CME

Can biomarkers help identify sepsis in adults?

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ABSTRACT

Sepsis is increasing in incidence in the United States and is one of the most common causes of death in hospitalized patients. Sepsis affects different biochemical and immunologic pathways and can present variably. Despite efforts to unify definitions of sepsis, increase awareness, and improve treatment, mortality remains high. Because of sepsis's complex pathophysiology, diagnosis can be challenging. No diagnostic test is sensitive or specific enough to diagnose sepsis in isolation. However, three biomarkers—lactate, C-reactive protein, and procalcitonin—in combination with other diagnostics may help clinicians diagnose sepsis earlier, leading to better patient outcomes.

Keywords: sepsis, biomarkers, lactate, CRP, procalcitonin, qSOFA

Learning objectives

- List the incidence, prevalence, morbidity, and mortality of sepsis.
- Describe the clinical presentation of sepsis.
- Discuss the difference between infection and sepsis.
- Describe systematic approaches to diagnosing sepsis.

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The Third International Consensus Definitions for Sepsis and Septic Shock defines sepsis as a "life-threatening organ dysfunction caused by a dysregulated host response to infection," leading to a complex and potentially fatal syndrome that is common in hospitalized patients and constitutes one of the leading causes of death in ICUs.[1] Sepsis is multifaceted and involves a patient's response to an infecting pathogen, influenced by both host and pathogen factors.[1] The Third International Consensus Definitions for Sepsis and Septic Shock defines septic shock as a "subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone."[1]

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Previously, sepsis was thought of as mainly an inflammatory process; however, sepsis now is recognized to involve pro- and anti-inflammatory responses, as well as cardiovascular, neuronal, hormonal, metabolic, and coagulation changes.[1,2]

The incidence of sepsis is reported as 2% of all hospitalizations in developed nations and 6% to 30% among patients in ICUs.[3] Severe sepsis is reported in 50 to 100 per 100,000 patients in the United States.[3] The CDC reports that in a typical year, at least 1.7 million adults in the United States develop sepsis.[4] At least 350,000 adults who develop sepsis die during their hospitalization or are discharged to hospice.[4] One in three people who die in a hospital experienced sepsis during that hospitalization.[4]

Between 40% and 50% of sepsis cases are associated with respiratory infections.[5] Genitourinary and gastrointestinal infections also are common causes. Other sources include skin, soft tissue, bone, joint, and central nervous system infections as well as primary bacteremia.[5] Sepsis is a public health concern, accounting for about 5.2% of total US hospital costs, and is the leading cause of mortality and severe illness among critically ill patients.[1,6] The incidence of sepsis is increasing, possibly attributable to aging populations with significant comorbidities. Furthermore, patients who recover from sepsis often have long-term medical and psychologic disabilities.[1] Risk factors for sepsis include older age, comorbid medical conditions, and a compromised immune system.[5] Both in the United Kingdom (35% higher in winter than summer) and the United States (17.7% higher in fall than in summer), severe sepsis

Key points

- Sepsis is the main cause of infection-related death and requires early detection and prompt interventions.
- The presence of factors such as dysregulated host response and organ failure differentiates sepsis from infection.
- Sepsis must be considered in patients presenting with infection.
- Causative pathogens of sepsis can be determined by appreciating hallmark signs of various infections and host factors such as age, sex, and comorbidities.

TABLE 1. SIRS criteria

Each criterion is worth 1 point. A score of 2 or greater meets the definition of SIRS.

- Temperature greater than 38° C (100.4° F) or less than 36° C (98.6° F)
- Heart rate greater than 90 beats/minute
- Respirations greater than 20 or $PaCO_2$ less than 32 mm Hg
- White blood cell count greater than 12,000 cells/mm^3, less than 4,000 cells/mm^3, or more than 10% bands

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is more prevalent during the colder months, potentially correlating with fluctuations in viral respiratory illnesses.[6]

