# Chapter 142: Sepsis and Septic Shock

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## UPDATE SUMMARY

**Update Summary**

May 17, 2023

The following section was updated:

- Corrections were made to the answers for self-assessment questions #2, #6, #8, and #15

## CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 46, Sepsis and Septic Shock.

## KEY CONCEPTS

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1. Gram-negative organisms are isolated in 44% to 59% in sepsis or septic shock, followed by gram-positive bacteria in 37% to 52%, and fungi in 4% to 10%. *Candida albicans* remains the most prevalent *Candida* species: however, non-*albicans Candida* species collectively is more frequently isolated.

2. Pathogenesis of sepsis is complex and multifactorial consisting of causative pathogen, host characteristics, and the inflammatory responses during which the interactions between pro- and anti-inflammatory cytokines, procoagulant state, and decreased fibrinolysis occur simultaneously.

3. The highest mortality is reported in patients with complicated intra-abdominal infections, chronic kidney disease, renal replacement therapy, multiple organ dysfunction, candidemia, and septic shock.

4. Initial resuscitation from sepsis-induced hypoperfusion should begin with at least 30 mL/kg of IV crystalloid fluid. Dynamic fluid responsiveness assessment by examining cardiac output with fluid bolus is essential to avoid fluid overload.

5. Prompt initiation of empiric broad-spectrum intravenous (IV) antibiotics within 1 hour of recognition of sepsis or septic shock improves survival, and the regimen should be assessed daily for potential de-escalation.

6. Norepinephrine is the preferred vasopressor in fluid-resuscitation refractory septic shock, and vasopressin may be added to achieve and maintain mean arterial pressure (MAP) goal of at least 65 mm Hg.

7. Implementation of a performance improvement program encompassing sepsis screening for high-risk patients and immediate treatment including fluid resuscitation, antimicrobial agents, treatment includes echinocandins, triazoles, or a formulation of amphotericin B and faster transition to vasopressor to meet MAP goal improves patient outcomes.

8. Intravenous hydrocortisone is recommended for patients with septic shock who require ongoing norepinephrine to maintain target MAP.

9. Initiate insulin therapy at a glucose level of greater than 180 mg/dL (10 mmol/L) with a target range between 144 and 180 mg/dL (8-10 mmol/L) to reduce potential hypoglycemia and associated mortality.

## BEYOND THE BOOK

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Watch the video entitled “Four Ways to Get Ahead of Sepsis” by the Centers for Disease Control and Prevention (CDC), https://www.youtube.com/watch?v=5JvGiAFLels. This 2-minute video provides an overview of manifestation of sepsis especially among individuals who are at high risk of infection. It highlights the importance of prevention, recognition of the signs and symptoms of sepsis, and awareness of sepsis as medical emergency. This video will enhance the students’ understanding regarding the COLLECT and ASSESS steps in the patient care process. In a small group, create your own treatment summary pocket card for sepsis and septic shock based on the 2021 Surviving Sepsis Campaign international guidelines. Name the preferred initial treatment regimen and monitoring plan for the following: fluid resuscitation, antimicrobial therapy, vasopressor, and adjunct therapy including glucose control, corticosteroid, venous thromboembolism prophylaxis and stress ulcer prophylaxis. This activity will enhance the student understanding of key treatment elements of the PLAN step in the patient care process.

## INTRODUCTION

Sepsis is a medical emergency when left untreated has a high probability of death. It has a unique disease process where it may impact multiple organ

systems. The inflammatory response with the release of numerous cytokines will directly affect the vasculature causing a capillary leak, hypovolemia, decreased cardiac output, and hypotension leading to renal failure, heart failure, brain failure, also puts stress on our endocrine system, etc. Due to the potential expansive downward spiral, sepsis requires a prompt recognition, efficient assessment, and aggressive treatment.

The sepsis guidelines published in 2016 (Sepsis-3) derived new categorization and definition of the sepsis continuum.[1] However, it is still important to recognize the old definitions related to the spectrum of sepsis and how they were utilized in the clinical trials and guidelines prior to the 2016 revision. Periods of bacteremia, systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, or multiple organ dysfunction syndrome often overlap, and they signify an important continuum of progressive physiologic decline. *Severe sepsis* was defined in patients with an acute organ dysfunction, such as acute renal failure or respiratory failure in 2012 guidelines (Sepsis-2).[2] Sepsis-induced hypotension is defined as a systolic BP less than 90 mm Hg or MAP less than 70 mm Hg (Table 142-1).[2] *Septic shock* refers to sepsis patients with sepsis-induced hypotension that is refractory to adequate fluid resuscitation, thus requiring vasopressor administration. Sepsis-induced tissue hypoperfusion is defined as infection-induced hypotension, elevated lactate, or oliguria.[2,3] Sepsis-3 redefined sepsis by combining sepsis and severe sepsis from Sepsis-2 guideline as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[1] The definition of septic shock is when a septic patient has persistent hypotension (MAP <65 mm Hg) requiring vasopressor along with continued elevated serum lactate (≥18 mg/dL [2 mmol/L]) post adequate fluid resuscitation defined as 30 mL/kg of crystalloids.

TABLE 142-1

**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 is defined as having two or more of the following:<br>• Temperature >38°C or <36°C<br>• Heart rate >90 beats/minute<br>• Respiratory rate >20 breaths/minute<br>• WBC >12,000/$mm^3$ (12 × $10^9$/L) or <4,000 cells/$mm^3$ (4 × $10^9$/L) or >10% (0.10) immature bands<br><br>**Sepsis**: SIRS + probable or documented infection<br>**Severe sepsis**: Sepsis + one or more organ dysfunction or hypoperfusion<br>**Septic shock**: Sepsis + refractory hypotension despite fluid resuscitation (30 mL/kg) or serum lactate >9 mg/dL (1 mmol/L) | **Sepsis**: Life-threatening organ dysfunction caused by a dysregulated host response to infection<br>• Acute change in total SOFA score ≥2 points<br><br>**Septic shock**: Sepsis + persistent hypotension requiring vasopressor use and serum lactate >18 mg/dL (2 mmol/L) despite adequate fluid resuscitation |

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

*Data from References 1,2.*

## EPIDEMIOLOGY

Sepsis continues to pose a major healthcare burden. The US Nationwide Inpatient Sample reported a significant increase in the hospitalizations due to sepsis from 1.2% in 2005 to 2.7% in 2014.[4] Despite aggressive, prompt medical care and advances, overall in-hospital deaths remain approximately 15%, but the mortality rate may be as high as 50.7% in septic shock.[4-6] In addition, the total cost of hospitalization due to sepsis increased from $22.2 to $38.1 billion between 2005 and 2014, making it the most expensive condition to be treated in US hospitals.[4] Given the public health and financial burden, there is a vital need for clinicians to comprehend the pathophysiology and optimal management approaches for acutely ill patients with sepsis or septic shock.

# ETIOLOGY

## Risk Factors for Infection

Pathogenesis of sepsis is multifactorial, which begins with the patient's specific predisposition to infection. Advanced or young age, and preexisting conditions including heart failure, diabetes, chronic obstructive pulmonary disease, cirrhosis, alcohol dependence, end-stage renal disease, and other immunosuppressive diseases such as neoplasm and human immunodeficiency virus (HIV) predispose patients at risk for infection.[4,7] Male sex has been associated with a higher incidence of sepsis in prior studies; however, the difference between the sexes is diminishing.[7,8] Once the infection occurs, the risk factors for developing sepsis and organ dysfunction have not been well described. However, multiple factors including patients' risk factors for infection, site of infection, etiologic microorganism, and a specific organ dysfunction as well as the number of organs contribute to poor prognosis.[7,9]

## Pathogens

1 Among the microorganisms isolated from blood cultures, gram-negative organisms were isolated in 44% to 59% of patients with sepsis or septic shock, gram-positive bacteria in 37% to 52%, anaerobic organisms in 5%, and fungi in 4% to 10%.[8-12] However, in the majority (approximately 70%) of sepsis cases, a specific causal microorganism was not documented.[8,10]

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%).[9-11]

## Gram-Negative Bacteria

*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*.[9,11,13,14] *P. aeruginosa* and *Acinetobacter* species are more likely to be associated with prior antibiotic exposure and usually exhibit multidrug resistance.[14,15]

Mortality increases significantly with increasing severity of sepsis (3.5% for sepsis, 9.9% in severe sepsis, and 29% in septic shock), especially in the presence of *P. aeruginosa*.[14] Furthermore, the severity of underlying conditions is a major factor associated with the negative outcome of gram-negative sepsis. For example, patients with severe or fatal conditions, such as acute leukemia, aplastic anemia, cirrhosis, or HIV, have a significantly worse prognosis than those patients with nonfatal underlying conditions such as diabetes mellitus or chronic renal insufficiency.[7]

## Gram-Positive Bacteria

The most common gram-positive organisms are *Staphylococcus aureus*, followed by coagulase-negative *Staphylococci*, *Enterococcus* species, and *Streptococcus pneumoniae*.[9,11,13] Higher mortality in *S. aureus* bacteremia was reported in older age, shock, preexisting renal failure, and the presence of a rapidly fatal underlying disease. Enterococci are most commonly isolated from blood cultures following a prolonged hospitalization and treatment with broad-spectrum cephalosporins.

## Anaerobic Bacteria

Anaerobic bacteria, most commonly *Bacteroides fragilis* and *Clostridium* species, are usually considered low-risk organisms for the development of sepsis. If present, anaerobes are often found together with other pathogenic bacteria that are commonly found in sepsis. Polymicrobial infections accounted for 5% to 39% of sepsis, especially in cases of intra-abdominal infections.[7,11,13] Mortality rates associated with polymicrobial infections are similar to sepsis caused by a single organism.

