CHAPTER 12

Update on Sepsis Diagnosis and Management

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INTRODUCTION

Sepsis and septic shock have become a large problem in the health care system that affects at least 1 million people annually in the US. It has become one of the leading causes of death in hospitals due to an infection, especially in the intensive care unit (ICU) setting. Although overall mortality rates from sepsis over the last few years have been declining, the incidence has been steadily climbing. Unfortunately, this illness is a financial health care burden as well. Sepsis has become one of the most expensive health care problems in the US with a cost of roughly more than 20 billion dollars annually.

Sepsis is currently being defined as a clinically life-threatening, acute organ dysfunction that is secondary to a dysregulated host response to infection. This syndrome is heavily shaped by pathogen and host factors with characteristics that evolve over time (1). The main dilemma with understanding sepsis is there is no gold standard in the definition or diagnosis. It can represent a wide range of different pathology with mortality risks that vary by patient. Clinicians have attempted to diagnose it by combining nonspecific physiological and laboratory anomalies (2). Due to its high complexity and its association with other pathology, it has become increasingly difficult to diagnose. Recognition and early intervention of sepsis is imperative in order to decrease morbidity and mortality rates in at-risk patients.

ETIOLOGY

Between 1979 and 2000, the incidence of sepsis has increased by at least 8.7% annually. These trends have been appreciated throughout the world and will likely continue to increase with an increasing aging population. Newer innovations such as organ transplantation, prosthetic implants, and vascular devices contribute to this increasingly vulnerable population (3). In the US alone, the incidence of sepsis and septic shock continue to increase, with greater than 750,000 cases each year, contributing to more than 200,000 deaths annually. Sepsis-related incidence and mortality rates have been associated with an increase with age and pre-existing comorbidity, with two-thirds of cases occurring in patients with significant underlying disease (4).

PATHOPHYSIOLOGY

Due to its complexity, sepsis can be triggered by local and systemic responses, as well as organ dysfunction and shock. Local and systemic host responses can release cytokines that increase blood flow and neutrophil migration to the infection site, which enhance vascular permeability and elicit pain. Vascular endothelial injury has been believed to be a major mechanism for multi-organ dysfunction. Septic shock can be characterized as compromised oxygen delivery to tissues followed by vasodilation (4).

In sepsis, the host immune response fails to control and/or overreacts to invasive pathogens, leading to 2 critical events. The first event involves marked abnormalities in the inflammatory response in the host. This can range from a hyper-inflammatory response in early stages of sepsis to a blunted response in the later stages. This places a patient at increased risk of hospital-acquired infections. The blunted inflammatory response results in programmed death of key immune, epithelial, and endothelial cells, leading to tissue injury and perpetuating the onset of multi-organ dysfunction. The second event is an imbalance in procoagulant and anticoagulant functioning. This can result in disseminated intravascular coagulation (DIC). DIC results in micro and macrovascular clot formation, impaired tissue perfusion, and thrombosis of the small vessels. Continued microvascular ischemia likely contributes to organ failure, as well as to the release of proinflammatory intracellular contents, which further stimulates the innate immune response and perpetuates the underlying pathology. As these events continue, they intensify the inflammatory response and a destructive process begins (Table 1).

RISK FACTORS

There are several predisposing risk factors that make patients more at-risk for developing sepsis. Among the predisposing risk factors are patients staying for long periods in the ICU where advanced technologies are used, the increasing elderly population, immune suppression resulting from malignant diseases and their aggressive treatment, increasing transplantation practices and use of related immunosuppressive drugs, invasive procedures, antibiotic resistance, and society-sourced and nosocomial infections (2).

