Pathologic Difference between Sepsis and Bloodstream Infections

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Background: Sepsis, defined as life-threatening organ failure caused by a dysregulated host response to infection, is a major cause of morbidity and mortality in hospitalized patients. Understanding the features that distinguish sepsis from bloodstream infections (and other types of infection) can help clinicians appropriately and efficiently target their diagnostic workup and therapeutic interventions, especially early in the disease course.

Content: In this review, sepsis and bloodstream infections are both defined, with a focus on recent changes in the sepsis definition. The molecular and cellular pathways involved in sepsis pathogenesis are described, including cytokines, the coagulation cascade, apoptosis, and mitochondrial dysfunction. Laboratory tests that have been evaluated for their utility in sepsis diagnosis are discussed.

Summary: Sepsis is defined not only by the presence of an infection, but also by organ dysfunction from a dysregulated host response to that infection. Numerous pathways, including proinflammatory and antiinflammatory cytokines, the coagulation cascade, apoptosis, and mitochondrial dysfunction, help determine if a bloodstream infection (or any other infection) progresses to sepsis. Many biomarkers, including C-reactive protein, procalcitonin, and lactic acid have been evaluated for use in sepsis diagnosis, although none are routinely recommended for that purpose in current clinical practice. While some laboratory tests can help distinguish the 2, the presence of organ dysfunction is what separates sepsis from routine infections.

IMPACT STATEMENT

This review article gives readers a broad overview of the distinction between sepsis and bloodstream infections, focusing on the pathophysiology of sepsis and the utility of several laboratory tests in distinguishing the 2. Recent developments, including major changes in the sepsis definition, are also discussed. This article also serves as a useful reference for those wishing to understand current theories of sepsis pathophysiology.

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DOI: 10.1373/jalm.2018.026245

[2] **Nonstandard abbreviations:** SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; CRP, C-reactive protein.

Table 1. Sepsis definitions.

	Description
Original sepsis definition (*5*)	Systemic inflammatory process occurring in response to an infection
Original sepsis criteria (*5*)	Two or more of the following in the setting of an infection:
	Temperature <36 °C or >38 °C
	Heart rate >90 beats/minute
	Respiratory rate >20 breaths/minute or PaCO2 <32 mmHg (<4.3 kPa)
	White blood cell count <4000 cells/mm^3 or >12000 cells/mm^3 or >10% immature neutrophils (bands)
Sepsis-3 definition (*9*)	Life-threatening organ dysfunction caused by a dysregulated host response to infection
Sepsis-3 criteria (*9*)	Increase in the SOFA score of at least 2 points from baseline in the setting of an infection

BACKGROUND

Sepsis, and its more severe manifestation, septic shock, is a major healthcare problem in the US. As of 2014, an estimated 1.5–1.7 million adults in the US are hospitalized annually for sepsis, with 270 000 annual attributable deaths (*1*, *2*). Each individual sepsis hospitalization is estimated to cost about $35 000, leading to an estimated annual cost of almost $60 billion in the US alone (*3*). Globally, 31.5 million cases of sepsis are estimated to occur annually, with 5.3 million deaths attributed to it (*4*).

Not all infections result in sepsis; therefore, a precise definition is needed to identify septic patients, particularly given its high morbidity and mortality. As a result of an improved understanding of its pathogenesis, the definition of sepsis has changed substantially in recent years. In 1991, sepsis was formally defined as the presence of an inflammatory response to infection, requiring the presence of at least 2 out of the 4 systemic inflammatory response syndrome (SIRS)[2] criteria in the setting of an infection (*5*). This definition was broadened to include markers of organ dysfunction in the early 2000s, but the SIRS criteria remained part of the formal sepsis definition until recently (*6*).