## Fungi

Candidemia is among the most common fungal etiologic causes of bloodstream infections. *Candida albicans* remains the most prevalent *Candida*

species from blood isolates (38%-61%), but there are increasing incidences of invasive infections due to non-*albicans* species.[9,12,16-18] Non-*albicans* *Candida* species include *C. glabrata* (16%-28%), *C. parapsilosis* (14%-17%), *C. tropicalis* (7.5%-17%), and *C. krusei* (4.1%). Traditionally, risk factors for fungal infection include abdominal surgery, poorly controlled diabetes mellitus, prolonged granulocytopenia, use of broad-spectrum antibiotics or corticosteroids, prolonged hospitalization, central venous catheter, total parenteral nutrition, hematologic malignancy, and chronic indwelling bladder (Foley) catheter. Patients with candidemia and severe sepsis and septic shock were more likely to have been admitted from nursing homes or transferred from outside hospitals.[12]

The use of azoles in response to the rising incidences of *Candida* bloodstream infection has led to fluconazole-resistant *Candida* species. Resistance to fluconazole occurs in 17% of *C. albicans*, 58% of *C. parapsilosis*, 33% of *C. glabrata*, and 100% of *C. krusei* among critically ill patients with invasive candidiasis.[17]

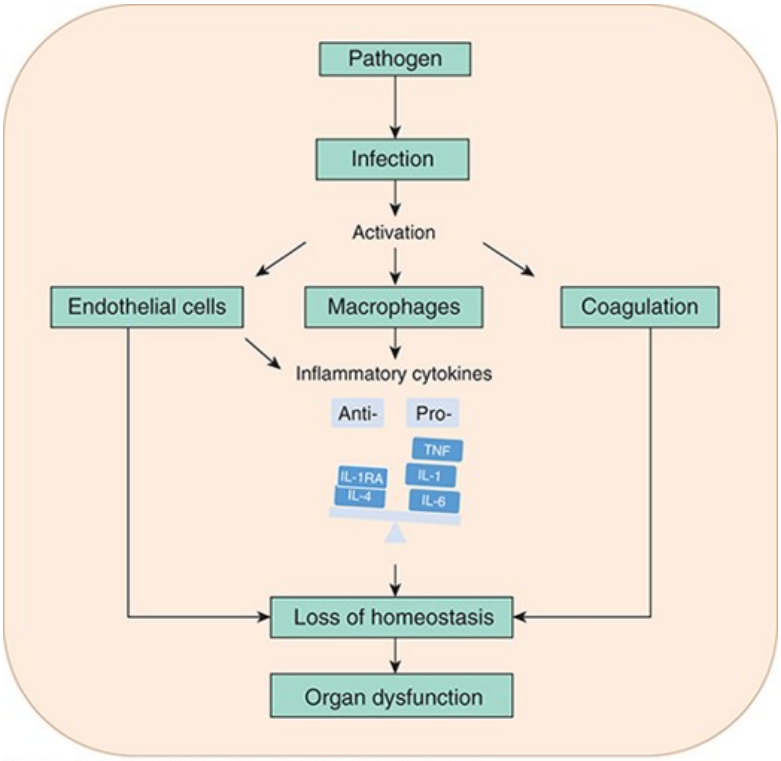
Patients with septic shock due to candidemia had a 30-day mortality rate of 54%. A higher in-hospital mortality of 61% was reported among patients with healthcare-associated candidemia. The mortality rate was 53% in patients with *C. krusei* candidemia; *C. parapsilosis* candidemia was associated with the lowest 12-week mortality rate of 24%.[19]

## PATHOPHYSIOLOGY

2 The cascade leading to the development of sepsis is complex and multifactorial, involving causative pathogen (virulence and organism load), host characteristics (comorbidities and immunosuppression), and the inflammatory responses (Fig. 142-1). The inflammatory responses lead to damage to host tissue, and the anti-inflammatory response causes leukocytes to activate. If the balance to control the local inflammatory process and to eradicate the invading pathogens is lost, systemic inflammatory response occurs which may lead to sepsis and septic shock.

**FIGURE 142-1**

Pathophysiology of sepsis.




Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

### Cellular Components for Initiating the Inflammatory Process

The pathophysiologic focus of gram-negative sepsis has been on the lipopolysaccharide component of the gram-negative bacterial outer cell membrane. Commonly referred to as endotoxin, this substance is generally released with bacterial lysis. Upon its release, it forms a complex with an endogenous protein called a lipopolysaccharide-binding protein. Lipid A is the innermost region of the lipopolysaccharide and is highly immunoreactive. Its predominant effect is to activate macrophages through the CD14 receptor located on the macrophage. This endotoxin-lipopolysaccharide–binding protein complex is responsible for most of the toxic effects—the release of cytokine mediators which triggers the inflammatory cascade that is critical in the progression to sepsis and/or septic shock.[20]

In gram-positive sepsis, the exotoxin peptidoglycan on the cell wall surface exhibits pro-inflammatory activity. Similar to lipid A component of gram-negative bacteria, the exotoxin peptidoglycan binds to the CD14 receptors of the macrophages. However, the potency of exotoxin peptidoglycan is less than that of endotoxin.[20] Clinically important exotoxins are those produced by *S. aureus* and *Streptococcus pyogenes* in septic shock.

### Pro- and Anti-Inflammatory Mediators

A complex interaction between pro-inflammatory and anti-inflammatory mediators plays a major role in the pathogenesis of sepsis. In general, pro-inflammatory reactions are directed at eliminating invading pathogens and the anti-inflammatory reactions limit local and systemic tissue injury. The key pro-inflammatory mediators are tumor necrosis factor (TNF) and interleukin (IL)-1, IL-6, and IL-12, which are released by activated macrophages and endothelial cells. The TNF level is highly elevated early in the inflammatory response in the majority of patients with sepsis, which leads to activation of other cytokines such as IL-1 and IL-6, associated with cellular damage. There is a correlation between the plasma TNF levels and the severity of sepsis and poor prognosis. In addition, higher levels of IL-6 have been reported in patients with septic shock than in those with SIRS.[21] TNF also stimulates the release of cyclooxygenase-derived arachidonic acid metabolites (thromboxane $A_2$ and prostaglandins) that contribute to vascular endothelial damage.

The significant anti-inflammatory mediators include interleukin-1 receptor antagonist (IL-1RA) IL-4, and IL-10. IL-1RA binds to IL-1, blocking its activity. Furthermore, anti-inflammatory cytokines inhibit the production of the pro-inflammatory cytokines and down-regulate some inflammatory cells. Levels of IL-10 and IL-1RA are higher in septic shock than in sepsis, and higher levels are found among nonsurviving patients than in survivor.[21,22]

The activation and secretion of pro- and anti-inflammatory mediators in septic shock occur as a simultaneous immune response as early as the first 24 hours of diagnosis, but the balance between pro- and anti-inflammatory mechanisms determines the degree of inflammation, ranging from local antibacterial activity to systemic tissue toxicity, organ failure, shock, or death (Fig. 142-1).

### Cascade of Sepsis

Macrophages and endothelial cells produce a variety of cytokines that mediate a primary mechanism of injury in sepsis. When injured, endothelial cells allow circulating cells such as granulocytes and plasma constituents to enter inflamed tissues, which can result in organ damage.

The microcirculation is also affected by sepsis-induced inflammation. The arterioles become less responsive to either vasoconstrictors or vasodilators. The capillaries are less perfused even at the early phases of septic shock, and there is neutrophil infiltration and protein leakage into the venules.[23]

The inflammatory process in sepsis is also directly linked to the coagulation system. Pro-inflammatory mechanisms that promote sepsis are also procoagulant and antifibrinolytic, whereas fibrinolytic mechanisms can be anti-inflammatory.[24] A key endogenous substance involved in inflammation of sepsis is activated protein C, which enhances fibrinolysis and inhibits inflammation. Levels of protein C are generally reduced in patients with sepsis.[24]

## COMPLICATIONS

Sepsis may lead to several complications including disseminated intravascular coagulation (DIC) and multiple organ dysfunctions, which are important predictors of patient outcome. Among the patients admitted to US hospitals between 2009 and 2014 due to sepsis, approximately half had at least two acute organ dysfunctions.[5] National inpatient data between 2005 and 2014 reported approximately 20% of patients with sepsis having three-organ

dysfunction, and an increase in the proportion of patients having four or more organ dysfunction from 16% to 24%.[4] The organ dysfunction occurred most frequently in kidneys (39%-49%), lungs (24%-43%), and heart (28%-40%).[4,5,8,25,26] Septic shock is the most ominous complication associated with sepsis. Among the patients who presented to the emergency department with sepsis, 3.6% progressed to septic shock within the first 4 hours, and 8.4% progressed to septic shock between 4 and 48 hours.[27] The predictors for progression to septic shock in the latter group included female gender, nonpersistent hypotension, band neutrophils of at least 10% (0.1) in blood, lactate of at least 36 mg/dL (4 mmol/L), and past medical history of coronary artery disease.[27]

## Disseminated Intravascular Coagulation

The host inflammatory response to infection is a protective mechanism against the infecting pathogen. However, it also triggers disturbances in coagulation. A dynamic process between procoagulant mechanisms and naturally occurring anticoagulants occurs nearly universally in septic patients.

The initial procoagulant state is the interaction between the pro-inflammatory cytokines, such as TNF, IL-1, and IL-6, tissue factor expression by endothelial cells and mononuclear phagocytes, and platelet-activating factor, which together contributes to hypercoagulopathy in the early inflammatory state.[28] Simultaneously, antithrombin synthesis is down-regulated, allowing ongoing thrombin formation. This acute phase interaction of the pro-inflammatory and hypercoagulative state is believed to sequester bacteria as part of compartmentalization.[28] Coagulation abnormalities consisting of excessive fibrin formation, compromised fibrin removal from a depressed fibrinolytic system, and endothelial injury may manifest as a small reduction in platelet count and subclinical clotting time prolongation or in more severe cases, DIC.

Simultaneous widespread microvascular thrombosis and profuse bleeding from various sites characterize DIC. Consumption of clotting factors from ongoing thrombosis eventually leads to a hypocoagulable state. Various degrees of coagulation abnormalities may be present in 50% to 70% of septic patients. However, about 35% will progress to DIC.[28] Complications of DIC vary and depend on the affected organ and the severity of the coagulopathy. 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. As the procoagulant state is the key to the ignition of the pathogenesis to DIC and multiple organ dysfunction, coagulation dysfunction and organ dysfunction often coexist in sepsis.

## Acute Kidney Injury

The acute kidney injury (AKI), defined as an absolute increase in serum creatinine of 0.3 mg/dL (27 mmol/L) or more within a 48-hour period, not only affects survival but also leads to worsening of chronic kidney disease or failure requiring renal replacement therapy. Sepsis-induced AKI has been reported up to 49% and was associated with hypoperfusion, leading to renal ischemia. However, normal or even increased renal blood flow may be present in sepsis-induced AKI, providing an explanation for lack of beneficial evidence with the use of dopamine, a renal vasodilator in the treatment of AKI in septic patients. Rather, AKI develops from a complex relationship between the activation of inflammation and pro-inflammatory molecules causing renal tubular injury and tubular epithelial dysfunction.[29] Subsequently, the injured kidney is unable to regulate the blood flow, making it more vulnerable to changes in blood flow as BP varies and ultimately lead to progression to multiple organ dysfunction.

## Acute Respiratory Distress Syndrome

ARDS is a serious and potentially fatal condition, characterized by severe hypoxemia that is resistant to oxygen. The National Inpatient Sample reported increased incidence of ARDS in the United States from 2006 to 2014, and sepsis is one of the most common risk factors (47%), followed by pneumonia (45%) and shock (44%). Moreover, sepsis-associated ARDS had a higher mortality rate in comparison to other risk factors.

ARDS involves multifactorial processes which begin with activated neutrophils and platelets adhering to the pulmonary capillary endothelium which then initiates multiple inflammatory cascades with a release of a variety of toxic substances. There is diffuse pulmonary endothelial cell injury, increased capillary permeability, and alveolar epithelial cell injury. Consequently, interstitial pulmonary edema occurs that gradually progresses to alveolar flooding and collapse. The end result is loss of functional alveolar volume, impaired pulmonary compliance, and profound hypoxemia.[30]

Abnormalities of coagulation and fibrinolysis are also integral to the pathogenesis of ARDS. Coagulation is locally upregulated in the injured lung, whereas fibrinolytic activity is depressed. These abnormalities occur concurrently, but favor alveolar fibrin deposition, leading to local inflammation, macrophage migration, and increased vascular permeability.