Table 1

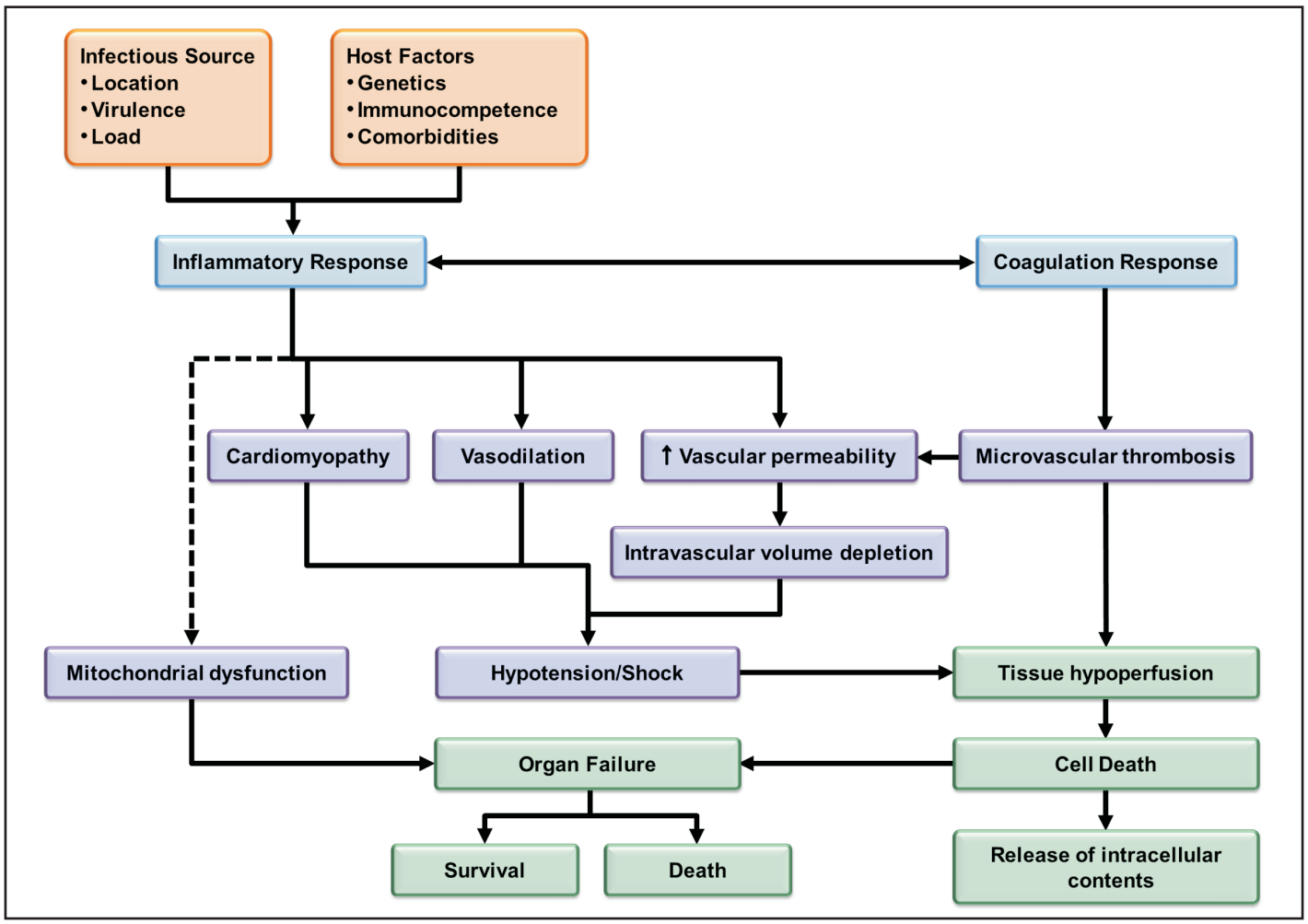

Table 1. Pathophysiology of sepsis. Adapted from (Ref. 9)

SEPSIS: DEFINITIONS

The concept of the systemic inflammatory response syndrome (SIRS), which is defined by certain vital sign abnormalities and laboratory values has long been used to identify early sepsis. SIRS included 4 clinical signs (temperature, white blood count, respiratory rate, heart rate), which when altered were thought to represent an inflammatory response. One major problem with the SIRS criteria is that it has been found to lack sensitivity and specificity for an increased mortality risk in a patient. Research has shown that sepsis is not just a proinflammatory condition, but rather may evolve anti-inflammatory responses. SIRS criteria was also too sensitive and insufficiently specific to identify infected patients at risk for a complicated hospital course (5).

The original definition "Sepsis-1" was created in 1991. It defined sepsis as the identification of 2 or more SIRS criteria in addition to known/suspected infection. Sepsis-1 was revised in 2001 and renamed "Sepsis-2" with the addition of clinical criteria for inadequate tissue perfusion. A total of 19 sepsis clinicians known as the Third International Consensus Definitions Task Force convened in 2014 to review current evidence and revise the definitions of sepsis. Up to the time of the creation of the Task Force, several members advocated change to the Sepsis-2 definition based on a growing and substantial body of evidence that sepsis was more than just an uncontrolled inflammatory process. Sepsis according to "Sepsis-1" was a cytokine inflammatory response to an infectious trigger.