In 2016, the sepsis definition was significantly modified to incorporate a more modern understanding of the disease. By this time, it had become clear that an inflammatory response could be part of a normal response to infection and by itself did not necessarily indicate sepsis. Furthermore, the SIRS criteria had been found to be a poor marker of sepsis, lacking both sensitivity and specificity. In fact, almost half of all hospitalized patients have ≥2 SIRS criteria present at least once during their hospitalization, many for reasons unrelated to infection (*7*). Despite such a high prevalence of SIRS in hospitalized patients, another study of over 100 intensive care units found that 12% of patients with sepsis were not detected by the SIRS criteria (*8*). As a result, sepsis was redefined in 2016 as a "life-threatening organ dysfunction caused by a dysregulated host response to infection" (*9*), with organ dysfunction identified on the basis of an increase of at least 2 points in the sequential organ failure assessment (SOFA) score, a marker of severity of illness incorporating various clinical and laboratory measures, including creatinine, platelet count, total bilirubin, and the partial pressure of oxygen in arterial blood (*10*) (Table 1). This definition of sepsis incorporating organ dysfunction is very similar to the prior concept of severe sepsis, which denoted a subset of septic patients with evidence of organ dysfunction. As a result, the distinction between sepsis and severe sepsis was eliminated from the 2016 sepsis definitions, with those patients previously considered to have

severe sepsis now categorized as patients with sepsis.

Septic shock, a more severe manifestation of infection, is considered to be "a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone" (*9*). Clinically, this definition was operationalized as patients with "a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate concentration <2 mmol/L (>18 mg/dL) in the absence of hypovolemia" (*9*), reflecting the more recent concept that lactate is not simply a marker of poor perfusion but also an indication that mitochondrial dysfunction is present.

While sepsis and bloodstream infection are often used interchangeably in nonmedical literature, the 2 terms refer to different concepts. A bloodstream infection refers to a pathogenic organism in the bloodstream that causes disease. It is typically defined by the growth of a pathogenic organism in culture or by the growth of an atypical organism in combination with symptoms of infection (*11*). If that organism is a bacterium, the bloodstream infection is called bacteremia. While bloodstream infections, like any other infection, can ultimately lead to a dysregulated immune response, sepsis is not the inevitable result of a bloodstream infection. In many cases, the pathogen is controlled before a dysregulated host response and organ dysfunction develop, and sepsis never occurs. Furthermore, not all cases of sepsis are due to bloodstream infections. In fact, bloodstream infections cause only 25%–30% of sepsis cases (*12*).

Clinically, symptoms of both sepsis and bloodstream infections are varied and nonspecific. Symptoms in both groups of patients include fever, chills, and malaise. More focal symptoms may also develop depending on the site of infection. For example, a patient with pneumonia leading to bloodstream infection may have a productive cough, while one with a urinary tract infection may develop painful urination. Once an infection has progressed and sepsis has developed, symptoms of organ dysfunction develop, including confusion, decreased urination, and shortness of breath, among many others, depending on the specific organs affected.

PATHOPHYSIOLOGY

Ideally, the body's immune system clears a bloodstream infection without any complications. In patients who develop sepsis, however, a dysregulated host response leads to organ dysfunction. On a cellular and molecular level, progress has been made in delineating the specific dysregulated pathways. This work has made it clear that there is not 1 specific "sepsis pathway." Rather, numerous interrelated molecular pathways contribute to the development of sepsis.

The host response to infection begins with pathogen recognition by the innate immune system. Receptors from several families, the best known of which are the toll-like receptors, recognize structures on the surface of pathogens known as pathogen-associated molecular patterns, which are preserved across many pathogen species (*13*). These receptors are located on multiple immune cell types, including dendritic cells, macrophages, and some epithelial cells.