CLINICAL PRESENTATION

The clinical presentation of sepsis is highly variable and often includes nonspecific features such as fever, tachypnea, altered mental status, tachycardia, and cold or clammy skin. Therefore, clinicians need to have a high index of suspicion for infections, especially those most likely to cause sepsis. A task force convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine determined that because no clinical measurements reflect a dysregulated host response, physical examination findings can be indicative of inflammation or organ dysfunction.[1] Looking for hallmark signs and symptoms will aid in identifying a source of infection. For example, consider bacterial meningitis as a source of sepsis if the patient presents with fever, headache, photophobia, and meningismus.[7] Consider bacterial pneumonia as the source in a patient with fever, tachypnea, hypoxemia, dullness to percussion, and bibasilar crackles.[7] Hallmark signs including new cardiac murmur, Roth spots, splinter hemorrhages, Osler nodes, or Janeway lesions are indicative of infective endocarditis.[7] Fever in a patient with an indwelling peripheral or central catheter is consistent with catheter line sepsis.[7] Additionally, signs such as fever and dysuria common with urinary tract infections and fever with acute abdominal pain, fever, guarding, and tachycardia are consistent with bacterial peritonitis.[7]

What differentiates sepsis from infection is a dysregulated host response and the presence of organ dysfunction, which may or may not be evident on physical examination and history alone. An initial infection triggers cytokine release, causing inflammation. However, when an excess of cytokines is produced (cytokine storm), tissue and organ damage may occur, resulting in organ dysfunction. This immune dysregulation causing tissue damage results in fever, mental status changes, headache, and myalgia and can rapidly progress to coagulopathy, acute liver injury, respiratory failure, or renal failure.[8] A patient may have occult organ dysfunction, so consider sepsis in all patients with any form of infection.[1] Organ dysfunction without an obvious cause, such as a causative pathogen identified by culture, may be the first sign of an infection, necessitating further investigation.

DISCUSSION

An organized and systematic approach is essential in diagnosing sepsis because of the complexity and variety of predisposing risks and illnesses responsible for this condition. Thoroughly evaluate the patient's history, physical examination findings, and laboratory results and consider common causes of sepsis. The defining criteria of sepsis include a possible source of infection, organ dysfunction, and symptoms of the systemic inflammatory response (SIRS): tachycardia, tachypnea, fever, and an elevated white blood cell (WBC) count with a left shift (**Table 1**).[9] However, SIRS criteria often are criticized for lacking sensitivity and specificity.[10] For example, not all patients with infection present with a fever and elevated WBC count, and patients may have these features without an infection.[10]

No consistent and accurate diagnostic criteria existed for sepsis until a task force convened in 2016 to compile and publish the Third International Consensus Definitions for Sepsis and Septic Shock, which recommended the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score to differentiate sepsis from uncomplicated infection and to unify a definition (**Table 2**).[1, 11] The goal of the SOFA score is to quantify and objectively describe the degree of organ dysfunction or organ failure over time in patients.[12] The score is determined 24 hours after ICU admission and then every 48 hours to determine risk of mortality.[12]

No one test or score is accurate enough to definitively diagnose sepsis, making the diagnosis extremely challenging, especially in patients with comorbidities. This can lead to delayed treatment and affect patient prognosis because sepsis is a time-critical condition. The SOFA score uses parameters accessible in clinical practice to identify key organ dysfunction.[12] A score of 2 or greater is associated with a mortality greater than 10%.[10] Furthermore, regardless of the original score, an increase in score in the first 48 hours of critical illness predicts a mortality of 50%.[10] Therefore, the SOFA score can be used for diagnosis and

TABLE 2. SOFA score

A score of 2 or greater is associated with a mortality greater than 10%, and an increase in score in the first 48 hours of critical illness predicts a mortality of 50%.

	0	1	2	3	4
Pao_2/Fio_2 (mm Hg)	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Platelets (cells/mm^3)	≥150,000	<150,000	<100,000	<50,000	<20,000
Bilirubin (mg/dL)	<1.2	1.2-1.9	2-5.9	6-11.9	>12
Cardiovascular criteria	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 mcg/kg/min or dobutamine (any dose)	Dopamine 5.1-15 mcg/kg/min or epinephrine ≤0.1 mg/mL or norepinephrine ≤0.1 mg/mL	Dopamine >15 mcg/kg/min or epinephrine >0.1 mg/mL or norepinephrine >0.1 mg/mL
Glasgow Coma Scale score	15	13-14	10-12	6-9	<6
Creatinine (mg/dL)	<1.2	1.2-1.9	2-3.4	3.5-4.9	>5

Adapted with permission from Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* 1996;22(7):707–710.