### Hemodynamic Effects

Sepsis and septic shock are associated with excessive sympathetic outflow, high plasma catecholamine levels, myocardial depression, vascular hyporeactivity, and autonomic dysfunction. 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.[23,31]

Sepsis-induced myocardial dysfunction, defined as the intrinsic myocardial systolic and diastolic dysfunction of both the left and right sides of the heart, occurs from excessive adrenergic stress.[32] Sepsis from overwhelming inflammation may cause direct myocardial damage (eg, cardiomyopathy and tachyarrhythmia). Simultaneously, the heart, as part of the circulatory system responding to peripheral hemodynamics, may be responding to alterations in preload, afterload, and microcirculation during sepsis. The microvasculature system, consisting of arterioles, capillaries, venules, and microlymphatics, is a functional system that responds promptly to changes in blood flow to the tissues and metabolic demand. It regulates adequate blood flow to tissues, ensuring adequate oxygen delivery and meet the oxygen demand. During sepsis and septic shock, massive pro-inflammatory cytokines are released, targeting the endothelium, the key component of this microvascular blood flow. Consequently, microvascular impairment leads to loss of ability to regulate oxygen distribution within the capillary network.[23] The severity of microcirculatory abnormalities and their persistence are associated with organ dysfunction. The combination of decreased preload, reduced afterload, myocardial dysfunction, microcirculatory impairments, and blood flow redistribution between organs lead to hemodynamic alterations during sepsis.

### Septic Shock

There are four different types of shock syndrome: hypovolemic, cardiogenic, obstructive, and vasodilatory/distributive. Septic shock falls under the vasodilatory/distributive shock. Distributive shock results from overall systemic vasodilation leading to hypoperfusion. Hallmark signs and symptoms of distributive shock include a decrease in BP, an increase in heart rate in response to a decrease in SVR, and pulmonary capillary wedge pressure. The cardiac output is typically normal after adequate fluid resuscitation in vasodilatory shock unlike other syndromes which are expected to have a low cardiac output. Details of the different shock syndromes are discussed in Chapter e42, “Shock Syndromes.”

## CLINICAL PRESENTATION

**CLINICAL PRESENTATION: Sepsis and Septic Shock**

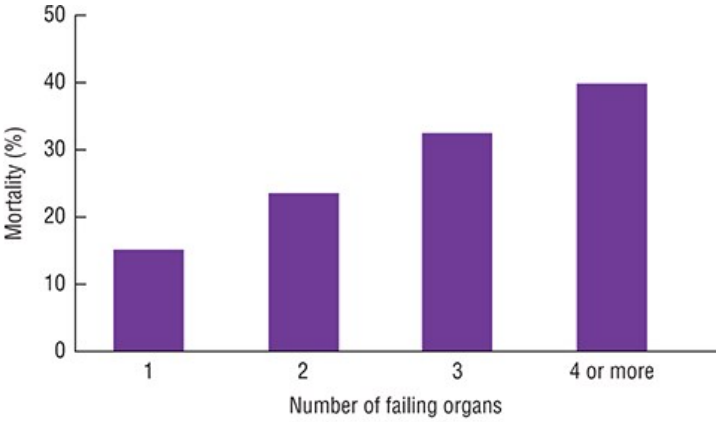
The clinical presentation of sepsis varies significantly depending on the site of the infection (ie, pulmonary versus urinary tract), host response to the infection based on the patient’s underlying health status and risk factors, and organ dysfunction. The initial presentations may include general malaise or myalgia and nonspecific signs such as fever (or hypothermia), chills, tachycardia, tachypnea, or change in mental status. As uncontrolled sepsis progresses, the presentation varies again depending on the specific organ system dysfunction. Arterial hypotension can be present, which may compromise organ perfusion, leading to oliguria. Hyperventilation can occur, causing impaired gas exchange which can then lead to respiratory alkalosis. Altered glucose metabolism, including impaired gluconeogenesis and excessive insulin release, is evidenced by either hyperglycemia or hypoglycemia. Increased glycolysis with impaired clearance of lactate by the hypoperfused liver and kidneys result in elevated lactate levels which then contributes to metabolic acidosis.

### Prognostic Factors

3 The highest mortality was reported in patients with intra-abdominal infection secondary to ischemic bowel (75%), whereas obstructive uropathy-associated urinary tract infection was associated with the lowest hospital mortality (26%).[10] In-hospital mortality rate with AKI in sepsis was two- to threefold higher in patients with stage 3 kidney disease compared to those without kidney disease. Furthermore, the mortality rate was significantly higher in patients receiving renal replacement therapy than those without (40% vs 22%, respectively).[33] Associated mortality rates were also high in patients with severe sepsis and ARDS and DIC (36% and 29%, respectively).[26] As the number of failing organs increased from one to four or more, the mortality rate increased from 15% to 40% (Fig. 142-2).[5] Patients with candidemia generally have septic shock, and the associated mortality is significantly higher in comparison to patients with bacteremia (47% vs 28%, respectively).[12]

FIGURE 142-2

Mortality related to the number of failing organs.




Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*


An elevated serum lactate concentration of more than 36 mg/dL (4 mmol/L) upon initial presentation and persistent elevation in lactate for more than 24 hours were associated with an increased mortality rate.[34] Furthermore, the 28-day mortality rate was the highest (45%) among patients with septic shock and hyperlactatemia of more than 23 mg/dL (2.5 mmol/L), followed by hyperlactatemia without vasopressor need (35%), and no hyperlactatemia with vasopressor need (28%). Hyperlactatemia increased the risk of 28-day mortality independent of vasopressor need.[35]

## Diagnosis

### Identification of Pathogens

The presence of clinical features suggesting sepsis should prompt further evaluation of the patient. In addition to obtaining a careful history of any underlying conditions and recent travel, injury, animal exposure, infection, or use of antibiotics, a complete physical examination should be performed to determine the source of the infection.

A collection of specimens should be sent for culture prior to initiating any antimicrobial therapy to increase the yield of cultures, making identification of a pathogen more likely. Minimally, two sets of blood cultures (both aerobic and anaerobic bottles) should be collected without temporal separation between the sets.[2] Culturing of all body sites is not generally recommended, but the decision regarding which sites to culture requires careful consideration and should be based on the patient presentation and the likely site of infection. With suspected catheter-related infection, one set of blood cultures should be drawn through every lumen of each vascular access device along with peripheral blood cultures. In severe community-acquired pneumonia, respiratory secretions along with blood cultures must be obtained. Urinary antigen detection of *S. pneumoniae* and *Legionella* serogroup 1 is recommended to yield identification. To document a soft tissue infection, a Gram stain and bacterial culture of any obvious wound exudates should be performed. A needle aspiration of a closed infection such as cellulitis or abscess may be needed for Gram stain and bacterial culture. In abdominal infections, fluid collections identified by imaging studies should be aspirated for Gram stains and aerobic and anaerobic cultures. Implementation of accurate and rapid molecular diagnostic testing has demonstrated a positive impact on prescribing appropriate therapy in bloodstream infections such as methicillin-resistant *S. aureus* (MRSA) and *Candida* species.[2,36,37]

A lumbar puncture is indicated in altered mental status, severe headache, or a seizure, assuming there are no focal cranial lesions identified by computed tomography scan. Further tests may be indicated to assess any systemic organ dysfunction caused by severe sepsis. The laboratory tests should include WBC with differential, hemoglobin, platelet count, complete chemistry profile, coagulation parameters, serum lactate, and arterial blood gases. The potential role of biomarkers such as PCT levels or C-reactive protein for diagnosis of infection in patients with sepsis remains undefined as there is no definitive way to discriminate the acute inflammatory pattern of sepsis from other generalized inflammation.[2]

### Assessment of Acutely Ill, High-Risk Patients

Sepsis-3 redefined sepsis to "life-threatening organ dysfunction caused by a dysregulated host response to infection" based on the evidence of greater in-hospital mortality among patients with sequential sepsis-related organ failure.[1,38] As such, early recognition of sepsis using a formal screening tool is critical. Organ dysfunction can be evaluated by using the SOFA scoring system. SOFA encompasses various organ systems such as pulmonary, coagulation, hepatic, cardiovascular, renal, and neurological and gives a score ranging from 0 to 4 for each system to characterize a septic patient's prognosis (Table 142-2). Higher total score is associated with an increased probability of mortality. A SOFA score of 2 or more is associated with an increased risk of mortality by 10% in hospitalized patients with presumed infection.[1] One of the difficulties in using the SOFA score is that clinicians need laboratory results such as platelets, bilirubin, and creatinine, which may not be available initially. Quick SOFA (qSOFA), on the other hand, utilizes three data elements: respiratory rate ≥22 breaths/min, altered mental status, and systolic BP ≤100 mm Hg. qSOFA of ≥2 or SOFA score change of ≥2 can serve as an indication for higher vigilance and potentially quicker escalation of care. If baseline SOFA score is unknown, then score of zero is used as baseline. If a patient has all three mentioned elements, in-hospital mortality can be as high as 40% to 50%.[1] However, the 2021 Surviving Sepsis Campaign guideline recommends that qSOFA should not be used as a single screen tool since it is less sensitive than having two of four SIRS criteria in identifying sepsis-induced organ dysfunction.[39]

TABLE 142-2

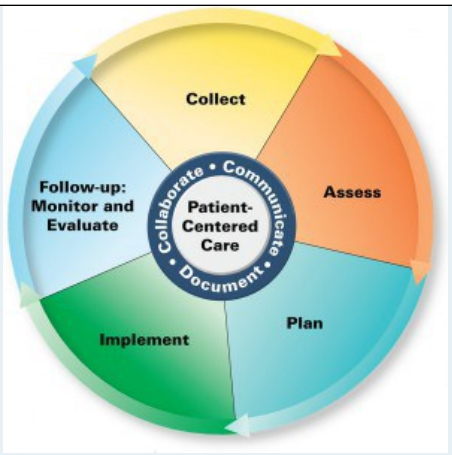
**Abbreviated Sepsis-Related Sequential Organ Failure Assessment**

| Organ System | Measured Variables for Scoring System |
|---|---|
| Pulmonary | $PaO_2/FiO_2$ (<200 to ≥400 mm Hg [26.6-53.2 kPa]) |
| Coagulation | Platelets (<50 to ≥150 × $10^3$/$mm^3$ [50 × $10^9$-150 × $10^9$/L]) |
| Liver | Bilirubin (<1.2-11.9 mg/dL [20.5-203.5 µmol/L]) |
| Cardiovascular | MAP (<70 with or without vasopressor to ≥70 mm Hg) |
| Central nervous system | Glasgow Coma Scale (6-15) |
| Renal | Serum creatinine (<1.2-4.9 mg/dL [106-433 µmol/L]), urine output (<500 mL/d) |

$FiO_2$, fraction of inspired oxygen; MAP, mean arterial pressure; $PaO_2$, partial pressure of oxygen.