Inflammation

After a pathogen-associated molecular pattern binds to a host cell receptor, proinflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL) 1, and IL6 are released by the cell (*13*). These cytokines recruit additional immune cells, including neutrophils and macrophages. In a healthy response to infection, these recruited cells eliminate pathogens through phagocytosis and the release of cytotoxic substances such as reactive oxygen species, resulting in clearance of the infection with minimal tissue damage. In sepsis,

however, an excessive inflammatory response results in these cells releasing large amounts of reactive oxygen species, damaging neighboring tissues. Furthermore, host cells damaged by the body's response release their own proinflammatory cytokines in response to the damage. This response leads to a positive feedback loop of progressive inflammation, with further recruitment of immune cells and additional tissue damage. This proinflammatory pathway was initially thought to be the sole driver of sepsis, and various inhibitors of either the individual components of, or the overall, inflammatory response were tested as treatments for sepsis (*14*). After some success in improving outcomes in animal models of sepsis, multiple randomized trials in humans with sepsis and/or septic shock were undertaken. These trials were unable to demonstrate improvement in mortality or other clinical outcomes (*14*). More recently, other molecular pathways have been found to contribute to sepsis pathogenesis, potentially explaining the negative results when targeting only the proinflammatory pathway.

Paradoxically, the antiinflammatory response is also prominently involved in sepsis. Researchers have discovered that antiinflammatory cytokines, including IL10, are released in response to infection, directly or indirectly downregulating the concentrations of proinflammatory cytokines (*13*). These antiinflammatory cytokines also contribute to an increase in regulatory T cells and antiinflammatory activity from phagocytes (*13*). A healthy antiinflammatory response serves to limit excessive host inflammation and therefore prevents damage to host tissues. In sepsis, however, the antiinflammatory response may suppress the immune system before recovery from the initial infection, leading to immune suppression and a vulnerability to secondary infections. In addition, the antiinflammatory response may also be prolonged, continuing long after sepsis has resolved and the infection is cleared. This prolonged response also increases the risk of secondary infections, often later in the hospital course.

Coagulation

Noninflammatory pathways also contribute to sepsis, including the coagulation cascade. Specifically, sepsis leads to increased tissue factor activity and a resulting increase in fibrin deposition (*15*). At the same time, an increase in plasminogen activator inhibitor-1 (PAI-1) leads to a decrease in fibrinolysis (*15*). The increase in fibrin deposition and decrease in fibrin breakdown overall lead to a prothrombotic state. Normally, activation of the coagulation system in response to infection leads to bacterial trapping and limits the delivery of oxygen and nutrients to the affected area, preventing pathogens from spreading and multiplying (*15*). In septic patients, however, dysregulated activation of the coagulation system leads to areas of thrombosis extensive enough to cause organ damage. This results in a sepsis-associated coagulopathy, with alterations in components of the coagulation system such as thrombocytopenia (low platelet count), abnormalities in coagulation factors (increased prothrombin or partial thromboplastin time), or increased fibrin split products. In extreme cases, sepsis can lead to disseminated intravascular coagulation, in which excess thrombosis leads to consumption of the body's coagulation factors and in which all the aforementioned alterations in coagulation system components are present simultaneously. This activity results in both thrombosis and hemorrhage throughout the body.

Apoptosis

Apoptosis, or programed cell death, is also dysregulated in septic patients, particularly within the immune system. Humans have a baseline level of lymphocyte apoptosis useful for regulating autoreactive cells (*16*). In infected patients, this baseline level of apoptosis increases late in the course of infection, helping terminate the proinflammatory

response and preventing additional damage to the patient. Septic patients, however, have a highly upregulated lymphocyte apoptosis, suppressing their overall immune response and increasing their vulnerability to secondary infections (*16*). In contrast, neutrophil apoptosis is delayed in patients with an inflammatory response (*17*). While increased neutrophil activity allows neutrophils more time to eliminate pathogens in those with a healthy response to infection, it contributes to worsening inflammation and tissue damage in septic patients whose response to infection is already dysregulated.

Mitochondrial dysfunction

Mitochondrial dysfunction is another distinguishing characteristic of sepsis. In sepsis, the increase in production of reactive oxygen species leads to diffuse mitochondrial damage, even in the absence of widespread cell death (*18*). This damage has been noted in animal and human experiments to be present in multiple tissues, including skeletal muscle, liver, heart, and kidneys (*19*). Mitochondrial protein expression is also downregulated through cytokine signaling (*18*). Affected cells decrease their energy expenditure and enter a state similar to hibernation. While there is some controversy over the degree to which this cellular "hibernation" is pathogenic vs adaptive vs merely a marker of the severity of disease, it is generally felt to contribute to the organ dysfunction seen in sepsis (*20*).