prognosis of sepsis. The Third International Consensus Definitions for Sepsis and Septic Shock task force also suggested a more time-efficient score called the quickSOFA (qSOFA), which is easier to use in the outpatient setting because it relies only on clinical examination findings.[1, 10] The three qSOFA criteria, each worth 1 point, are respiratory rate greater than 22, altered mentation, and systolic BP of 100 mm Hg or lower. In patients meeting at least two of the criteria, the qSOFA has a similar predictive value as the original SOFA score in detecting sepsis and a probable poor patient outcome.[10] According to the task force, septic shock can be recognized clinically when patients require a vasopressor to maintain a mean arterial pressure (MAP) of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L in the absence of hypovolemia.[1]

In addition to these scoring criteria, laboratory studies and radiologic imaging can aid in the diagnosis of sepsis. For every hour delay in administering antimicrobial therapy, patient mortality rises an estimated 8% to 10%.[13] Blood, urine, and respiratory cultures are used to identify the infectious pathogen. Other samples such as cerebrospinal fluid, ascitic fluid, or bronchial or alveolar lavage may be used if indicated by the clinical scenario.[5] Furthermore, WBC counts with differential can be used to help identify an infection.[3] Complete metabolic panels can evaluate electrolytes and major organ function. Platelet count, prothrombin time, and partial thromboplastin time can assess dysfunction in coagulation pathways.[3] Arterial blood gas analysis can be useful in patients with respiratory dysfunction. Radiographs, ultrasound, and CT all can be used to help identify the source of infection and evaluate organ dysfunction.[3] Although these modalities are necessary in the investigation and treatment of sepsis, there are still many limitations in the diagnosis of sepsis. Sepsis is a syndrome without any validated standardized diagnostic test.[1] Cultures are slow and are not useful for quickly recognizing sepsis, and only 30% of patients with sepsis have positive blood cultures.[14] The SOFA and qSOFA scores, although better than the previously used SIRS criteria, are not completely sensitive nor specific.[10] According to Raith and colleagues, SOFA demonstrated significantly greater discrimination for in-hospital mortality [99% CI, 0.750-0.757] than SIRS criteria [99% CI, 0.585-0.593] or qSOFA [99% CI, 0.603-0.611].[15] These scores also are not intended to stand alone as the only definition or diagnostic tool for sepsis.[1]

TURNING TO BIOMARKERS

Because of the difficulty in diagnosing sepsis and its rising incidence over the past decade, research now focuses on the use of biomarkers. A biomarker is defined by the National Institutes of Health as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[10] In clinical practice, biomarkers may be used for a variety of diseases and can aid in diagnosis, prognosis, and treatment. They can identify patients who may benefit from a specific therapy or predict the risk and benefit of treatments.[10] Biomarkers may be useful in diagnosing sepsis and predicting patient prognosis, and several have been studied for this purpose.

Biomarkers used frequently in a clinical setting include lactate, C-reactive protein (CRP), and procalcitonin. Lactate generally represents hypoperfusion. This biomarker is produced by cells from pyruvate and is essential for anaerobic glycolysis during tissue hypoperfusion.[16] Increases in serum lactate levels generally imply organ dysfunction and a potential progression to septic shock. Elevations are associated with an increased mortality from 35% to 70%.[10] However, elevated lactate levels can be seen in several medical conditions other than sepsis, including myocardial infarction, trauma, and seizure.[17] Using a cutoff of 3.5 mmol/L for lactate results in a specificity of

97% and accuracy of 92% for severe bacterial sepsis and septic shock.[17] Lactate also is included in the criteria for septic shock presented in the Third International Consensus Definitions for Sepsis and Septic Shock.[1] A patient with severe sepsis and lactate greater than 4 mmol/L is considered to be in septic shock even without other evidence of hypoperfusion.[1] Lactate also has proven valuable as a marker for prognosis of sepsis. Research shows that patients with a higher lactate clearance after 6 hours had a more favorable outcome.[16] Evidence suggests that point-of-care lactate testing is associated with subsequent decreased mortality and time to IV fluids and antibiotics.[13] Therefore, lactate is an accurate marker for recognizing severe illness or septic shock and can help predict prognosis, although it is not completely specific to infection.