*Data from Reference 1.*

## Patient Care Process for Sepsis and Septic Shock




### Collect

- Patient characteristics (eg, age, sex)
- Patient medical history (including recent hospitalization and infection within last 6 months)
- Social history (eg, tobacco/ethanol use/intravenous drug user/place of residence)
- Current medications (prescription and nonprescription; including recent history of antibiotic usage within last 6 months)
- Subjective data (including general constitutional and infection-site specific, onset)
- Objective data
  - Temperature, blood pressure (BP), heart rate, respiratory rate, mean arterial pressure (MAP), $O_2$-saturation, height, and weight
  - Labs including white blood cell (WBC) count with differential, hemoglobin, platelet count, complete serum chemistry including serum creatinine, and bilirubin, lactate, procalcitonin (PCT), coagulation panel including prothrombin time and activated partial thromboplastin time, and arterial blood gas including pH, $PaCO_2$, $PaO_2$, and $HCO_3$
  - Objective parameters for sequential organ failure assessment (see sequential organ failure assessment [SOFA]; Table 142-2)
  - Microbiology data (including Gram stain, culture, rapid diagnostic testing)

### Assess

- Mental status
- Systemic inflammatory response (SIRS) criteria (Table 142-1)
- Hemodynamic stability (eg, systolic BP >100 mm Hg, MAP>65 mm Hg)
- Presence of organ dysfunction (lactate >18 mg/dL (2 mmol/L), baseline; SOFA/qSOFA; Table 142-2)
- Identification of pathogen and antibiotic susceptibility
- Risk of multidrug-resistant bacterial pathogen (recent hospitalization, infection, antibiotic-resistant organism, broad-spectrum antibiotic usage)
- Risk of fungal pathogen (recent usage of broad-spectrum antibiotics/corticosteroids/total parenteral nutrition, abdominal surgery, etc.)

### Plan*

- Initiate 1-hour performance improvement bundle (Table 142-7)
- Initial fluid resuscitation with intravenous (IV) balanced crystalloid for hypotension
- Begin antimicrobial therapy regimen based on site of infection (Table 142-5)
- Perform passive leg raise to assess response to fluid resuscitation (increase in stroke volume by 10%-15%)
- Initiate vasopressor if MAP <65 mm Hg with adequate fluid resuscitation (Table 142-6)
- Administer IV hydrocortisone if ongoing requirement for vasopressor to maintain MAP
- Initiate adjunct therapy including glucose control, venous thromboembolism prophylaxis, and stress ulcer prophylaxis
- Monitoring parameters: including efficacy (eg, signs and symptoms of infection, mental status, MAP, lactate, WBC with differential) and safety

**Implement***

- Management of vasopressor selection after initial norepinephrine
- Daily assessment for opportunities to de-escalate antimicrobial therapy
- Design tapering schedule of IV hydrocortisone
- Coordination of treatment plan during transitioning from the ICU to a medicine unit

**Follow-up: Monitor and Evaluate**

- Resolution of symptoms of infection
- PCT levels along with clinical evaluation to determine the antimicrobial treatment duration
- Normalization of lactate and MAP >65 mm Hg for discontinuation of vasopressors
- Presence of adverse effects of antimicrobial agents and vasopressors

**Collaborate with other healthcare professionals.*

## TREATMENT

Since publication of the Surviving Sepsis Campaign in 2003, key concepts have changed the way we recognize and treat septic patients over the decades.[40] In 2001, early goal-directed therapy (EGDT) with resuscitation targets was introduced, and it heavily influenced the Sepsis-2 guideline.[2,41] The 2016 guideline (Sepsis-3) incorporated the data from the Protocolized Care for Early Septic Shock (ProCESS), Australasian Resuscitation in Sepsis Evaluation (ARISE), and Protocolized Management in Sepsis (ProMISe) trials which failed to confirm the survival advantage of protocolized EGDT.[42-44] In addition, Sepsis-3 not only changed the definition of classifying categories of sepsis but also emphasized the use of dynamic resuscitation markers.

It is important to discuss EGDT since the 2001 trial put the emphasis in early recognition of sepsis and a protocolized, quantitative approach to patient care for this disease state.[41] This was a single center, prospective, randomized study that included 263 patients who met the SIRS criteria and systolic BP ≤90 mm Hg or lactate ≥36 mg/dL (4 mmol/L). Specific resuscitation targets (ie, central venous pressure [CVP] of 8 to 12 mm Hg, MAP ≥65, hematocrit of ≥30% [0.30], and central venous oxygen saturation [$Scvo_2$]≥70% [0.70]) were evaluated for reducing mortality. When EGDT and standard therapy were compared, the standard therapy led to significantly higher 28-day mortality rate. Subsequently, EGDT was quickly adopted and redefined the early, aggressive resuscitation of patients with sepsis and septic shock for the next decade. Notably, the ProCESS (1,341 subjects), ProMISe (1,234 subjects), and ARISE (1,588 subjects) investigators failed to confirm the survival benefits of protocolized targets for CVP and hemoglobin between

EGDT and usual care.[42-44] However, these investigators were able to recognize the disease early allowing for quicker admission of patients from the emergency department to the inpatient care setting which may assist in overall mortality benefit in both standard therapy and EGDT.[45]

## Desired Outcomes

In addition to timely recognition and diagnosis of sepsis, other primary goals include prompt hemodynamic support, rapid identification of the pathogen, source control either medically and/or surgically, early initiation of appropriate IV antimicrobial therapy, and avoidance of complications such as organ failure and septic shock. Supportive care such as stress ulcer prophylaxis and venous thromboembolism prophylaxis is important to prevent complications during the stay in the ICU. Table 142-3 describes the selected treatment recommendations from the surviving sepsis campaign.

TABLE 142-3

**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 |
| Balanced crystalloids instead of normal saline for additional fluids guided by frequent assessment of dynamic measures | 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 |
| Empiric MRSA coverage for patients at high risk for MRSA | Best practices statement |
| Reassess antibiotic therapy daily with microbiology and clinical data to narrow coverage (de-escalation) | Best practices statement |
| Combination therapy for patients at high risk for multidrug-resistant bacterial pathogens | Weak recommendation, low quality evidence |
| Optimize dosing strategies based on pharmacokinetics/pharmacodynamics parameters | Best practices statement (PS) |
| Empiric antifungal therapy for patients at high risk of fungal infection | Weak recommendation, low evidence |
| Shorter duration of treatment duration using clinical evaluation and procalcitonin | 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 to norepinephrine instead of increasing norepinephrine dose to achieve adequate MAP | Weak recommendation, moderate evidence |
| **Corticosteroids** | |
| IV hydrocortisone for septic shock with ongoing requirement for vasopressor | 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 |
| **Venous thomboembolism prophylaxis** | |
| Use daily low-molecular-weight heparin (LMWH) over unfractionated heparin | Strong recommendation, moderate 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 |

MAP, mean arterial pressure; MRSA, Methicillin-resistant *Staphylococcus aureus*.

*Data from Reference 46.*

## Initial Resuscitation

4 Once the patient is recognized for sepsis and septic shock, early effective fluid resuscitation is crucial for preventing further sepsis-induced tissue hypoperfusion. The guidelines recommend at least 30 mL/kg of IV crystalloid fluid within the first 3 hours. The patient should be reassessed for hemodynamic status by measurements with better diagnostic accuracy at predicting those who are likely to respond to additional fluid.[39,46] It also recommends target MAP of 65 mg Hg to assess the need for vasopressors. While MAP indicates degree of tissue perfusion, elevated serum lactate represents tissue hypoxia and therefore should be normalized.

## Fluid Therapy

Initial resuscitation effort with fluid therapy for a septic patient with tissue hypoperfusion or in septic shock is a key therapy.[47] The fluid therapy is closely related to the inflammatory cytokines that are released by the body in response to an infection. The pro-inflammatory cytokines lead to capillary leak. As the fluid travels more freely from intravascular to extravascular space, there is an overall increase in fluid in the extravascular space leading to intravascular hypovolemia. In turn, this causes end-organ edema, dysfunction, and ultimately organ failure. Therefore, understanding how the administered fluid will move within the body is essential. It is important to consider both the indication and the contraindications of available IV fluids carefully, and fluid therapy should be considered as a drug with potential benefits and risks that require frequent assessment.

There are few considerations regarding fluid therapy: initial amount, type of fluid, and duration of therapy.[48] The guidelines recommend the administration of at least 30 mL/kg crystalloids within the first 3 hours. This 30 mL/kg dose was based on observational study. Despite the lack of a robust quality of evidence this dose has been widely used in many landmark trials such as the ProCESS, ARISE, and ProMISe.[42-44] However, this amount of fluid is to be given judiciously within 3 hours. For example, if an 80-kg patient requires 30 mL/kg fluid resuscitation, the complete 2.4 L should not be administered as a single bolus dose, but as needed based on the proper assessment of fluid status and fluid responsiveness. To reduce fluid overload associated with static measurements using an invasive placement of a central venous catheter, dynamic assessment of fluid responsiveness has been used with goal-directed therapy.[49] Dynamic assessment was defined as an increase in stroke volume of more than 10% to 15% after a fluid challenge of 250 to 500 mL of crystalloids or from endogenous source by using the passive leg raise. Passive leg raise is performed by laying the patient in a supine position and raising both legs 45° at the same time. This will allow the blood from the leg to act as a bolus back to the heart. Using the passive leg raise test to check for fluid responsiveness intermittently leads to decreased use of IV fluids, especially for patients who are no longer responding adequately to IV fluid alone. Fluid therapy guided by dynamic assessment of fluid responsiveness by examining cardiac output was associated with decreased mortality compared to standard care.[49] Furthermore, the use of a dynamic assessment also decreased the length of stay in the ICU and the duration of mechanical ventilation.[50]

Guidelines recommend using ideal body weight in fluid resuscition.[39,46] However, the optimal dosing strategy for obese patients with septic shock is unknown. Dosing based on adjusted body weight was associated with improved mortality compared to actual body weight and ideal body weight.[51] Further prospective studies are needed to confirm the optimal fluid dosing in obese patients.

The type of fluid administered (ie, crystalloids such as dextrose, sodium chloride, lactated ringer, and Plasma-Lyte) or colloid (ie, albumin) serves as an important factor in resuscitation (Table 142-4). Ideally, the fluid should expand the intravascular volume without providing excess free water leading to tissue edema.[52] The Saline versus Albumin Fluid Evaluation (SAFE) trial found similar safety but no significant benefit in length of stay in ICUs and mortality between crystalloids and albumin.[53] Based on cost and accessibility, the guidelines recommend a crystalloid product (balanced solution such as lactated ringers and Plasma-Lyte or normal saline) as first-line fluid for resuscitation. Colloid (ie, albumin) can be utilized in patients who have already received considerable amount of crystalloids and continue to require fluid.[46] Hetastarch products should be avoided at all times as they increase the risk of renal failure, requiring renal replacement therapy and death in multiple studies.[46]

TABLE 142-4

**Comparison of IV Fluids–Crystalloids and Colloid**

| | Crystalloids | | | | | Colloid |
|---|---|---|---|---|---|---|
| | Human Plasma | Dextrose 5% | Sodium chloride 0.9% | Lactated ringers | Plasma-Lyte 148 | Albumin 5% |
| pH | 7.35-7.45 | 4 | 5 | 6.5 | 5.5 | 7.4 |
| Osmolarity (mOsmol/L) | 291 | 252 | 308 | 273 | 294 | 330 |
| Sodium (mEq/L or mmol/L) | 135-145 | – | 154 | 130 | 140 | – |
| Chloride (mEq/L or mmol/L) | 96-106 | – | 154 | 109 | 98 | – |
| Potassium (mEq/L or mmol/L) | 3.5-5 | – | – | 4 | 5 | – |
| Bicarbonate (mEq/L or mmol/L) | 23-27 | – | – | 28 (lactate) | 27 (acetate) | – |
| Calcium (mg/dL [mmol/L]) | 8.5-10.5 [2.13-2.63] | – | – | 2.7 | – | – |
| Magnesium (mEq/L [mmol/L]) | 1.8-2.4 [0.9-1.2] | – | – | – | 3 | – |
| Glucose (mg/dL [mmol/L]) | 70-100 [3.9-5.6] | 50 | – | – | – | – |
| Tonicity[a] | | Isotonic[b] | Isotonic | Isotonic | Isotonic | Isotonic |

[a]Tonicity is based on comparison of osmolarity of the product and human plasma. Hypotonic is defined as osmolarity <250 mOsmol/L, isotonic is between 250 and 375 mOsmol/L, and hypertonic is >375 mOsmol/L.