Pathway interactions

These various pathways do not exist in isolation. Rather, complex interactions between them determine the host response to infection and thus whether organ dysfunction and sepsis develop. For example, inflammation contributes to activation of the coagulation system through upregulation of tissue factor and downregulation of anticoagulant molecules such as protein C and antithrombin (*21*). Similarly, the coagulation system can itself promote further inflammation. Specifically, proteases in the coagulation system bind to protease-activated receptors, which in turn activate proinflammatory cytokines including IL1, IL6, and IL8 (*21*). Apoptosis can lead to either pro- or antiinflammatory responses depending on the severity of infection and the cells affected. The ultimate response to infection can thus range from rapid clearance of infection with restoration of homeostasis and minimal collateral damage to sepsis, multiple organ failure, and death. The specific response depends on the multiple interconnected molecular systems described above and pathogen and host factors, including genetic predisposition and preexisting comorbidities.

Organ dysfunction

In patients who do develop sepsis, dysregulation of these cellular and molecular pathways can lead to dysfunction in multiple organ systems. Increased neutrophil activity leads to the release of reactive oxygen species and proteases that directly damage neighboring tissues (*20*), and apoptosis leads to the death of some cells, primarily within the immune system, although there is relatively little apoptosis in other organ systems (*18*). Both the procoagulant response and inflammation-induced vasodilation leading to hypotension contribute to tissue hypoxia, which also contributes to organ dysfunction. Some patients, however, develop organ dysfunction without evidence of extensive hypoxia or cell death. While there is some controversy over the cause of dysfunction in these organs, mitochondrial dysfunction appears to play some role, impairing the ability of cells to effectively use the oxygen that is being delivered (*20*). Finally, the inflammatory response leads to direct endothelial damage, which contributes to manifestations of sepsis such as acute respiratory distress syndrome (*22*).

Regardless of the exact mechanism, organ dysfunction in sepsis manifests in various ways,

including acute kidney injury, disseminated intravascular coagulation, encephalopathy, respiratory failure from acute respiratory distress syndrome, vasodilatory shock, and myocardial depression. In severe cases, progression to septic shock, cardiovascular collapse, and death may occur. In contrast, in patients with infection who do not develop sepsis, some of the same molecular pathways can be activated, including the inflammatory response, procoagulant activity, and apoptosis, but these pathways remain appropriately regulated, leading to clearance of infection and restoration of homeostasis without significant organ dysfunction.

LABORATORY TESTING

The role of laboratory testing in the diagnosis of bloodstream infections is relatively straightforward. A diagnosis of a bloodstream infection is most commonly based on positive blood cultures, with the number of positive blood cultures required to diagnose an infection depending on the specific organism isolated (*11*). Cultures, however, can take several days to grow, with identification of a specific pathogen taking longer. Furthermore, approximately 30% of infected patients in the intensive care unit never have a causative organism identified in cultures, making them an imperfect test (*23*). Recently, rapid molecular testing, often using PCR technology, has shortened the time until identification of certain organisms, making it possible to identify specific pathogens in the setting of positive blood cultures and implement targeted treatments more quickly (*24*). Studies, however, have not demonstrated a consistent improvement in mortality from this testing (*24*). Direct molecular testing on blood samples without requiring positive blood cultures has the potential to reduce time to detection even further and to expand the number of organisms detected, but evidence regarding clinical outcomes with these tests is more limited, with one cluster-randomized trial failing to show a difference in 7-day mortality despite increased numbers of microbes being detected and a faster time to detection with direct molecular testing (*25*). Neither method has been universally adopted, leaving blood cultures as the current usual method of diagnosing bloodstream infections.

