Bacteremia and Sepsis

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General Principles

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Sepsis is the sixth most common reason for hospitalization in the United States [1], with severe sepsis being the leading cause of in-hospital death [2]. Over 750,000 people develop sepsis annually, and almost one in four of these people die [1, 2]. Sepsis has an in-hospital mortality rate of approximately 16 %; this is eight times higher than other stays [1].

From 1997 to 2008, the cost of treating patients hospitalized for sepsis in the United States increased by almost 12 % annually. This increase may be attributed to an aging population with more chronic illnesses, greater use of invasive procedures, immunosuppressive drugs, chemotherapy, transplantation, and increasing microbial resistance to antibiotics. Hospitalization rates for sepsis increase with advanced age; patients over 65 years account for more than two thirds of sepsis hospitalizations in the United States [1, 3]. Globally, it is estimated that 18 million people are diagnosed with sepsis annually [4]. The case-fatality rate depends on the setting and severity of disease. Mortality can be as high as 30 % for sepsis, 50 % for severe sepsis, and 80 % for septic shock [5]. *Escherichia coli* is the most commonly identified organism in patients with a primary diagnosis of sepsis, while methicillin-resistant *Staphylococcus aureus* (MRSA) is most common for patients with a secondary diagnosis of sepsis [3].

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Definitions and Classification

Bacteremia is the presence of viable bacteria in circulating blood. Bacteremia is usually associated with a symptomatic infection and is demonstrable by bacterial growth from an aseptically collected blood culture specimen [6]. Bacteremia often occurs transiently without any clinical consequences.

Systemic inflammatory response syndrome (SIRS) is an uncontrolled inflammatory response to an insult without probable or documented infection [7]. The clinical manifestations of SIRS are often identical to those occurring in sepsis and may occur in a number of conditions (Table 1). Therefore, it is important to exclude sepsis when SIRS is diagnosed. Excluding sepsis is often a challenge, as microbiological investigations are often negative for various reasons including antibiotic administration prior to sample collection or technical issues related to blood culture. Only 30–60 % of patients diagnosed with sepsis have positive blood cultures [9]. Negative or inconclusive blood cultures do not exclude the possibility of sepsis in patients when there is a high index of suspicion. In the clinical setting, the diagnosis of sepsis is often made retrospectively.

Table 1 Causes of the systemic inflammatory response syndrome (SIRS) [8]

Differential diagnosis of sepsis
Anaphylaxis
Sterile inflammation, e.g., vasculitis, acute pancreatitis
Hypovolemia
Acute blood loss
Chemical aspiration
Acute respiratory failure
Acute myocardial infarction
Diabetic ketoacidosis
Adrenal insufficiency
Transfusion reaction
Acute mesenteric ischemia
Autoimmune disorder
Substance abuse or intoxication
Drug overdose
Inborn errors of metabolism

Sepsis is defined as a known or suspected infection plus systemic manifestations of infection [10].

Severe sepsis is sepsis with infection-induced organ dysfunction or infection-induced acute tissue hypoperfusion. Organ dysfunctions associated with sepsis include acute lung injury, acute kidney injury, coagulopathy, liver dysfunction, and cardiovascular abnormalities. Sepsis-induced tissue hypoperfusion abnormalities include hypotension, elevated lactate, oliguria, and altered mental status [10].

Septic shock is defined as sepsis-induced hypotension which is not responsive to adequate fluid resuscitation [9].

Multiple organ dysfunction syndrome (MODS) is a progressive organ dysfunction in an acutely ill patient such that homeostasis cannot be maintained without intervention. It is at the severe end of the severity spectrum of both SIRS and sepsis.

The sepsis spectrum begins with infection, which progresses to bacteremia, sepsis, severe sepsis, septic shock, and death.

Approach to the Patient

Clinical presentation: Early identification and appropriate evidence-based medical care are key to increasing the chance of survival and improving overall outcomes in sepsis [1, 10, 11].

The most common sites of infection are the respiratory, genitourinary, and gastrointestinal systems, as well as the skin and soft tissue [12]. These sites account for over 80 % of all cases of sepsis [13]. Among nursing home residents 65 and older, the urinary tract was found to be the most common source of sepsis [14].

Overall, fever is often the first manifestation of sepsis [12]. However, neonates, immunocompromised or chronically ill patients, and the elderly may have sepsis without meeting the sepsis criteria. Therefore, clinical suspicion is key to appropriate and timely diagnosis. In the elderly, for example, failure to eat, withdrawal, agitation, disorientation, and confusion may be early signs of sepsis [12, 15]. In neonates, exaggerated physiologic jaundice,

Table 2 Sepsis spectrum diagnostic criteria [16]