[b]Dextrose 5% acts as hypotonic solution in body. It can also increase $CO_2$ and lactate production.

*Data from Reference 52.*

Among crystalloid solutions, there is increasing evidence of potential harm in developing hyperchloridemic metabolic acidosis from excessive administration of normal saline and subsequent increased renal failure and mortality in comparison to balanced salt solutions.[54-56] The 2021 Surviving Sepsis Campaign guideline updated their nonspecific fluid recommendation to favoring balanced crystalloid over normal saline for resuscitation.[39,54,55,57]

Lastly, the total duration of fluid therapy is based on the four phases of septic shock: ROSE—resuscitation, optimization, stabilization, and evacuation.[48] *Resuscitation* phase occurs within minutes and the patient will most likely have a positive fluid balance especially after the 30 mL/kg bolus. During the second phase of optimization (within hours), the goal is to keep a neutral fluid balance between intake and output. During this time, the clinician should consider the source of infection as well as any potential organ dysfunction when deciding volume and end point in fluid administration. For instance, a patient with peritonitis-related septic shock will most likely require more fluid than pneumonia-associated septic shock. Also, it is important to avoid fluid overload to decrease the risk of ARDS and other consequences such as intra-abdominal hypertension. During

the third phase, *stabilization,* which usually occurs in days, the focus should be on organ support and keeping fluid balance neutral to net negative. During this time, the patient would most likely need maintenance doses (30 mL/kg/day) of fluid only. Finally, the *evacuation* phase occurs in days to weeks, and it is suggested to keep fluid balance negative. While attempting to achieve negative balance, careful deliberation to avoid excess fluid removal is crucial. Another hypotensive event in a recovering septic shock patient can lead to a further damage.

## Infection Source Control

Once the anatomic site of infection is identified, prompt efforts to eradicate that source should be made as source control has been associated with increased survival. In sepsis and septic shock, the infectious foci should be controlled once the patient is stabilized after initial resuscitation, but optimally no more than 6 to 12 hours after diagnosis. With an infected intravascular catheter, the catheter should be removed and cultured. However, infected central venous catheters without septic shock or fungemia may be treated with prolonged antimicrobial therapy if catheter removal is not practical. Urinary tract catheters should be removed if association with sepsis is suspected. Suspicion of soft tissue infections such as cellulitis or wound infection or bone involvement should lead to aggressive debridement of the affected area. Evidence of an abscess or sepsis associated with any intra-abdominal pathology (ie, GI perforation, ischemic bowel, cholecystitis, infected pancreatic necrosis) should prompt surgical intervention. Reduced survival with delayed surgical source control was reported in observational studies, and as such, the Surgical Infection Society guidelines on the management of intra-abdominal infections suggest earlier source control, allowing only a short delay for rapid resuscitation in patients who are hemodynamically unstable with sepsis.[39,46,58]

## Antimicrobial Therapy

5 Empiric IV antibiotics should be administered immediately after initial recognition of sepsis or septic shock as a strong correlation has been reported between time to antimicrobials and mortality.[39,46,47,59]

In addition to the timing of the empiric antibiotic, administration of appropriate antibiotic, especially for multidrug-resistant bacteria, has a great impact in reducing mortality.[14,15,34,60] Inappropriate initial antimicrobial therapy occurred in about 20% of patients with septic shock, and was associated with a fivefold reduction in survival in comparison to those who received appropriate therapy (52% vs 10%, respectively).[61] Early and appropriate antibiotic administration improves the mortality in patients with sepsis and septic shock.[62] Therefore, the guidelines recommend immediate administration of IV antimicrobials, ideally within 1 hour in patients with possible septic shock or a high likelihood for sepsis, but administration within 3 hours may be reasonable in patients with possible sepsis without shock.[39]

Septic shock caused by *C. albicans* demonstrated 25% survival with initial appropriate therapy but only 4.6% survival without.[61] Among the patients with candidemia, delayed appropriate antifungal treatment, especially in the presence of septic shock and failure to achieve timely source control, was independently associated with a greater risk of hospital mortality.[18,63,64] Hence, accurate and rapid identification of candidemia is critical in prompt initiation of appropriate therapy.[37,46]

## Selection of Antimicrobial Agents

The selection of an optimal empiric regimen requires assessment of several factors. Key patient factors include age, concomitant underlying diseases, chronic organ dysfunction (ie, liver or renal failure), presence of immunosuppression (ie, active cancer, neutropenia, or uncontrolled HIV infection), or presence of indwelling devices (ie, central venous lines or urinary catheter). Interviewing the patient or the patient's representative for recent hospitalization, recent history or colonization with specific pathogens, and the receipt of antimicrobials within the previous 3 months is helpful in assessing risk for infection with multidrug-resistant pathogens. Infection factors include 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.

Table 142-5 lists specific empiric antimicrobial regimens for the anatomic site of infection based on the most likely pathogens.[46,58,65-68] However, general suggestions can be made when treating critically ill patients with sepsis or septic shock.

TABLE 142-5

**Empiric Antimicrobial Regimens in Sepsis**

| Infection (site or type) | Antimicrobial regimen | | |
|---|---|---|---|
| | **Community-acquired** | **Hospital-acquired** | **Additional considerations** |
| Urinary tract | Ceftriaxone or ciprofloxacin or levofloxacin | Ceftriaxone or ceftazidime or ciprofloxacin or levofloxacin | |
| Respiratory tract | Levofloxacin[a] or moxifloxacin or ceftriaxone + clarithromycin or azithromycin | Piperacillin/tazobactam or ceftazidime or cefepime or carbapenem[b] + levofloxacin or ciprofloxacin or aminoglycoside | ± Vancomycin or linezolid |
| Intra-abdominal | Ertapenem or ciprofloxacin or levofloxacin + metronidazole or Ceftriaxone + metronidazole | Carbapenem[b] or Piperacillin/tazobactam or Ceftazidime or 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 and meropenem.

For patients at risk for sepsis or septic shock with MRSA, an anti-MRSA agent should be initiated empirically.[40] Risk factors for MRSA include prior history of MRSA infection or colonization, recent IV antibiotics or hospitalization, history of recurrent skin infections, presence of invasive devices, and hemodialysis. Vancomycin remains the mainstay of therapy for MRSA-associated infections.[69] Revised therapeutic monitoring of vancomycin guideline recommends monitoring area under the curve (AUC) over 24 hours in place of monitoring trough levels based on efficacy and nephrotoxicity data in patients with serious infections due to MRSA.[70] The 2016 Infectious Diseases Society of America (IDSA) guidelines recommend either vancomycin or linezolid for hospital-acquired/ventilator-associated pneumonia.[65] Linezolid has better lung penetration into epithelial lining fluids than vancomycin. However, linezolid was not superior to vancomycin in microbiological and clinical cure rates in patients with nosocomial pneumonia due to MRSA.[69]

Daptomycin is a cyclic lipopeptide that exhibits rapid bactericidal activity against gram-positive microorganisms including MRSA and vancomycin-resistant enterococci (VRE).[71] Daptomycin resulted in a 70% success rate for critically ill septic patients with bacteremia due to MRSA, VRE, *E. faecium* or coagulase-negative staphylococci.[71] The daptomycin cohort had significantly lower clinical failure for MRSA bacteremia when matched with vancomycin cohort patients (29% vs 45%) and lower all-cause 30-day mortality (6.1% vs 15.3%).[72]

Bloodstream infections caused by extended-spectrum beta-lactamases (ESBL)-producing Enterobacterales are associated with high rates of morbidity and mortality of up to 44% in patients with sepsis or septic shock.[73] Mortality was especially high with a delay in appropriate antimicrobial therapy.[73,74] The appropriate empiric antibiotic therapy in critically ill patients with sepsis or septic shock is crucial. Carbapenems remain active and have been regarded as the treatment of choice for serious infections due to ESBL pathogens. However, increased use of carbapenems has led to the emergence of carbapenem-resistant Enterobacterales which represents a greater threat. Piperacillin/tazobactam has been evaluated in observational studies as carbapenem-sparing therapy with conflicting results.[74,75] In a meta-analysis of 25 observational studies describing 3,824 participants who received

either beta-lactam/beta-lactamase inhibitor or carbapenem as empiric or definitive therapy for ESBL-producing bacterial bloodstream infections, 30-day mortality was not significantly different.[74] However, all-cause 30-day mortality was 12.3% in the piperacillin/tazobactam group and 3.7% in the meropenem group (absolute risk difference of 8.6%) in hospitalized patients who received definitive treatment for bloodstream infections due to ceftriaxone-resistant *Escherichia coli* or *Klebsiella pneumoniae.*[76] Piperacillin/tazobactam should no longer be considered an alternative to meropenem for definitive treatment of bloodstream infection due to ESBL-producing gram-negative pathogens.

Combination therapy does not appear to be more effective than monotherapy in reducing organ failure or mortality in low-risk patients including sepsis without shock.[13] However, multidrug resistance in sepsis due to gram-negative bacteremia was strongly associated with the receipt of inappropriate empiric therapy and a threefold increase in the risk of hospital mortality.[15] The guidelines suggest using two antimicrobial agents in patients at risk of multidrug-resistant pathogens.[39] Risk factors include recent history of infection due to antibiotic-resistant organism, hospital-acquired infection, and recent history of hospitalization or use of broad-spectrum antibiotics. Once the pathogen and its susceptibilities are reported, double gram-negative coverage is no longer necessary except for highly resistant organisms. The greatest benefit of combination therapy appeared to be in patients with septic shock due to *Pseudomonas* or multidrug-resistant gram-negative bacteremia such as *Acinetobacter* and in neutropenic patients with sepsis or septic shock.[77-79] Combination therapy consisting of antibiotics from two different classes increases the probability of at least one active agent. For instance, if *P. aeruginosa* infection is suspected, beta-lactam antipseudomonal agents (ceftazidime or cefepime), antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin), or an aminoglycoside should be included in the regimen.[65]

## Antifungal Therapy

Patients with candidemia are generally sicker based on their higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores and have a higher mortality rate than those with bacteremia.[12] However, the use of empiric antifungal in all critically ill patients is not supported.[80] As such, clinicians should consider empiric antifungal therapy based on the risk factors for invasive *Candida* infections and no other known cause of fever.[39] The risk factors include febrile neutropenic patients after 4-7 days of broad-spectrum antibiotics, immunocompromised status, dialysis, prolonged invasive vascular devices, total parental nutrition, necrotizing pancreatitis, major surgery especially abdominal, corticosteroids, prolonged ICU stay, or fungal colonization.[39,81]