At the core of the 1991 and 2001 sepsis definitions, severe sepsis and septic shock definitions were part of SIRS criteria. In order to be diagnosed with sepsis under Sepsis-1 and Sepsis-2 definitions, individuals must have at least 2 SIRS criteria and a confirmed or suspected infection. Under Sepsis-1 and Sepsis-2, sepsis, severe sepsis, and septic shocks were seen as steps in a continuum. Essentially, as a patient's condition declined they advanced from 1 stage of the continuum to the next with unresolved septic shock resulting in death. Many patients however lacked sufficient SIRS criteria under previous definitions to receive a sepsis diagnosis, but had complicated courses similar to those with diagnoses resulting in death. While individuals with at least

Table 2

Definitions of Sepsis			
Older Definitions		**Newer Definition: Sepsis 3**	
Sepsis 1	**Sepsis 2**	**Definition**	**Clinical Criteria**
Systemic inflammatory response syndrome (SIRS) = the systemic inflammatory response to a variety of severe clinical insults 1. Temperature >38°C or <36°C; 2. Heart rate >90 beats per minute; 3. Respiratory rate >20 beats per minute or $PaCO_2$ <32 mmHg; and 4. White blood cell count >12,000/cu mm, <4,000/cu mm, or 10% immature (band) forms.	**Diagnosis criteria for sepsis** Infection Documented or suspected and some of the following: **General parameters** Fever (core temperature >38.3°C) Hypothermia (core temperature <36°C) Heart rate >90 bpm or >2 SD above the normal value for age Tachypnea: >30 bpm Altered mental status Significant edema or positive fluid balance (>20 ml. kg^1 over 24 h) Hyperglycemia (plasma glucose >110 mg dL^{-1} or 7.7 mM L□1) in the absence of diabetes	**Screening for Sepsis** qSOFA (quick Sequential Organ Failure Assessment) scoring system Accordingly, an increase of 2 or more in the qSOFA score should create a suspicion of sepsis and organ dysfunction.	qSOFA 1. Altered mental status (GCS score <15) 2. Systolic blood pressure <100 mmHg 3. Respiratory rate >22/min If 2/3 of these 3 criteria are positive, the qSOFA would be positive!
Sepsis = the systemic response to infection, manifested by two or more of the SIRS criteria as a result of infection	**Inflammatory parameters** Leukocytosis (white blood cell count >12,000/□L) Leukopenia (white blood cell count <4,000/□L) Normal white blood cell count with >10% immature forms Plasma C reactive protein >2 SD above the normal value Plasma procalcitonin >2 SD above the normal value	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction as shown in Table 3)
Severe sepsis = sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status	**Hemodynamic parameters** Arterial hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age) Mixed venous oxygen saturation >70% Cardiac index >3.5 l $min^{□1}$ $m^{□2}$		
Septic shock = sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured..	**Organ dysfunction parameters** Arterial hypoxemia (PaO_2/FiO_2 <300) Acute oliguria (urine output <0.5 ml $kg^{□1}$ h□1 or 45 mM $L^{□1}$ for at least 2 h) Creatinine increase ≥0.5 mg $dL^{□1}$ Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s) Ileus (absent bowel sounds) Thrombocytopenia (platelet count <100,000/□L) Hyperbilirubinemia (plasma total bilirubin >4 mg $dL^{□1}$ or 70 mmol $L^{□1}$) **Tissue perfusion parameters** Hyperlactatemia (>3 mmol $L^{□1}$) Decreased capillary refill or mottling	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.	Sepsis and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol $L^{□1}$ (18 mg $dL^{□1}$) despite adequate fluid resuscitation

Table 2. Definitions of sepsis. Adapted from (Ref. 2).

Table 3

The Sequential Organ Failure Assessment (SOFA) Score				
SOFA score	**1**	**2**	**3**	**4**
Respiration			------ with respiratory support ------	
PaO_2/FiO_2 (mm Hg)	<400	<300	<200	<100
Coagulation				
Platelets $\times 10^3/mm^3$	<150	<100	<50	<20
Liver				
Bilirubin (mg dL^{-1})	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular				
Hypotension	MAP <70	Dopamine ≤5 or dobutamine (any)	Dopamine >5 or norepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
Central Nervous System				
Bilirubin (mg dL^{-1})	13-14	10-12	6-9	<6
Renal				
Creatinine (mg dL^{-1}) or urine output (mL)	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

MAP: mean arterial pressure; vasoactive mediations administered for at least 1 hr (dopamine and norepinephrine μg kg^{-1} min^{-1}).

Table 3. SOFA score. Adapted from (Ref. 2).

