Sepsis: Diagnosis and Management

Self-Assessment Questions

1 . In the Sepsis 3 report, sepsis is defined as

A) temperature of 36.5°C (97.7°F).

B) a severe infection caused by specific pathogens.

C) leukocyte count between 5,000 and 11,000 cells/mm³.

D) life-threatening organ dysfunction caused by a dysregulated host response to infection.

INTRODUCTION AND DEFINITIONS

The Sepsis 3 report defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. This new definition emphasizes the loss of adaptive homeostasis in response to infection, the potential lethality of infection when any degree of organ dysfunction is present, and the importance of urgent assessment and prompt treatment. Because even modest organ dysfunction has been found to confer a mortality risk in excess of 10%, sepsis is inherently a serious condition and the term "severe sepsis" is no longer considered useful [6].

2 . All of the following are manifestations of organ dysfunction, EXCEPT:

A) Oliguria

B) Metabolic acidosis

C) Altered mental status

D) A ratio of arterial oxygen tension to fraction of inspired oxygen of 380 or more

INTRODUCTION AND DEFINITIONS

The presence and extent of organ dysfunction can be assessed with various scoring systems that rely on clinical and laboratory parameters, such as the following [6,7,62]:

o Acute lung injury: A ratio of arterial oxygen tension to fraction of inspired oxygen of 280 or less

o The presence of a metabolic acidosis (e.g., lactate >2 mmol/L)

o Oliguria: Urinary output of less than 0.5 mL/kg body weight/hour for at least two hours in a patient with a urinary catheter in place

o Coagulation abnormalities: International normalized ratio (INR) >1.5

o   Thrombocytopenia: Platelet count <100,000 cells/mcL
o   Elevated bilirubin: >2 mg/dL
o   Acute alteration in mental status

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3 . Which of the following is NOT one of the elements in the quick Sequential Organ Failure Assessment (qSOFA) tool?

A) Altered mentation

B) Elevated bilirubin (>2 mg/dL)
C) Systolic blood pressure 100 mm Hg or less
D) Respiratory rate of at least 22 breaths per minute

INTRODUCTION AND DEFINITIONS

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

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

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4 . Severe insults, including infection and shock, can lead to a reaction involving

A) hyperoxemia.

B) widespread endothelial damage.
C) decreased vascular permeability.
D) All of the above

EPIDEMIOLOGY AND BURDEN OF SEPSIS

The first description of multiple organ failure appeared in 1973 in a discussion of three patients who died of distal organ failure that followed ruptured aortic aneurysms. Multiple organ failure was subsequently described as multiple, progressive, or sequential systems organ failure. It was

noted that shock or infection alone did not cause the distal organ dysfunction. Other severe insults could set in motion an underlying reaction that would lead to widespread endothelial damage, edema resulting from increased vascular permeability, and impaired availability of oxygen [8,9,10].

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5 . The majority of sepsis cases occur in

A) women.

B) patients 25 to 44 years of age.
C) patients 65 years of age or older.
D) patients younger than 5 years of age.

EPIDEMIOLOGY AND BURDEN OF SEPSIS

The reported incidence rates of sepsis increase with advanced age. Two-thirds of all sepsis cases occur in people 65 years of age and older, with case fatality rates as high as 40% [16]. Age-adjusted rates for sepsis hospitalization and mortality increased annually by 8.2% and 5.6%, respectively, between 1993 and 2003, whereas the fatality rate decreased by 1.4% [15]. Sepsis is more common among men than women, and the fatality rate is greater in men and nonwhite populations [22].

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6 . All of the following factors are considered important in the development of sepsis, EXCEPT:

A) Fungal organisms

B) Burns or other trauma
C) Appropriate narrow-spectrum antibiotic therapy
D) Progressive clinical conditions, such as diabetes

RISK FACTORS AND PREVENTION

Factors considered important in the development of sepsis include: inappropriate broad-spectrum antibiotic therapy; immunosuppressive treatments, such as cancer chemotherapy; invasive procedures; transplantations; fungal organisms; burns or other trauma; anatomic obstruction; intestinal ulceration; age (the very young and the very old); and progressive clinical conditions, such as malignancy, diabetes, or AIDS [24].

7 . A major cause of sepsis among hospitalized, severely ill patients is

A) malignancy.