Invasive candidiasis remains the most common form of fungal infections, and empiric parenteral treatment includes echinocandins, triazoles, or a formulation of amphotericin B.[81,82] The selection 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. Recent exposure to antibiotics and fluconazole has been associated with fluconazole-resistant *Candida* species.[83] Fluconazole resistance among *Candida* species from bloodstream infections ranges between 12% and 28%.[16,17] *C. glabrata* was the only species that may exhibit resistance to both triazoles and echinocandins. Among the 180 isolates of *C. glabrata* isolated from nosocomial bloodstream infections, 62% were nonsusceptible to caspofungin.[16]

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.[81] However, preferred empiric therapy for suspected invasive candidiasis in nonneutropenic patients in the ICU is an echinocandin (anidulafungin, micafungin, or caspofungin). Ecinocandins exhibit potent activity against all *Candida* species, including *C. krusei* that is typically resistant to an azole, as well as *Aspergillus* species. Empiric use of an echinocandin should be considered in most patients, despite the severity of illness including septic shock, who have been treated with other antifungal agents or suspected *C. glabrata* or *C. krusei* infection.[81]

Resistance to fluconazole, caspofungin, and amphotericin B was reported in 28%, 2.9%, and 3.1%, respectively, of adults admitted to ICUs with invasive candidiasis who received antifungal therapy empirically.[17] Approximately 20% of the antifungal agents were changed primarily based on *Candida* susceptibility, followed by inadequate clinical response. Hospital mortality was comparable between echinocandin (caspofungin/anidulafungin) and fluconazole (56% vs 58%, respectively). Micafungin 100 mg daily was noninferior to liposomal amphotericin B 3 mg/kg daily or caspofungin 70 mg followed by 50 mg daily for the treatment of invasive candidiasis in patients with or without neutropenia. Overall treatment success was numerically lower in patients with neutropenia than those without (64% vs 73%).[84] All three echinocandins appear to be comparable in terms of efficacy, pharmacology, and adverse effects, and the guidelines do not make a distinction or recommend a preferred agent.[81]

There was no difference in treatment efficacy or mortality outcomes in critically ill patients with invasive candidiasis receiving an amphotericin B formulation compared with those receiving an echinocandin or voriconazole.[82] However, amphotericin B was poorly tolerated. Liposomal formulation of amphotericin B (3-5 mg/kg daily) remains as an alternative to echinocandins in patients with echinocandin intolerance or toxicity.

## Pharmacokinetics and Pharmacodynamic Principles of Antimicrobial Agents in Sepsis

Physiologic changes during sepsis including unstable hemodynamics, increased cardiac output, variable kidney, and hepatic perfusions, or hypoalbuminemia can dramatically alter antimicrobial pharmacokinetics.[85] Initially, high creatinine clearance can be seen in patients with normal serum creatinine because of increased renal preload. Reduced serum albumin leads to altered drug binding. Volume of distribution may be increased because of fluid accumulation from leaky capillaries into the extracellular space from aggressive fluid resuscitation. Consequently, some antimicrobial agents especially hydrophilic antimicrobials including aminoglycosides, beta-lactams, carbapenems, and vancomycin can result in suboptimal serum concentrations with standard doses. Hence, optimal dosing strategies based on pharmacokinetic and pharmacodynamic principles targets are recommended in critically ill patients.[39]

Inadequate vancomycin trough plasma concentrations in relation to the MIC of the pathogen has been associated with clinical failure in septic shock due to MRSA.[86] Trough concentrations of 15 to 20 mg/L (10.4-13.8 µmol/L) and AUC/MIC higher than 400 were associated with improved survival. The revised vancomycin dosing guideline recommends a target AUC/MIC of 400 to 600 in serious MRSA infections.[70]

Daptomycin plasma concentrations after a dose of 6 to 8 mg/kg/day for primarily staphylococcal-related infections were lower in critically ill patients than healthy volunteers.[87] Daptomycin clearance did not change significantly in patients with or without sepsis. However, volume of distribution appeared to be larger. Consequently, weight-based daptomycin dose of at least 10 mg/kg/day was recommended.[87]

The time the plasma drug concentration remains above the pathogen MIC in relation to the dosing interval (T > MIC) best describes the pharmacodynamics of beta-lactams. A minimum T > MIC of 60% of the dosing interval generally provides a good clinical response. However, sepsis or septic shock may require longer duration of T > MIC.[88] Extended infusion or continuous infusion rather than the standard 30 minutes to achieve longer T > MIC as well as a loading dosing prior to the prolonged infusion to achieve effective beta-lactam concentration without delay optimizes the pharmacokinetics and pharmacodynamics of beta-lactam antibiotics. A prolonged infusion of beta-lactams after an initial bolus dose is preferred in place of a short intermittent infusion.[39,89,90] Continuous infusion of meropenem was associated with improved clinical cure rate in patients with sepsis, greater microbiological eradication, and decreased hospital mortality compared with a standard 30-minute intermittent infusion.[91]

Based on its concentration-depending killing activity, the Sepsis-3 guidelines recommend once daily dosing of 5-7 mg/kg daily gentamicin or an equivalent aminoglycoside in patients without severely reduced renal function. This high dosing strategy yielded comparable clinical efficacy but decreased renal toxicity compared to the multiple daily dosing regimens.[46] However, suboptimal aminoglycoside concentrations may occur in the early phase of therapy in critically ill patients, suggesting higher dosing of 8 mg/kg gentamicin may be required for optimal effect.[92] Target trough concentrations of below 2 mg/L (4.18 µmol/L) should be monitored to detect potential renal toxicity.

As sepsis progresses, organ perfusion decreases because of significant myocardial depression and leads to multiple organ dysfunction. Consequently, clearance of antimicrobial agents is decreased, prolonging the elimination half-life and accumulation of metabolites. Dosing strategies need to be assessed and modified continuously through the course of treatment for optimal efficacy.

## De-escalation

Empiric antimicrobial agents should be initiated immediately after the diagnosis of sepsis and septic shock is suspected due to the serious nature of the disease, but the antimicrobial regimen should be reassessed daily based on the microbiological and clinical data. This creates a potential de-escalation opportunity as part of good antibiotic stewardship to narrow down the spectrum once the pathogen has been identified to avoid unnecessary use of antimicrobials.[39,46,93] De-escalation may also prevent drug toxicities and the development of nosocomial super infections with *Candida* species, *Clostridioides*, or VRE. Improved patient care outcomes have been demonstrated with such de-escalation of antibiotic therapy. The hospital mortality rate among patients admitted to the ICU with severe sepsis or septic shock was 27% in whom therapy was de-escalated, 33% in the category of no change, and 43% in the escalation group.[94]

The data on timing or precise criteria to de-escalate in case of negative cultures is lacking. However, antimicrobial regimens should still be assessed daily for opportunity for de-escalation in response to clinical improvement including shock resolution or decrease in vasopressor requirement and/or evidence of infection resolution by biomarkers, especially PCT.[39,46]

## EVALUATION OF THERAPEUTIC OUTCOMES

PCT is a serum biomarker that increases in response to endotoxins and inflammatory cytokines that are released during systemic bacterial infections, and it rises early in severe sepsis by pneumonia and bloodstream infections. Measurements of PCT concentrations may assist in determining the duration of antimicrobial therapy in sepsis.[39,46] The use of PCT concentration in critically ill patients was associated with reduced daily doses of antimicrobials, duration of antimicrobial treatment, and mortality.[95]

### Duration of Therapy

The average duration of antimicrobial therapy in a patient with sepsis is 7 to 10 days in the absence of source control issues, and fungal infections can require 10 to 14 days.[46,81] However, the duration can be longer in patients with a compromised immune status, slow clinical response, large infection site, undrainable focus of infection, bacteremia with *S. aureus*, multidrug-resistant gram-negative pathogens.

However, over the past two decades, clinical trials have demonstrated that shorter courses are as efficacious as longer courses, especially with successful source control and are associated with fewer adverse events.[96,97] A 7-day course of therapy for both hospital-acquired and ventilator-associated pneumonia is recommended.[65] A short course of antimicrobial treatment (median duration of 4 days) for patients with complicated intra-abdominal infection and adequate source control had similar surgical site infection, recurrent intra-abdominal infection, or death as the control group with a median of 8 days of antibiotics whose antibiotic duration was based on symptoms (ie, fever, leukocytosis, and ileus).[97] 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 to 7 days in patients in whom a definitive source control was not performed.[58]

Once adequate source control is achieved, the guidelines suggest shorter duration of antimicrobial therapy in place of historically longer duration.[39] However, when optimal duration of therapy is unclear especially in the absence of identifiable causative pathogen, PCT along with clinical evaluation is suggested in determining the antimicrobial treatment duration.

### Hemodynamic Support with Vasopressors

The Surviving Sepsis Campaign guidelines recommend a target MAP of at least 65 mm Hg (MAP = [SBP + 2*DBP]/3).[39,46] Achievement of a high (MAP of 80-85 mm Hg) or low (MAP of 65-70 mm Hg) target did not result in significant difference in mortality at 28 and 90 days.[98] Among the patients with preexisting hypertension, those in the high target group had less renal dysfunction and need for renal replacement therapy. However, the incidence of newly diagnosed atrial fibrillation was significantly higher in the high target group. The number needed to treat was 9.5 to prevent one patient from necessitating renal replacement therapy.[99]

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. There are several adrenergic receptors that are the key to understanding the mechanism of action of various vasopressors (Table 142-6). Alpha-adrenergic receptors are located in the vascular wall and in the heart, and the alpha-receptor agonists induce peripheral vasoconstriction as well as increase the duration of contraction in the heart. Beta-adrenergic receptors are primarily found in the heart. Stimulation of the beta receptors causes inotropic and chronotropic effect. Dopamine receptors are in the renal, splanchnic, coronary, and cerebral vascular beds. Dopamine receptor agonists cause vasodilation of the renal and splanchnic vessels. As dopamine is a precursor to epinephrine and norepinephrine, it affects both alpha-1 and beta-1 receptors, causing peripheral vasoconstriction and inotropy. There are three types of vasopressin receptors: V1, V2, and V3 receptors. Vasopressin works on the V1 and V2 receptors, which are in vascular smooth muscles and basolateral membrane of the collecting duck, respectively. Vasopressin contracts vascular smooth muscle mainly through the V1 receptor and retains water via V2 receptors.

TABLE 142-6

**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 ↑ | ↑ | ↔ or ↑ | ↑ |
| Dopamine (5-10)[a] | ++ | + | +++ | + | ↑ | ↑ | ↔ or ↑ | ↑↑ |
| Dopamine (10-20)[a] | ++ | +++ | ++ | – | ↑ | ↑ | ↑↑ | ↑ |
| Epinephrine | – | ++++ | ++++ | +++ | ↑ | ↑ | ↑↑ | ↑↑ |
| Norepinephrine | – | ++++ | ++ | + | ↔ or ↑ | ↔ | ↑↑ | ↑ |
| Phenylephrine | – | +++ | – | – | ↔ or ↓ | – | ↑↑ | ↔ |
| Vasopressin | V1 receptor | | | | ↔ or ↓ | – | ↑↑ | ↔ or ↓ |
| Angiotensin II | AT receptor | | | | ↑ | – | ↑ | ↑ |

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

[a]mcg/kg/min.