2 abnormalities in SIRS criteria are often septic, many are not. This is partly because clinicians often confuse a normal inflammatory response with that of sepsis. Research has shown that SIRS is a normal response to any infection and most people do not require hospitalization or antibiotics when an immune response is activated. Conditions that can be mistaken for sepsis include postoperative inflammatory responses, endocrine disorders, autoimmune disorders, primary hypothermia, cardiac and pulmonary disorders, and uncomplicated infections without an extended inflammatory response. There is a clear direct association between the number of SIRS criteria and risk for organ failure and mortality, but presence of 2 or more SIRS criteria as part of sepsis diagnosis appears to be overly sensitive and may lead to inflated sepsis incidence data. The Task Force aimed to increase specificity using criteria that identified infection, host response, and organ dysfunction. The term severe sepsis was eliminated because it was redundant. The goal was to differentiate between an infection and sepsis (6) (Table 2).

CURRENT UPDATE IN SEPSIS DIAGNOSIS: SEPSIS-3

Under "Sepsis-3," there are only 2 diagnostic categories: sepsis and septic shock. The Task Force defined sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection" with the following clinical operationalized definition: organ dysfunction can be represented by an increase in Sequential Organ Failure Assessment (SOFA) score of 2 points or more. Septic shock was defined as "subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater increase of mortality than with sepsis alone." The SOFA score is a validated risk stratification tool for ICU patients with organ dysfunction (6) (Table 3).

A different scoring system, the quick SOFA (qSOFA), which is derived from the SOFA score can be utilized as a risk stratification tool for the non-ICU patient. The qSOFA score has 3 variables (6) (Table 4), which any combination of 2 variables demonstrated predictive validity similar to

Table 4

qSOFA (Quick SOFA) Criteria	Points
Respiratory rate ≥ 22/min	1
Change in mental status	1
Systolic blood pressure ≤ 100 mmHg	1

Table 4. Scoring system for qSOFA. Adapted from (Ref 10).

that of SOFA score when used in non-ICU settings. The benefits of the qSOFA system include obtaining a score without labwork. This tool may aid clinicians in recognizing sepsis rapidly, which can kickstart a process to more timely treat patients for successful outcomes. The use of qSOFA will likely result in earlier identification of septic patients, while adoption of the operationalized Sepsis-3 definition into practice settings may result in less resource utilization as clinicians are able to better differentiate between sepsis and inflammatory events (6).

MANAGEMENT GUIDELINES

New guidelines for the international management of sepsis and septic shock have been generated with the development of Sepsis-3. Some of the major recommendations for management include initial resuscitation, diagnosis, anti-microbial therapy, and source control. Sepsis and septic shock are both medical emergencies. A hemodynamic assessment is critical with these patients. Within 3 hours of presentation in suspected septic patients, lactate levels, and blood cultures should be obtained. An intravenous bolus of 30 ml/kg crystalloid can be administered as initial resuscitation for hypotension or lactate ≥ 4 mmol/liter. If there is persistent hypotension and mean arterial pressure of ≤65 mm Hg within 6 hours following initial resuscitation, vasopressors may be considered (7).

Early sepsis diagnosis is critical, so it is recommended that appropriate microbiologic cultures are taken before starting antibiotic therapy in patients who are suspected with sepsis or septic shock, only if doing so results in no significant delay in start of antimicrobial therapy. It is important to always include 2 sets of blood cultures: aerobic and anaerobic. Obtaining cultures prior to administrating anti-infective therapy increases yield of cultures making pathogen identification more likely. The administration of intravenous antimicrobials is recommended as soon as possible after recognition of sepsis. As far as source control, recommendations are that specific anatomic diagnosis of infection requiring emergence source control be identified or excluded rapidly in patients with sepsis. Principles of source control include rapid diagnosis of specific site of infection and determination of whether infection site is amenable to source control measurings such as incision and drainages, debridement of infected/necrotic tissue, removal of infected devices, and definitive control of a source of ongoing microbial contamination (8).

While there is still no gold standard for diagnosing or defining sepsis, the newer Sepsis-3 definition attempts to assist clinicians in recognizing the syndrome in a rapid manner. The most critical key to understand with sepsis is that early detection and treatment will provide the patient a better overall prognosis. Early recognition will provide the clinician the ability to efficiently utilize antimicrobial therapy.

Although not perfect, the SOFA and qSOFA risk stratification tools may be more clinically applicable and easier to utilize as compared to SIRS criteria, which was relatively nonspecific. Studies have shown great efficacy in recognizing sepsis via the qSOFA risk stratification in non-ICU patients. In the absence of labwork, the qSOFA score can provide a quick picture of a patient's status with suspected sepsis. This would allow the clinician to quickly intervene in patient treatment with antimicrobial therapy and possibly source control. Despite newer innovations in technology, diagnosis of sepsis has still become increasingly difficult. The current evolution in sepsis definitions and management seeks to help clinicians efficiently recognize and treat sepsis at its early stages. Further updates and progress in research to sepsis is warranted until a gold standard obtained.

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