CRP is an acute-phase protein produced by the liver and other cells, including alveolar macrophages.[10] CRP is the most-studied biomarker of infection and inflammation.[16] Plasma concentrations of CRP remain stable in healthy patients and increase after inflammation, trauma, or tissue damage. Bacterial infections in particular produce a rapid rise of CRP levels in the bloodstream.[10] CRP typically rises 12 to 24 hours after infection, reaches its peak at 2 to 3 days, and has a half-life of 19 hours.[14] CRP has a low test specificity for sepsis because it can increase in several diseases, which limits its use as a diagnostic marker in adults with sepsis.[16] Tan and colleagues found the diagnostic accuracy of CRP in sepsis to have a sensitivity of 73% and a specificity of 80%.[14] However, CRP is used as a screening tool in the first 24 hours of life in newborns because it has a higher sensitivity in this age group.[14] CRP also has been proven to be a reliable tool for monitoring postoperative patients for sepsis because the level decreases postoperatively unless the patient develops an infection.[16] Moreover, CRP has been proven to evaluate the response to antimicrobials in patients with sepsis.[16] CRP can be a useful biomarker for early detection of infection, but it is not specific enough to solely diagnose sepsis or septic shock.[16]

Procalcitonin is a peptide normally produced by the thyroid gland and is the precursor of calcitonin. In inflammatory conditions such as sepsis, other types of cells can produce procalcitonin.[17] This production is most likely driven by cytokines and different microbial byproducts.[17] Procalcitonin is stable in blood indexes and is easily and quickly obtained in a clinical setting. It rises 2 to 3 hours after infection, usually exceeds normal limits at 6 to 12 hours, and peaks at 24 hours.[14]

Procalcitonin has the potential to differentiate between infectious and noninfectious systemic inflammation as well as viral and bacterial infections.[10] Tan and colleagues found that procalcitonin had a sensitivity of 80% and a specificity of 77% for sepsis.[14] The FDA has approved procalcitonin as a tool for assessing risk of progression to septic shock for day 1 ICU admissions.[16] Procalcitonin also has proven to be successful in guiding antibiotic therapy in patients with sepsis.[16] Ljungstrom and colleagues found that procalcitonin had a high specificity in diagnosing bacterial sepsis at a cutoff of 10 ng/mL.[18] This means that with a concentration of procalcitonin of 10 ng/mL or higher, patients are extremely likely to have bacterial sepsis.[18] Therefore, procalcitonin can be a helpful tool in ruling out noninfectious causes of symptoms.

Tan and colleagues found procalcitonin and CRP to have a moderate degree of value in diagnosing sepsis in adults.[14] They also found that procalcitonin had greater diagnostic accuracy than CRP.[14] Giannakopoulos and colleagues found procalcitonin to be more sensitive and specific than CRP for detecting bacterial infections.[16]

In a study comparing these three biomarkers as well as neutrophil-lymphocyte count ratio, Ljungstrom and colleagues found that CRP with a cutoff of 20 mg/mL had the highest sensitivity for sepsis (88%); procalcitonin at a cutoff of 10 ng/mL and lactate at a cutoff of 4 mmol/L showed the highest specificity (97%).[18] Procalcitonin also showed the greatest ability to correctly classify patients with and without sepsis.[18] Furthermore, this study found that the discriminatory power of diagnosis is improved when combining several biomarkers.[18] However, limitations to a multimarker approach in diagnosing sepsis include high cost and less availability than a single biomarker.[18]

Several other biomarkers involved in different aspects of the pathophysiology of sepsis have been studied, although they are not used often clinically. These include chemokines, cell markers, cellular receptors, coagulation markers, markers of vascular endothelial damage, vasodilation molecules, acute phase proteins, complement proteins, markers of organ dysfunction, natriuretic peptides, adipokines, and markers of the infectious organism.[16]

Sepsis represents a complex interplay of factors and mediators involving the infectious pathogen, host immune response, inflammatory response, coagulation, and individual organ response. More research is needed on biomarkers in sepsis, because they can be measured objectively, can be reproduced easily, are cost-effective, and have well-known kinetics. An ideal biomarker would be sensitive and specific enough to diagnose sepsis, predictive of the clinical course, and easily obtainable in clinical practice. No one biomarker has been proven to be sufficient to diagnose or predict the prognosis of sepsis in adults in isolation. However, of the biomarkers used, procalcitonin appears to be more accurate than CRP in the early diagnosis of sepsis.[14,17,18] Lactate appears to be the most suggestive of septic shock or a poorer prognosis.[10,13] Studies using panels of biomarkers to diagnose sepsis are encouraging.[18]