*Data from Reference 100.*

6 The guidelines recommend norepinephrine as the first-line agent for patients with septic shock.[40] Norepinephrine, a potent alpha-adrenergic agent with less pronounced beta-adrenergic activity than epinephrine, is the preferred vasopressor to correct hypotension in fluid refractory septic shock.[39,46,100] It increases MAP and SVR via vasoconstrictive effects on peripheral vascular beds with little changes in heart rate and less increase in stroke volume compared to dopamine. Norepinephrine is more potent than dopamine in refractory septic shock. Norepinephrine was associated with lower risk of mortality and lower risk of arrhythmia compared to dopamine.[101]

Dopamine may be considered as an alternative agent to norepinephrine in a small subset of patients who have bradycardia or are at low risk of developing arrhythmia.[46,99] Dopamine increases MAP and cardiac output by increasing the heart rate and cardiac contractility, making it potentially useful for patients with compromised systolic function. However, it is arrhythmogenic and can cause tachycardia, limiting its role in maintaining MAP.[101]

Epinephrine is a nonspecific alpha- and beta-adrenergic agonist (Table 142-6). Overall mortality at 90 days between norepinephrine and epinephrine was not significantly different in patients with septic shock.[101] However, there are several adverse effects associated with epinephrine including tachycardia, lactic acidosis, and impaired blood flow to the splanchnic system.

Optimal dosing of norepinephrine among obese patients with septic shock is important to consider as many drug studies do not include obese patients and therefore leave clinicians to extrapolate pharmacokinetic parameters from nonobese patients at bedside. Weight-based dosing of norepinephrine in obese adult patients (body mass index [BMI] >30 kg/m$^2$) did not achieve goal MAP earlier than the non-WBD group, and there was no difference in mortality (23.6% vs 23.1%, respectively).[102] However, morbidly obese (BMI >40 kg/m$^2$) patients had significantly higher cumulative norepinephrine use in the WBD group compared to the non-WBD group, and higher cumulative dose was identified as an independent risk factor for

mortality during hospitalization and at 1 year.[103] Further studies are needed to assess appropriate norepinephrine dosing strategies.

Vasopressin, also known as antidiuretic hormone, is produced in the hypothalamus and released from pituitary. In a healthy individual, it controls osmolality by stimulating the V2 receptors in the kidneys, but has little effect on BP. However, in a state of distributive shock, vasopressin binds to V1 receptors in vascular smooth muscle, which leads to vasoconstriction, thereby increasing BP. In contrast, after the initial rise in vasopressin concentration in septic shock, vasopressin level decreases to normal range due to the combination of depletion of vasopressin stores and inhibition of synthesis and release.[99] A synthetic formulation of vasopressin is dosed at 0.03 U/min without titration unlike most vasopressors, as higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischemia.

The role of vasopressin as a single vasoactive agent or in combination with norepinephrine remains controversial. The VANISH trial compared vasopressin to norepinephrine in patients with septic shock and reported no significant difference between the two groups in 28-day mortality or kidney injury.[104] The VASST trial comparing norepinephrine alone and norepinephrine with low dose (0.01-0.03 U/min) vasopressin in patients with septic shock showed similar mortality rates (39% vs 35%, respectively). When the investigators reevaluated the VASST trial, using the new definition of septic shock from the Sepsis-3 guidelines, the sample size decreased by half, and the 28-day mortality rates were increased by about 10% for both groups.[105] Patients with less severe sepsis who received norepinephrine less than 15 mcg/min had improved survival in the combination group than in the norepinephrine alone group (36% vs 27%, respectively). Combination therapy of vasopressin with norepinephrine reduced mortality in comparison to norepinephrine alone (RR 0.91; 95% CI 0.83-0.99).[105] There was no difference in risks for digital ischemia or arrythmias. Adding vasopressin to norepinephrine is recommended (dose ranging from 0.25-0.5 mcg/kg/min) rather than increasing the norepinephrine dose to achieve adequate MAP.

The first synthetic angiotensin II was approved for the use in vasopressor refractory septic shock. In the setting of decreased renal perfusion, the angiotensinogen from liver and renin produced by the kidney come together to form angiotensin I which is then transformed to angiotensin II by angiotensin-converting enzyme. Angiotensin II ultimately increases BP by increasing sympathetic activity that stimulates pituitary gland to increase antidiuretic hormone secretion to promote sodium, chloride, and water reabsorption in the kidneys. It also continues to promote aldosterone secretion from the adrenal gland, where aldosterone will carry on the sodium and water reabsorption in the distal tubule and collecting duct of the kidney via sodium-potassium pump. Angiotensin II was evaluated in adult patients with persistent hypotension despite adequate fluid resuscitation and received >0.2 ng/kg/min norepinephrine equivalent vasopressor use (ATHOS-3 trial).[106] A greater response in MAP was reported in 321 patients who received angiotensin II versus placebo (69.9% vs 23.4%). Patients in the ATHOS-3 trial who had AKI requiring renal replacement therapy (RRT) at initiation of angiotensin II had significantly higher 28-day survival (53% vs 30%) and discontinuation of RRT in the angiotension II group (38% vs 15%) compared with placebo.[107] Based on limited clinical experience in sepsis and safety data, synthetic angiotensin II's place of therapy in septic shock remains unclear.

Sepsis-induced myocardial dysfunction can exacerbate hemodynamic instability which may lead to worse outcomes in septic shock. Inotropic agents such as dobutamine and epinephrine have been used in patients with persistent hypoperfusion despite adequate fluid resuscitation. However, no randomized comparative trials have been conducted in this population. There was no clear reduction in mortality in dobutamine combined with norepinephrine to norepinephrine alone or between dobutamine and epinephrine.[108] Hence, the guidelines provided a weak recommendation to use either drug only in selected situations of persistent hypoperfusion despite adequate fluid resuscitation and arterial BP.[39,46]

## Performance Improvement Bundle

The Surviving Sepsis Campaign recommends implementation of hospital-based performance improvement efforts such as a core set of recommendation ("bundle") because they have been associated with improved patient outcomes.[2,46] While the details of each institution's performance improvement bundle may be different, there is a common theme of improved management of patients with sepsis and septic shock.[109] Hospital mortality rates dropped 0.7% per site for every 3 months of participation. Hospital and ICU lengths of stay decreased by 4% for every 10% increase in site compliance in a 7.5-year study.[110]

7 The Sepsis-3 guidelines described a 1-hour care, consisting of three major components of initial treatment immediately after early recognition of sepsis: administration of fluid, administration of parenteral antibiotics, and use of vasopressor agents (Table 142-7).[47] Resolution of serum lactate is desired to indicate adequate tissue perfusion and therefore should be repeated within 2 to 4 hours of the initial level. The interpretation of repeat

lactate requires careful consideration especially in patients with concomitant hepatic and/or renal failure as metabolism and elimination of lactate may be decreased in this setting. The guidelines endorse using a performance improvement program including sepsis screening and prompt initial treatment considered as standard of care for sepsis and septic shock.[39]

TABLE 142-7

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

**One-hour bundle**

- Measure initial lactate
- Repeat in 2 hours if initial lactate >18 mg/dL (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 ≥36 mg/dL (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

MAP, mean arterial pressure.

*Data from References 46,47.*

## Adjunctive Therapies

Sepsis and septic shock present multitudes of complications in a relative short span of time. In addition to prompt initiation of a performance improvement bundle, several adjunctive therapies including transfusions of blood products, oxygen supplement, mechanical ventilation, or RRT may be required. Key pharmacological adjunctive therapies are described below.

In Sepsis-3 guidelines, IV hydrocortisone is recommended for adult patients with septic shock who are hemodynamically unstable after initial resuscitation with IV fluids and vasopressors.[46] Cortisol levels vary widely in patients with septic shock, and an increased mortality has been associated with both low and high serum cortisol levels. Data on the benefits of corticosteroids as adjunct therapy in patients with sepsis and septic shock are conflicting with regards to reduction of overall mortality.[111-117] A significant shock reversal and reduction in mortality were reported in patients with septic shock unresponsive to fluid resuscitation and vasopressors for more than an hour and had relative adrenal insufficiency who received prolonged courses (>5 days) of low-dose corticosteroid therapy compared to placebo (38% vs 44%; relative risk 0.84).[111] The Corticosteroid Therapy of Septic Shock (CORTICUS) found no survival benefit for patients who were unresponsive to adequate fluid replacement and required vasopressors, with or without adrenal insufficiency.[112] However, CORTICUS included patients with septic shock regardless of their responsiveness to vasopressor therapy. Subsequent meta-analyses and systematic reviews continue to present conflicting data. Low-dose corticosteroids reduced 28-day mortality, increased shock reversal, and reduced organ injury based in an analysis of 22 randomized controlled trials.[113] Another systematic review of 35 trials of sepsis detected no significant benefit on mortality.[114]

After publication of the Sepsis-3 guidelines, two large, randomized, blinded, multicenter, controlled trials of low-dose corticosteroids use in patients with septic shock did not confirm or refute previously published data on reduction of mortality.[115,116] However, these landmark studies offer other practical benefits of low-dose corticosteroids. Both trials clearly defined adequate fluid resuscitation, vasopressor-dependent shock, and appropriate antimicrobial therapy. The 90-day mortality in the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial was

similar between continuous infusion of hydrocortisone 200 mg/day for maximum of 7 days and placebo (27.9% vs 28.8%, respectively).[115,117] The 90-day mortality in the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial was 43% with hydrocortisone 50 mg IV bolus every 6 hours plus fludrocortisone 50 mcg tablet via a nasogastric tube once daily for 7 days and 49% with placebo.[116] The dramatic difference in the mortality data may rise from the patients' severity of illness. The patients from the APROCCHSS trial may have been more seriously ill based on their SOFA and APACHE II scores and had higher proportions of patients who required RRT or who had bacteremia. Regardless, both trials showed significantly faster resolution of shock and increase in vasopressor-free days, providing reassurance of short-term benefits of low-dose hydrocortisone in selected patients even if there is not clear benefit for short- or long-term mortality.[115-118]

The 2021 guidelines updated the recommendation to adding low dose hydrocortisone 200 mg/day for patients with septic shock who require ongoing norepinephrine dose of >0.25 mcg/kg/min at least 4 hours to maintain the target MAP.[39] Continuous infusion of hydrocortisone may prevent a significant increase in blood glucose associated with repetitive bolus injections. Steroid should be tapered when vasopressors are no longer required as hemodynamic and immunologic rebound effects have been reported with abrupt cessation of corticosteroids.[46]

9 Hyperglycemia and insulin resistance are frequently associated with sepsis regardless of the presence of diabetes prior to sepsis, and more severe hyperglycemia is associated with higher morbidity and mortality.[2,46] The NICE-SUGAR trial, the largest study to date on glucose control in ICU patients, reported a higher incidence of mortality at 90 days with intensive insulin therapy (target glucose range of 81-108 mg/dL [4.5-6.0 mmol/L]) than with conventional therapy (target of <180 mg/dL [10.0 mmol/L]).[119] Intensive insulin therapy targeting blood glucose of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) in septic patients did not improve overall mortality and was associated with a higher incidence of hypoglycemia (blood glucose less than 40 mg/dL [2.2 mmol/L]).[120] The Sepsis-3 guidelines recommended initiating insulin when two consecutive blood glucose levels are greater than 180 mg/dL (10.0 mmol/L) based on the NICE-SUGAR trial. However, the guidelines do not give a specific target glucose range other than monitoring glucose of less than 180 mg/dL (10 mmol/L) every 1 to 2 hours until the glucose levels and insulin requirements are stable to avoid hypoglycemia.[46]