B) hyperglycemia.
C) intestinal ulceration.
D) <mark>healthcare-associated infection.</mark>

RISK FACTORS AND PREVENTION

Healthcare-associated infections are a major cause of sepsis among severely ill patients. Increased risk of nosocomial infection is associated with the presence of underlying chronic disease, alteration in host defenses, prolonged hospital stay, and the presence of invasive catheters or monitoring devices [27]. Pulmonary, urinary tract, gastrointestinal, and wound infections predominate [28,29]. In hospitalized adult patients, the etiology of sepsis has shifted from being predominantly gram-negative nosocomial infections (*Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., and *Pseudomonas aeruginosa*) to gram-positive infections (*Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*). The incidence of sepsis caused by gram-positive infections has increased by 26.3% per year over the last three decades [17]. Multidrug-resistant pathogens, such as *S. aureus*, now account for more than half of all sepsis cases. *S. aureus* is singly responsible for 40% of ventilator-associated pneumonia episodes and most cases of nosocomial pneumonia [17,25]. Group B streptococcus is a leading cause of neonatal sepsis in the United States [30].

8 . The natural defense against infection includes

A) macrophages.

B) T and B lymphocytes.
C) platelets and coagulation factors.
D) All of the above

PATHOGENESIS OF SIRS

The natural defense of the body to an infection, or other assault, involves a number of cellular and humoral factors. They include B and T lymphocytes, macrophages, neutrophils, platelets, tumor necrosis factor (TNF), interleukins, the coagulation factors, and probably several other products [26,37,38]. There are five rather distinct phases that describe how these biologic

products work together to overcome the assault and, paradoxically, how they can interact to cause SIRS and potentially lead to critical organ failure [26,39].

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9 . In the United States, the etiology of sepsis is characterized by a predominance of

A) viruses.

B) fungal organisms.
C) gram-negative bacteria.
D) gram-positive, drug-resistant bacteria.

PATHOPHYSIOLOGY OF SEPSIS

As noted, in the United States, the etiology of sepsis has shifted from a predominance of gram-negative bacteria to a predominance of gram-positive, drug-resistant bacteria [25]. This shift has led to a re-evaluation of basic assumptions about the pathogenesis of sepsis (e.g., there may or may not be differences in the host response to gram-negative organisms compared with the response to gram-positive organisms) [44,45]. It is important to note that discrimination between gram-negative and gram-positive organisms is based on the recovery of specific pathogens from blood or the presumed site of infection rather than from any specific immunologic criterion. In 30% to 50% of sepsis cases, the inciting organism is not identified [18,25].

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10 . The role of the coagulation system in the sepsis-induced inflammatory cascade includes

A) up-regulating fibrinolysis.

B) blocking further inflammation.
C) down-regulating the anticoagulant system.
D) All of the above

PATHOPHYSIOLOGY OF SEPSIS

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

sepsis is to limit the damage while retaining the benefits of localized clotting and controlled clearance of pathogens [5,14,47].

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11 . The common manifestations of sepsis are seen in all of the following organ systems, EXCEPT:

A) Skeletal

B) Pulmonary
C) Cardiovascular
D) Central nervous system

MANIFESTATIONS OF SEPSIS

Any patient with sepsis who has evidence of dysfunction in one organ in the absence of an obvious cause such as traumatic injury may have incipient dysfunction of other organs. The manifestations of sepsis may be seen in the cardiovascular, pulmonary, central nervous, renal, gastrointestinal, and hematologic systems of the body (most frequently in the lungs and circulatory system) [20].

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12 . Before the onset of shock, patients with sepsis

A) are hypodynamic.

B) have decreased pulse volume.
C) display narrowed pulse pressure.
D) have decreased systemic vascular resistance.

MANIFESTATIONS OF SEPSIS

Before the onset of shock, the patient's condition is usually hyperdynamic. The skin is warm and flushed, pulse volume is increased, and pulse pressure is wide. Cardiac output is typically elevated, and systemic vascular resistance (SVR) is usually decreased. Despite the increase in cardiac output, serum lactate levels are often elevated. Anaerobic metabolism occurs because of inadequate nutrient blood flow [24].

13 . Altered mental status is a common manifestation of sepsis. An early sign of this change may be

A) <mark>irritability or confusion.</mark>

B) hallucinations.
C) polyneuropathy.
D) nonfocal manifestations.

MANIFESTATIONS OF SEPSIS

Altered mental status may be the most common and most overlooked manifestation of sepsis. This causes elderly patients to be at particularly high risk. Early changes include withdrawal, confusion, irritability, or agitation. In patients with severe infection, one may see disorientation, lethargy, seizures, or frank obtundation [21,50].