In contrast to the role of laboratory testing in diagnosing bloodstream infections, its role in diagnosing sepsis is more complex. A variety of laboratory tests have attempted to take advantage of the pathophysiologic differences between infected patients who develop sepsis and those who do not. Indeed, as of 2010, at least 178 biomarkers had been evaluated for use in sepsis, 34 of which had been evaluated specifically for their diagnostic utility in sepsis (*26*). No single test, however, is currently sensitive or specific enough for this purpose. Similarly, a variety of laboratory tests can detect individual organ dysfunction, but none can yet accurately determine the cause of the organ failure. The most prominent biomarkers evaluated to date include procalcitonin, C-reactive protein, and lactic acid (Table 2).

Procalcitonin

Procalcitonin is an amino acid precursor of calcitonin, a protein that helps regulate calcium concentrations. As procalcitonin is part of the proinflammatory pathway, it has been evaluated extensively as a potential sepsis biomarker. In a metaanalysis of 30 studies evaluating procalcitonin for the diagnosis of sepsis in patients with the SIRS, increased procalcitonin concentration had a sensitivity of 0.77 and a specificity of 0.79 for the diagnosis of sepsis, with an area under the ROC curve of 0.85 (*27*). Increased procalcitonin concentrations have been detected in noninfectious inflammatory conditions, including trauma, burns, and pancreatitis (*28*), further

Table 2. Selected sepsis biomarkers.

Biomarker	Function	Utility in sepsis diagnosis	Guidelines	References
Procalcitonin	Precursor of calcitonin, a calcium regulator; procalcitonin is released as part of the inflammatory response, although its role is unclear	Sensitivity of 0.77 and specificity of 0.79 for sepsis diagnosis in patients with SIRS response, with an area under the curve of 0.85	Surviving Sepsis Guidelines support its use as an aid in diagnosing sepsis, although other guidelines do not	(*27–30*)
CRP	Directly binds to pathogens, activating complement system and neutrophils	Isolated admission CRP has sensitivity of 0.89 and specificity of 0.59 for sepsis diagnosis in critically ill patients	Not currently recommended for sepsis diagnosis by any major guidelines	(*31–34*)
Lactic acid	Metabolite produced during anaerobic metabolism	Increased lactic acid concentrations associated with increased mortality in septic patients	Included as part of Sepsis-3 definition of septic shock	(*9*, *35–37*)

complicating their use in differentiating patients with sepsis from those with noninfectious SIRS or other conditions.

Given its performance in sepsis diagnosis, 1 sepsis guideline, published by the Surviving Sepsis Campaign, recommends the use of procalcitonin to distinguish infected from noninfected patients among those already being empirically treated for sepsis but with limited clinical evidence of infection (*29*). This strategy potentially allows for the discontinuation of empiric antimicrobials in patients with low procalcitonin concentrations. This use of procalcitonin is controversial, however, and other societies do not recommend its use in diagnosis at this time (*30*). Even the Surviving Sepsis Campaign guidelines recommend against the exclusive use of procalcitonin when making treatment decisions, instead stating that procalcitonin results should be interpreted in conjunction with other clinical and laboratory data (*29*). Given its limited sensitivity and the potentially disastrous consequences of withholding antimicrobial treatment in a septic patient, procalcitonin lacks the required characteristics to reliably rule out sepsis in patients with potential infection.

C-reactive protein

C-reactive protein (CRP) is a protein synthesized in the liver and released in response to inflammation. It has been shown to bind directly to various pathogens and to play a role in activating both complement and neutrophils (*31*). CRP is also routinely available as a laboratory test. Given its ready availability in the clinical setting and the known role of inflammation in sepsis, CRP has also been investigated as a potential marker of sepsis. In one study of critically ill patients, a CRP concentration higher than 8.7 mg/dL (0.48 mmol/L) combined with a maximum daily CRP variation >4.1 mg/dL (0.23 mmol/L) had an 82.1% sensitivity and a 92.1% specificity for distinguishing infectious from noninfectious pathologies in patients (*32*). Another study showed an admission CRP higher than 5 mg/dL (0.28 mmol/L) had a sensitivity of 89% and a specificity of 59% for detecting infection in critically ill patients (*33*). Importantly, both studies included all critically ill patients, regardless of whether infection was suspected or whether a condition that could be mistaken for sepsis was present. Furthermore, CRP has been shown to be increased in

patients with noninfectious causes of inflammation, including rheumatologic disease, pancreatitis, and malignancy (*31*, *34*). Because of these limitations, diagnosing sepsis with CRP concentrations is not currently recommended.