CONCLUSION

Timely and accurate diagnosis of sepsis is imperative to improve patient survival and reduce morbidity and mortality. Therefore, clinicians need to be aware of the most

efficient and useful approach to diagnose sepsis. No single definitive diagnostic test is available. Blood cultures detect the causative organism allowing for targeted treatment. Biomarkers including procalcitonin, CRP, and lactate levels are used extensively to aid in diagnosing and determining the prognosis of sepsis. These tests must be interpreted in the context of other laboratory findings and clinical assessments. More studies need to be conducted with novel biomarkers that are not used clinically and with panels of biomarkers in order to evaluate their sensitivity, specificity, and potential clinical application. Clinicians also need to be aware of the clinical significance of the tests they may use regularly, such as those for lactate, CRP, and procalcitonin, and the implications they may have on the diagnosis of sepsis. Despite progress in researching sepsis, it remains a major health concern because of its high incidence, cost, and mortality. Prompt diagnosis using scoring systems, laboratory findings, imaging, and biomarkers leads to early intervention with correct treatment and can considerably improve patient outcomes. **JAAPA**

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REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus definitions for sepsis and septic shock (SEPSIS-3). *JAMA*. 2016;315(8):801-810.
2. Delano MJ, Ward PA. The immune system's role in sepsis progression, resolution, and long-term outcome. *Immunol Rev*. 2016;274(1):330-353.
3. Martin GS. Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. *Expert Rev Anti Infect Ther*. 2012;10(6):701-706.
4. Centers for Disease Control and Prevention. Get ahead of sepsis—know the risks. Spot the signs. Act fast. www.cdc.gov/patientsafety/features/get-ahead-of-sepsis.html. Accessed September 12, 2023.
5. Han J, Cribbs S, Martin G. Sepsis, severe sepsis, and septic shock. In: *Principles of Critical Care*. 4th ed. New York, NY: McGraw-Hill Education; 2015.
6. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. *Virulence*. 2014;5(1):4-11.
7. Gauer R, Forbes D, Boyer N. Sepsis: diagnosis and management. *Am Fam Physician*. 2020;101(7):409-418.
8. Fajgenbaum DC, June CH. Cytokine storm. *N Engl J Med*. 2020;383(23):2255-2273.
9. Chakraborty RK, Burns B. Systemic inflammatory response syndrome. Treasure Island, FL: StatPearls Publishing. www.ncbi.nlm.nih.gov/books/NBK547669. Accessed October 6, 2023.
10. Rello J, Valenzuela-Sanchez F, Ruiz-Rodriguez M, Moyano S. Sepsis: a review of advances in management. *Adv Ther*. 2017;34(11):2393-2411.
11. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-710.
12. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score—development, utility and challenges of accurate assessment in clinical trials. *Crit Care*. 2019;23(1).
13. Morris E, McCartney D, Lasserson D, et al. Point-of-care lactate testing for sepsis at presentation to health care: a systematic review of patient outcomes. *Br J Gen Pract*. 2017;67(665):e859-e870.
14. Tan M, Lu Y, Jiang H, Zhang L. The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: a systematic review and meta-analysis. *J Cell Biochem*. 2019;120(4):5852-5859.
15. Raith EP, Udy AA, Bailey M, et al. Prognostic accuracy of the SOFA Score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. *JAMA*. 2017;317(3):290-300.
16. Giannakopoulos K, Hoffman U, Ansari U, et al. The use of biomarkers in sepsis: a systematic review. *Curr Pharm Biotechnol*. 2017;18(6):499-507.
17. Andriolo BN, Andriolo RB, Salomão R, Atallah ÁN. Effectiveness and safety of procalcitonin evaluation for reducing mortality in adults with sepsis, severe sepsis or septic shock. *Cochrane Database Syst Rev*. 2017;1(1):CD010959.
18. Ljungstrom L, Pernestig A-K, Jacobsson G, et al. Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis. *PLoS One*. 2017;12(7):e0181704.