiotics that may be used for empiric treatment of sepsis based on site of infection are listed in **Table 46-3**.
- Patients with nosocomial infections are at risk for sepsis with MRSA, and an anti-MRSA agent such as vancomycin should be initiated empirically in most cases.
- If *P. aeruginosa* is suspected, or with sepsis from hospital-acquired infections, an antipseudomonal cephalosporin (**ceftazidime** or **cefepime**), antipseudomonal fluoroquinolone (**ciprofloxacin** or **levofloxacin**), or an aminoglycoside should be included in the regimen.
- When *S. aureus* is likely to be methicillin-resistant, **linezolid** may be preferred to vancomycin because of the poor penetration of vancomycin into the lungs, as well as the worldwide emergence of glycopeptide intermediately resistant *S. aureus.*
- The average duration of antimicrobial therapy in a patient with sepsis is 7–10 days in the absence of source control issues, and fungal infections can require 10–14 days. The Surgical Infection Society recommends no more than 4 full days of antimicrobial therapy for patients with adequate

source control and no more than 5–7 days in patients in whom a definitive source control was not performed.

- Empiric treatment of invasive candidiasis based on clinical assessment of risk factors, surrogate markers such as beta-D-glucan for invasive candidiasis, or culture includes echinocandins, triazoles, or a formulation of **amphotericin B**. The choice depends on the clinical status of the patient, the local susceptibility of the most prevalent *Candida* species, recent exposure to antifungal agents, relative drug toxicity, and the presence of organ dysfunction or shock that would affect drug clearance. Preferred empiric therapy for suspected invasive candidiasis in nonneutropenic patients in the ICU is an echinocandin (**anidulafungin, micafungin**, or **caspofungin**).
- Triazoles (**fluconazole, voriconazole**) are recommended in hemodynamically stable patients who have not had previous triazole exposure and not known to be colonized with azole-resistant *Candida* species.
- Broad-spectrum-antibiotics should be initiated empirically due to the serious nature of the disease, but the antimicrobial regimen should be reassessed daily based on the microbiological and clinical data.

TABLE 46-3

Empiric Antimicrobial Regimens in Sepsis

Infection (Site or Type)	Antimicrobial Regimen		
	Community-Acquired	Hospital-Acquired	
Urinary tract	Ceftriaxone or ciprofloxacin/levofloxacin	Ceftriaxone/ceftazidime or ciprofloxacin/levofloxacin	
Respiratory tract	Levofloxacin[a]/moxifloxacin or ceftriaxone + clarithromycin/azithromycin	Piperacillin/tazobactam or ceftazidime or cefepime or carbapenem[b] + levofloxacin/ciprofloxacin or aminoglycoside	±Vancomycin or linezolid
Intra-abdominal	Ertapenem or ciprofloxacin/levofloxacin + metronidazole or ceftriaxone + metronidazole	Carbapenem[b] or piperacillin/tazobactam or ceftazidime/cefepime + metronidazole	
Skin/Soft tissue	Vancomycin or linezolid or daptomycin	Vancomycin + piperacillin/tazobactam	
Catheter-related		Vancomycin	
Unknown	Piperacillin/Tazobactam or carbapenem[b]	Carbapenem[b]	

[a]750 mg once daily.

[b]Imipenem, meropenem, and doripenem.

Fluid and Hemodynamic Support

- Early effective fluid resuscitation is crucial for preventing further sepsis-induced tissue hypoperfusion or septic shock. The Sepsis-3 guidelines recommend treating and resuscitating from sepsis-induced hypoperfusion immediately with at least 30 mL/kg of IV crystalloid fluid given judiciously within the first 3 hours. Target MAP is 65 mm Hg (8.6 kPa) to assess the need for vasopressors. Lactate should be normalized in patients with elevated lactate levels as a marker of tissue hypoperfusion.
- Fluid therapy guided by dynamic assessment of fluid responsiveness by examining cardiac output was associated with decreased mortality

compared to standard care.

- The Sepsis-3 guidelines recommend a crystalloid product (balanced solution such as lactated Ringers and Plasma-Lyte or normal saline) based on accessibility and cost. Colloid (ie, albumin) can be used in patients who have already received considerable amount of crystalloids and continue to require fluid.
- Hetastarch products should be avoided at all times because they increased the risk of renal failure, need for renal replacement therapy, and death in multiple studies.
- Fluid therapy is based on the four phases of septic shock: ROSE—resuscitation, optimization, stabilization, and evacuation. **R**esuscitation phase occurs within minutes, and the patient will most likely have a positive fluid balance especially after the 30 mL/kg bolus. During the **O**ptimization phase, within hours, the goal is to keep a neutral fluid balance between intake and output. During the **S**tabilization phase, which usually occurs in days, the focus should be on organ support and keeping fluid balance neutral to net negative with maintenance doses (30 mL/kg/day) of fluid only. Lastly, the **E**vacuation phase occurs in days to weeks, and it is suggested to keep fluid balance negative.