Lactic acid

Lactic acid is another marker of disease whose utility in sepsis diagnosis has been evaluated. Lactic acid is a product of anaerobic glycolysis and therefore is increased in patients with tissue hypoxia, resulting in a switch from aerobic to anaerobic metabolism. Traditionally, this mechanism was considered the primary pathway through which lactic acid was increased in sepsis (*35*), but more recent evidence has shown that increased adrenergic stimulation and mitochondrial dysfunction may also be important triggers of lactic acid production (*36*). While lactic acid has been studied as a potential diagnostic marker for sepsis, lactic acid concentrations are also increased in numerous nonseptic causes of both tissue hypoxia and increased adrenergic stimulation, including seizures, ischemic limb and bowel, and adverse events from certain medications. Instead, lactic acid has been more useful as a predictor of mortality in sepsis because higher lactic acid concentrations are associated with increased mortality in septic patients (*37*). As a result of this association, a lactic acid concentration higher than 2 mmol/L (18 mg/dL) is a necessary criterion for septic shock in the most recent definition (*9*).

SOFA score components

The SOFA score, used to define organ failure in the most recent sepsis definition, contains a combination of clinical and laboratory values. Specific laboratory values needed to calculate a SOFA score are creatinine, total bilirubin, platelet count, and the partial pressure of oxygen in arterial blood (*10*). These laboratory studies help quantify organ dysfunction in individual organ systems, but none of them was developed to evaluate for sepsis and none can distinguish between infectious and noninfectious causes of organ failure. Instead, in cases of confirmed infection, including bloodstream infections, they can assist in determining if organ failure is present and therefore play a role in the diagnosis of sepsis.

Biomarker panels

Given the complex pathogenesis of sepsis, it is not surprising that no single laboratory test can yet reliably diagnose it. As a result, some groups have combined multiple biomarkers into laboratory panels for improved diagnostic accuracy. One of the largest attempts was a prospective cohort of 1000 patients, in which 150 prospective sepsis biomarkers were narrowed to a panel of 3 laboratory tests: 1 measuring organ failure, neutrophil gelatinase-associated lipocalin (NGAL); one measuring coagulation system abnormalities, protein C; and one measuring inflammation, interleukin 1 receptor antagonist (IL1ra) (*38*). When results from the 3 tests were combined to create a sepsis score, a score of 40 was 82% sensitive and 60% specific for severe sepsis, using the previous sepsis definitions (roughly equivalent to the current definition of sepsis, which requires an increase of ≥2 points in the SOFA score). Another group found a panel of 6 tests, including both CRP and procalcitonin, had a sensitivity of 89% and specificity of 84% for a bacterial infection when hospitalized adults meeting at least 2 SIRS criteria were analyzed (*39*). This study, however, did not evaluate for nonbacterial infections, so it is unclear how well the panel would perform in patients with sepsis from nonbacterial pathogens. Unfortunately, no sepsis laboratory panel has yet demonstrated the accuracy needed for routine clinical use.

CONCLUSIONS

Sepsis and bloodstream infections are 2 distinct but related entities, with sepsis requiring

not only an infection but also a maladaptive host response and organ dysfunction. Understanding the differences between the 2 has important implications for treatment and prognosis. While progress has been made on distinguishing the 2 entities with diagnostic laboratory tests, currently there is no single definitive test to distinguish sepsis from bloodstream infections, so differentiating between the 2 still requires a thorough clinical assessment.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.*

Authors' Disclosures or Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

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