14 . Which of the following is among the principal recommendations for fluid resuscitation in patients with sepsis?

A) <mark>Albumin should be added when patients require substantial amounts of crystalloids.</mark>

B) Administration of intravenous fluid should be delayed until the results of cultures are received.
C) Fluid resuscitation should initially target a mean arterial pressure (MAP) of 100 mm Hg in patients requiring vasopressors.
D) In patients with sepsis-induced hypoperfusion, no more than 15 mL/kg of intravenous crystalloid fluid should be given in the first three hours.

DIAGNOSIS AND MANAGEMENT

The principal recommendations for fluid resuscitation are [72]:

o Intravenous fluid resuscitation should be started immediately, beginning with crystalloids (grade strong, B).
o In the setting of sepsis-induced hypoperfusion, at least 30 mL/kg of intravenous crystalloid fluid should be given within the first three hours (grade strong, B),
o It is suggested that albumin be added when patients require substantial amounts of crystalloids (grade weak, C).

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

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15 . Which of the following statements regarding antibiotic therapy in patients with sepsis is TRUE?

A) Cultures should be obtained after antibiotic therapy is initiated, if possible.

B) The empirical antimicrobial regimen should not be changed based on culture results.

C) Generally, a 7- to 10-day course is considered adequate for most serious infections.

D) One should confirm the diagnosis by culture results before starting antibiotic treatment.

DIAGNOSIS AND MANAGEMENT

The SCCM recommends obtaining appropriate cultures before beginning antimicrobial therapy, but the process of doing so should not delay antibiotic administration. At least two sets (aerobic and anaerobic) of blood cultures should be obtained, including one drawn through any indwelling vascular catheter or device in place prior to onset of infection. Cultures from other suspected sites should be obtained as well. The guideline committee also recommends that imaging studies be performed to confirm the source of infection, assuming the patient's condition allows it [62,65,72].

Intravenous antimicrobial therapy should be started as early as possible, ideally within the first hour of recognition of sepsis or septic shock (grade strong, B). Clinical studies have shown that delay in antimicrobial therapy for serious infection and sepsis prolongs morbidity, lengthens hospital stay, and increases mortality [68]. A retrospective cohort study involving 2,731 patients with sepsis showed that initiation of antimicrobial therapy within the first hour of documented hypotension was associated with increased survival to discharge. Moreover, each hour of delay conferred an approximately 12% decreased probability of survival [69].

The initial choice of antibiotics will depend on the most likely pathogens associated with the source of infection as well as the prevalent micro-organisms in the local community and hospitals. The clinician should assess risk factors for multidrug-resistant pathogens, including prior hospitalization, health facility residence, recent antimicrobial use, and evidence of prior infection with resistant organism. The anticipated susceptibility profile of prevalent local pathogens and the ability of the antibiotic to penetrate to the source of the infection must also be considered. A combination of drugs with activity against all likely pathogens should be administered initially, but the regimen should be reassessed in light of culture results, the goal being to identify a single, narrow-spectrum antibiotic that will best control the infection [53,57]. It has been found that combining an extended-spectrum beta-lactam antibiotic (e.g., penicillins, cephalosporins) with an aminoglycoside (e.g., gentamicin) was no more effective in reducing mortality than using the beta-lactam agent alone. In addition, the combination carries an increased risk of renal damage [53,57]. A common approach is to initiate empiric therapy with a carbapenem or extended-spectrum penicillin/beta-lactamase inhibitor (e.g., ticarcillin/tazobactam) to cover gram-negative enteric bacilli and *Pseudomonas*, often in combination with vancomycin to cover *S. aureus* pending culture results.

The empirical antimicrobial regimen should be narrowed as soon as the pathogen has been identified and sensitivities are known. The duration of therapy will depend on the nature of the infection and other considerations specific to a given case. As a general rule, a 7- to 10-day course of bactericidal antimicrobial therapy is considered adequate for most serious infections associated with sepsis [72]. In the event that the syndrome is due to something other than an infectious cause, such as trauma, antibiotics should be discontinued as soon as possible.

16 . Which drug is the first choice vasopressor to restore blood pressure and perfusion in the patient with septic shock?