Inotrope and Vasoactive Drug Support

- Vasopressors should be used to achieve and maintain MAP goal in fluid-resuscitation refractory shock, and they are titrated up carefully to an end point of adequate organ perfusion. Selection and dosage are based on the pharmacologic properties of various catecholamines and how they influence hemodynamic parameters (**Table 46-4**).
- For septic patients with clinical signs of shock and significant hypotension unresponsive to aggressive fluid therapy, norepinephrine is the preferred agent for increasing MAP. In comparison to dopamine, it is less arrhythmogenic and was associated with lower risk of mortality. Epinephrine is an alternative to norepinephrine for refractory hypotension. Phenylephrine is only recommended as a salvage therapy only if tachycardia or arrhythmia makes norepinephrine intolerable.

TABLE 46-4

Mechanism of Action and Hemodynamic Effects of Vasopressors in Septic Shock

Drug	Receptor Affinity				Physiologic Outcome			
	Dopamine	Alpha-1	Beta-1	Beta-2	HR	SV	SVR	CO
Dopamine (0.5–2)[a]	+++	–	+	–	↔↑	↑	↔ or ↑	↑
Dopamine (5–10)[a]	++	+	+++	+	↑	↑	↔ or ↑	↑↑
Dopamine (10–20)[a]	++	+++	++	–	↑	↑	↑↑	↑
Epinephrine	–	++++	++++	+++	↑	↑	↑↑	↑↑
Norepinephrine	–	++++	++	+	↔ or ↑	↔	↑↑	↑
Phenylephrine	–	+++	–	–	↔ or ↓	–	↑↑	↔
Vasopressin	V1 receptor				↔ or ↓	–	↑↑	↔ or ↓
Angiotensin II	AT receptor				↑	–	↑	↑

[a]mcg/kg/min.

CO, cardiac output; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance; V1, vasopressin receptor 1; V2, vasopressin receptor 2.

Performance Improvement Bundle

- The Sepsis-3 guidelines recommend the 3-hour bundle with the use of a 1-hour care, putting the importance of beginning the initial treatment immediately (**Table 46-5**).

TABLE 46-5

Sepsis-3 (2016) Performance Improvement Checklist for Bundle-Care Compliance

One-hour bundle

- Measure initial lactate
- Repeat in 2 hours if initial lactate >2 mmol/L
- Obtain cultures (blood, urine, sputum, etc.) prior to administration of antibiotics
- Administer broad-spectrum IV antibiotics within 1 hour
- Initial fluid resuscitation of 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L
- Vasopressors if MAP <65 mm Hg during or after completion of fluid resuscitation

Outcome measurements

- Length of stay in ICU and hospital
- Rate of organ dysfunction
- Mortality rate

CVP, central venous pressure; MAP, mean arterial pressure; $ScvO_2$, central venous oxygen saturation.

Adjunctive Therapy

- Recommended blood glucose levels to initiate an insulin protocol are more than 180 mg/dL (>10 mmol/L) with an upper target blood glucose level <180 dL (10 mmol/L) for the majority of critically ill patients to improve the outcome while reducing the risk of hypoglycemia.
- Hydrocortisone 200 mg IV per day should be administered only if hemodynamic stability is not achieved after adequate fluid resuscitation and vasopressor therapy, regardless of the state of adrenal insufficiency. Hydrocortisone should be tapered when vasopressors are no longer required because hemodynamic and immunologic rebound effects have been reported with abrupt cessation of corticosteroids.
- Venous thromboembolism (VTE) prophylaxis with daily subcutaneous low-molecular-weight heparin should be initiated in all patients admitted to the ICU with sepsis and septic shock along with mechanical prophylaxis (intermittent pneumatic compression or graduated compression stockings) unless contraindicated.
- Stress ulcer prophylaxis should be initiated in all patients with sepsis and septic shock who have risk factors for GI bleeding.

See Chapter 137, Severe Sepsis and Septic Shock, authored by S. Lena Kang-Birken and Sul R. Jung, for a more detailed discussion of this topic.