A meta-analysis of 35 randomized controlled trials compared four blood glucose targets (180 mg/dL [10 mmol/L]) and risks of hospital mortality and hypoglycemia.[121] There were no significant differences in mortality among the groups. However, lower target ranges (less than 110 [6.1 mmol/L] and 110-144 mg/dL [6.1-8 mmol/L]) were associated with a four- to ninefold increased risk of hypoglycemia in comparison to the higher target ranges. No significant difference in risk of hypoglycemia was noted between a range of 144-180 mg/dL (8-10 mmol/L) and greater than 180 mg/dL (10 mmol/L). The current recommendation remains to initiate insulin therapy at a glucose level of greater than 180 mg/dL (10 mmol/L) with a target range between 144 and 180 mg/dL (8-10 mmol/L).[39]

Pharmacologic venous thromboembolism (VTE) prophylaxis should be initiated in all patients admitted to the ICU with sepsis and septic shock.[39,46]

Overall, the incidence of VTE in the ICU is approximately 10%. However, the incidence was much higher (37.2%) in patients with sepsis and septic shock which may increase the length of stay in ICU (18.2 vs 13.4 days, respectively).[122]

There is limited data comparing low molecular weight heparin to unfractionated heparin in VTE prophylaxis among septic patients. However, the overall rate of VTE and pulmonary embolism was lower in critically ill patients receiving LMWH in comparison to unfractionated heparin administered twice daily, and overall mortality was also reduced, albeit not significant.[123] The guideline continues to recommend LMWH over unfractionated heparin for VTE prophylaxis in patients with sepsis or septic shock.[39] If pharmacologic prophylaxis is contraindicated, mechanical prophylactic measures should be considered.[125]

An international prospective cohort study reported clinically important GI bleeding occurred in 2.6% in critically ill adult patients.[124] Prophylaxis with either a proton pump inhibitor (PPI) or histamine 2 receptor antagonist reduced the risk of GI bleeding in comparison to no prophylaxis.[124] The use of pantoprazole versus placebo did not demonstrate any effect on mortality.[126] However, PPI use did reduce GI bleeding. A higher risk of *C. difficile* infections was noted with PPI use.[39]

The guidelines continue to recommend stress ulcer prophylaxis should be initiated in all patients with sepsis and septic shock who have risk factors for GI bleeding.[39] Risk factors for clinically relevant GI bleeding include shock, coagulopathy, and chronic liver disease.[125] The selection of agent should also consider patient's renal, liver, hematologic dysfunction, as dose adjustments may be necessary. Although preventing clinically significant GI

bleeding is important, it also must be balanced with potential adverse events from decreasing pH of the stomach such as possibility of developing *C. difficil*e infection.[46]

## ABBREVIATIONS

| | |
|---|---|
| AKI | acute kidney injury |
| APACHE | acute physiology and chronic health evaluation |
| ARDS | acute respiratory distress syndrome |
| AUC | area under the curve |
| BMI | body mass index |
| BP | blood pressure |
| CVP | central venous pressure |
| DIC | disseminated intravascular coagulation |
| EGDT | early goal-directed therapy |
| ESBL | extended-spectrum beta-lactamases |
| GI | gastrointestinal |
| HIV | human immunodeficiency virus |
| H2RA | histamine 2 receptor antagonist |
| ICU | intensive care unit |
| IV | intravenous |
| IL | interleukin |
| IL-1RA | interleukin-1 receptor antagonist |
| LMWH | low-molecular-weight heparin |
| MAP | mean arterial pressure |
| MIC | minimum inhibitory concentration |
| MRSA | methicillin-resistant *Staphylococcus aureus* |
| PCT | procalcitonin |
| PPI | proton pump inhibitor |

| | |
|---|---|
| RRT | renal replacement therapy |
| $Scvo_2$ | central venous oxygen saturation |
| SIRS | systemic inflammatory response syndrome |
| SOFA | sequential organ failure assessment |
| SVR | systemic vascular resistance |
| T > MIC | time above minimum inhibitory concentration |
| TNF | tumor necrosis factor |
| qSOFA | quick sequential organ failure assessment |
| VRE | vancomycin-resistant enterococci |
| VTE | venous thromboembolism |
| WBC | white blood cell |
| WBD | weight-based dosing |

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## SELF-ASSESSMENT QUESTIONS

1. Regarding the common pathogens in sepsis and septic shock, which of the following statements is correct?

   A. Since the late 1970s, gram-positive organisms continued to be the predominant pathogens.

   B. Enterococci species are the common gram-positive pathogens.

   C. *Escherichia coli* is the most frequent cause of sepsis fatality.

   D. Non-albicans Candida collectively are common causes of fungal sepsis.

2. A complication associated with sepsis is:

   A. Persistent hypotension.

   B. Disseminated intravascular coagulation.

   C. Acute kidney injury.

   D. All of the above.

3. The preferred treatment option for a 56-year-old personwith community-acquired pneumonia who was recently prescribed azithromycin for sinusitis is:

   A. Ertapenem.

   B. Moxifloxacin.

   C. Tigecycline.

   D. Doxycycline.

4. Which of the following treatment regimens is preferred in case of nosocomial pneumonia with a suspicion for *Pseudomonas aeruginosa*?

   A. Ampicillin/sulbactam

   B. Ceftriaxone plus azithromycin

   C. Cefipime

   D. Vancomycin plus ertapenem

5. Which of the following agents may not be used to treat hospital-acquired pneumonia secondary to methicillin-resistant *S. aureus*?

   A. Daptomycin

   B. Vancomycin

   C. Linezolid

   D. Telavancin

6. Initial resuscitation bundle should take place within 1 hour in patients with sepsis or sepsis-induced tissue hypotension. What are the recommended activities?

   A. Norepinephrine if not responsive to fluid resuscitation

   B. Fluid resuscitation with balanced crystalloid

   C. Empiric IV antibiotics

   D. All of the above.

7. The preferred agent for a 37-year-old person with an advanced stage of AIDS and candidemia is:

   A. Imipenem.

   B. Caspofungin.

C. Itraconazole.

D. Ketoconazole.

8. Regarding hemodynamic support, which of the following agent is the best initial therapeutic intervention?

A. Plasma-Lyte

B. Lactated ringer solution

C. Albumin

D. Hetastarch

9. Norepinephrine affects the following receptors EXCEPT:

A. Alpha-1.

B. Dopamine.

C. Beta-1.

D. Beta-2.

10. Invasive candidiasis can be treated with the following agents EXCEPT:

A. Fluconazole.

B. Caspofungin.

C. Amphotericin B deoxycholate.

D. Itraconazole.

11. Which of the following agents is most effective in treatment of fungemia due to *Candida glabrata*?

A. Fluconazole

B. Clotrimazole

C. Micafungin

D. Itraconazole

12. Which of the following factors affect the overall prognosis?

A. Multi-organ failure

B. Septic shock associated with Candidemia

C. Elevated lactate level and slow clearance

D. All of the above

13. Which of the following conditions poses least risk of mortality?

A. Acute kidney injury

B. Obstructive urinary tract infection

C. Ischemic bowel obstruction

D. Multidrug resistant Pseudomonas aeruginosa

14. What is the regimen of choice for bloodstream infection caused by ESBL-producing *Klebsiella pneumoniae*?

A. Ceftriaxone

B. Colistin

C. Ertapenem

D. Piperacillin/tazobactam

15. What is the appropriate IV fluid therapy for a 80-kg male patient with septic shock?

A. 1,000 mL normal saline bolus

B. 2,400 mL Plasma-Lyte within 1 hour

C. 0.5 mcg/kg/min dopamine continuous infusion

D. 2,400 mL albumin bolus

## SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Non-albicans Candida species collectively is more frequently isolated over C. albicans specifically in sepsis or septic shock due to fungal infection. Gram-negative organisms continue to be most common. *Escherichia coli* is the most common gram-negative pathogen but *Pseudomonas aeruginosa* has been associated with increasing mortality. *S. aureus* is the most common gram-positive pathogen in sepsis.

2. **D.** Sepsis may rapidly lead to multiple complications of shock, disseminated intravascular coagulation, and multiple organ dysfunction such as acute kidney injury and acute respiratory distress syndrome.

3. **B.** Recent usage of azithromycin increases the risk of antibiotic-resistant *Streptococcus pneumoniae*, favoring respiratory fluoroquinolone such as moxifloxacin for treatment of community-acquired pneumonia.

4. **C.** Ampicillin/sulbactam and ceftriaxone plus azithromycin regimens lack activity against *P. aeruginosa*. In the absence of risk of methicillin-resistant *S. aureus*, addition of vancomycin is not recommended.

5. **A.** Daptomycin exhibits activity against MRSA. However, it is inactivated by pulmonary surfactant, rendering it less optimal choice for pneumonia.

6. **D.** Performance improvement bundle consisting of administration of IV fluids, parenteral antibiotics, and vasopressor with the first hour of sepsis recognition decreases mortality and lengths of stay in hospital and ICU.

7. **B.** Patients with fungemia generally have a higher mortality rate than bacteremia. In addition, increasing reports of azole-resistant Candida species and immunocompromised patient risk factor required echinocandin exhibiting potent activity against all Candida species and consistent serum concentrations.

8. **A.** Crystalloids (ie, normal saline, dextrose, lactated ringer, and Plasma-Lyte) are generally recommended over colloid (ie, Albumin) based on similar efficacy, accessibility, and lower cost. Among crystalloids, the guideline favors balanced crystalloid (Plasma-Lyte) over normal saline due to less incidence of hyperchloridemic metabolic acidosis.

9. **B.** Norepinephrine has highest affinity to alpha-1 receptors, followed by beta-1 and beta-2 receptors.

10. **D.** Treatment of invasive candidiasis includes parenteral administration of echinocandins, triazoles, or a formulation of amphotericin B. However,

itraconazole is only available as an oral capsule and solution.

11. **C.** Empiric use of an echinocandin should be considered in most patients, despite the severity of illness including septic shock, who have been treated with other antifungal agents or suspected *C. glabrata* or *C. krusei* infection.

12. **D.** As the number of failing organs increased from one to four or more, the mortality rate increased from 15% to 40%. Patients with candidemia generally have septic shock, and the mortality rate was approximately 50%. An elevated serum lactate of 36 mg/dL (4 mmol/L) upon initial presentation and persistent elevation were associated with an increased mortality rate. Combination of septic shock and hyperlactatemia further increased the 28-day mortality rate.

13. **B.** Higher mortality rate was reported in intra-abdominal infection due to ischemic bowel compared to obstructive uropathy-associated urinary tract infection and acute kidney injury (75%, 26%, and 22%, respectively).

14. **C.** Ceftriaxone is ineffective against ESBL-producing *K. pneumoniae*, and piperacillin/tazobactam failed to demonstrate noninferiority over carbapenem in bacteremia due to ceftriaxone-resistant *K. pneumoniae*. Colistin has limited usage due to significant toxicity.

15. **B.** Early effective fluid resuscitation is crucial for preventing further sepsis-induced tissue hypoperfusion. Initial resuscitation with 30 mL/kg of IV balanced crystalloid fluid is recommended.