A) Dobutamine

B) Phenylephrine

C) Norepinephrine

D) Chlorpromazine

DIAGNOSIS AND MANAGEMENT

Historically, norepinephrine, dopamine, and epinephrine were three inotrope-vasopressor used to correct hypotension in septic shock [53]. Based on comparison studies and a meta-analysis of six randomized trials, norepinephrine is considered superior to dopamine and is now the recommended first choice for vasopressor therapy in septic shock (grade strong, B) [65,70,72]. If a second agent is needed to maintain blood pressure, epinephrine is preferred (grade 2B). Dopamine is not recommended, as there are concerns that side effects (e.g., tachyarrhythmia) may be detrimental to patients in septic shock. Low-dose dopamine should not be used for renal protection [72]. For patient safety and effectiveness, intravenous vasopressor therapy should be administered via a central venous catheter.

17 . If corticosteroids are used in the management of sepsis, the recommended regimen in adults is

A) oral deflazacort 0.9 mg/kg once daily.

B) oral dexamethasone 2 mg/kg to a maximum dose of 80 mg.

C) IV methylprednisolone 400 mg per day by continuous infusion.

D) IV hydrocortisone 200 mg per day, in divided doses or by continuous infusion.

DIAGNOSIS AND MANAGEMENT

The patient with persistent hypotension despite fluids and vasopressors should be assessed for adrenal responsiveness and may benefit from corticosteroid therapy. If corticosteroids are to be given, the 2016 SCCM guideline suggests IV hydrocortisone at a dose of 200 mg per day, in divided doses or by continuous infusion (grade weak, D) [72]. In 2017, a multispecialty task force of 16 international experts in critical care medicine, endocrinology, and guideline methods, all members of the SCCM and/or the European Society of Intensive Care Medicine, published a guideline for the management of corticosteroid insufficiency in critically ill patients. This group suggests using IV hydrocortisone <400 mg/day for three or more days at full dose in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy. They suggest not using corticosteroids in adult patients with sepsis without shock [73].

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18 . Red blood cell transfusion is recommended for patients with sepsis when the hemoglobin level falls below

A) 7.0 g/L.

B) 7.5 g/L.
C) 10 g/L.
D) 11.5 g/L.

DIAGNOSIS AND MANAGEMENT

In some cases, blood product administration may be required. The 2016 guideline recommends RBC transfusion if the hemoglobin level falls below 7.0 g/L [72]. The routine use of erythropoietin is not recommended for treatment of anemia in patients with sepsis unless other conditions are present, such as the compromise of red blood cell production induced by renal failure. Prophylactic platelet transfusion is suggested when the platelet count is <10,000/mm^3 (10 × 10^9/L) in the absence of apparent bleeding and when counts are <20,000/mm^3 (20 × 10^9/L) if the patient has a significant risk of bleeding [72].

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19 . Diagnostic criteria for SIRS in children include

A) temperature of 36.5°C.

B) leukocyte count that is either elevated or depressed for the child's age.
C) tachycardia greater than one standard deviation above normal for the child's age.
D) mean respiratory rate greater than one standard deviation above normal for the child's age.

PEDIATRIC CONSIDERATIONS

The panel's definition of SIRS for children includes the presence of at least two of the following criteria (one of which must be abnormal temperature or leukocyte count) [51]:

o Core temperature greater than 38.5°C or less than 36°C (measured by rectal, bladder, oral, or central catheter probe). Hypothermia may indicate serious infection (especially in infants).

o Tachycardia greater than two standard deviations above normal for the child's age in the absence of external stimulus; or unexplained persistent elevation over a four-hour time period; or, for children younger than 1 year of age, bradycardia (as defined by the panel); or unexplained persistent depression over a 30-minute time period. Bradycardia is not a sign of SIRS in older children but may be a sign in the newborn.

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

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

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20 . In hyperdynamic pediatric septic shock, the child has

A) bounding pulses.

B) delayed capillary refill.
C) mottled, cool extremities.
D) no need for fluid replacement.

PEDIATRIC CONSIDERATIONS

Clinically, pediatric septic shock takes two forms. In hyperdynamic shock, the child has rapid capillary refill and bounding pulses. In hypodynamic shock, there is prolonged capillary refill, mottled cool extremities, and diminished pulses. In both types, immediate resuscitation involves maintaining necessary circulation with fluid replacement, assuring proper ventilation, and maintaining threshold heart rates. Suggested therapeutic end points include a capillary refill of less than two seconds, warm extremities, urine output greater than 1 mL/kg/hr, normal blood pressure, normal mental status, and normal pulses with no differential between peripheral and central pulses. Frequent monitoring is required as rapid changes may occur in the status of a child with sepsis [52,53].