Sepsis	Documented or suspected infection and some of the following:
	General variables:
	Fever > 38.3 °C
	Hypothermia (core temperature < 36 °C)
	Heart rate > 90/min or > 2 standard deviations (SD) above the normal value for age
	Tachypnea
	Altered mental status
	Significant edema or positive fluid balance > 20 mL/kg over 24 h
	Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes
	Inflammatory variables:
	Leukocytosis (WBC count > 12,000/μL)
	Leukopenia (WBC count < 4,000/μL)
	Normal WBC count with > 10 % immature forms
	Plasma C-reactive protein >2 SD above the normal value
	Plasma procalcitonin > 2 SD above the normal value
	Hemodynamic variables
	Arterial hypotension (SBP < 90 mmHg, MAP < 70 mmHg, or a SBP decrease > 40 mmHg in adults, or < 2 SD below normal for age)
	Organ dysfunction variables
	Arterial hypoxemia (PaO_2/FiO_2 < 300)
	Acute oliguria (urine output < 0.5 mL/kg/h for at least 2 h despite adequate fluid resuscitation)
	Creatinine increase > 0.5 mg/dL or 44.2 μmol/L
	Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
	Ileus (absent bowel sounds)
	Thrombocytopenia (platelet count < 100,000/μL)
	Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)
	Tissue perfusion variables
	Hyperlactatemia (>1 mmol/L)
	Decreased capillary refill or mottling

tachypnea, poor feeding, and reduced tone may be the only manifestations of sepsis.

History taking focused on the chief complaint with a pertinent review of systems is often adequate for initial triage. However, some patient with sepsis may present with nonspecific constitutional symptoms necessitating a more detailed history.

Physical Examination A complete physical examination is indicated. This is important because sepsis from an infection in less obvious areas such as the pelvis or perineum may occur. However, a thorough physical examination should not delay early initiation of life-saving care. General and hemodynamic variables that may indicate sepsis (Table 2) should be carefully noted to aid in the early identification of patients in the sepsis spectrum.

Diagnosis

Laboratory Workup and Imaging

Laboratory findings consistent with sepsis are as outlined in Table 2. Routine laboratory workup for sepsis includes two sets of blood cultures (drawn before starting antibiotics if possible). Urinalysis, urine culture, and cultures from other suspected sites (wound, respiratory secretions, CSF, or other body fluids) are also appropriate. Other laboratory tests and imaging studies should be individualized based on history and physical examination findings.

Lactate levels have been strongly correlated with mortality [17, 18].

Table 3 Surviving Sepsis Campaign care bundles [10, 16]

To be completed within 3 h of presentation:
1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L
To be completed within 6 h of presentation:
5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mmHg
6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
(a) Maintain adequate central venous pressure (CVP) [a]
(b) Maintain adequate central venous oxygen saturation ($ScvO_2$)[a]
7. Remeasure lactate if initial lactate was elevated[a]

[a]Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mmHg, $ScvO_2$ of ≥70 %, and normalization of lactate

Differential Diagnosis

Various conditions can mimic sepsis. Although the differential is very broad, Table 1 includes common causes of SIRS other than sepsis.

Treatment

Aggressive and timely management of patients with sepsis is paramount. Expeditious transfer to an inpatient setting should occur. Intravenous fluid resuscitation can be started in the ambulatory setting. Blood culture collection should not cause delay in necessary care at any point. Empiric antibiotics should be started after blood culture sample collection and in any case within 1 h of arrival at the hospital or emergency room. The antibiotic choice can be based on the patient's history (e.g., recent antibiotics used), clinical context (community vs. health setting-acquired infection), most likely pathogens, local susceptibility patterns, and cost-effectiveness. Fluid resuscitation should be initiated and continued upon arrival to the emergency room or hospital. If septic shock is present, vasopressor therapy should be considered.

If a localized source of infection is detected, intervention (such as abscess drainage) should be undertaken as soon as possible within the first 12 h after the diagnosis is made [16].

The Surviving Sepsis Campaign (SSC) care bundle (Table 3) is a selected set of elements of care distilled from evidence-based practice guidelines. Using the bundle simplifies complex processes of care of patients with severe sepsis and has demonstrated marked improvements in survival rates after sepsis [19, 20].

Prevention

Patients at increased risk of sepsis should be appropriately vaccinated against pneumococci, *Haemophilus influenzae* type b, meningococci, and the influenza virus. The Centers for Disease Control (CDC) strategies for preventing infections include promotion of vaccination for diseases like pneumococcus and meningitis, smoking cessation programs to prevent community-acquired pneumonia, and strategies to prevent healthcare-associated infections [21]. Early identification and appropriate treatment of infection in all patients especially those at increased risk of sepsis reduces chances of progression to bacteremia and sepsis. Good nutrition and lifestyle changes (including regular exercise) boost the body's natural defense system and ability to fight infection. Hand hygiene and good general hygiene practices reduce the rate of infection transmission. Antibiotic stewardship reduces

the prevalence of bacterial resistance in the community.

Family and Community Issues

Sepsis survivorship is a substantial and under-recognized public health problem with major implications for patients, families, and the healthcare system. Sepsis survivors often develop physical, cognitive, and affective deficits in the months and years after discharge. These new deficits are relatively more severe among patients who were in good health prior to hospitalization for sepsis [22]. Declines in the level of functioning impact many areas of a patient's life ranging from the ability to perform activities of daily living (ADL) to executive functioning. This may affect the structure and functioning of the family unit. Additional issues include caregiver fatigue, marital stress, and other psychosocial, medical, economic, and legal issues. It is important for family physicians to maintain vigilance for possible sequelae of sepsis among patients and their families beginning at the discharge planning phase of care. An understanding of immediate and long-term outcomes helps with managing expectations and setting goals of care especially when assessing options for short- or long-term care.

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