CHAPTER 86

Sepsis and Septic Shock

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OBJECTIVE

This chapter will:
1. Provide an overview of newly developed *definitions* for sepsis and septic shock
2. Summarize the manner in which the *clinical criteria* were derived and validated using clinical data in an evidence-based manner
3. Identify the need for additional validation, especially in under-resourced populations, and in a prospective manner.

The development of acute kidney injury (AKI) is a frequent complication in critically ill patients, affecting up to two thirds of patients admitted to intensive care units (ICUs).[1–4] The most commonly identified cause for AKI among the critically ill is sepsis.[5,6] A recent study using a nationally representative database demonstrated that the use of dialysis in septic patients is increasing and indicated that a need for dialysis remains an independent predictor of mortality.[7] Overall mortality, however, is declining. Analysis suggests that this improvement cannot be explained by an extension of dialysis to less critically ill patients or by an overall improvement in the care of all critically ill patients.[4] Thus our understanding of the pathobiologic relationship between sepsis and AKI is poorly understood, and further insight is needed if the care of patients with either condition is to improve. However, implicit in this statement is the notion that sepsis and AKI can be identified uniformly and reproducibly in at-risk patients. As it turns out, neither task is easy.

The first attempt to provide a uniform definition of sepsis (Sepsis-1) occurred in 1991 and was jointly published in *Critical Care Medicine* and *Chest* in 1992.[8] It presented the work of a consensus conference of international experts and contained several innovative concepts. First, *sepsis* was defined to consist of an infection-induced *systemic inflammatory response syndrome* (SIRS). SIRS, in turn, was identified by the presence of two of four clinical findings: fever, tachycardia, leukocytosis/leukopenia, or tachypnea. The presence of organ dysfunction in a patient with sepsis constituted *severe sepsis*. How organ dysfunction may be identified was not discussed. Concerns led to the convening of a second consensus in 2001 (Sepsis-2).[9] In this conference, the number of parameters that may be used to identify the septic patient was expanded greatly (Table 86.1 contains 25 different measures). Despite concerns and criticisms, the use of SIRS continued.

In 2014 the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) launched an effort reexamine, revise, and redefine sepsis. A task force of 17 recognized experts and two highly regarded junior individuals with expertise in epidemiologic research was formed and charged. The results of their deliberations were detailed in three papers published in the February 2016 edition of the *Journal of the American Medical Association*.[10] The findings (Sepsis-3) are summarized here.

LIMITATIONS OF SEPSIS-1 AND SEPSIS-2

At a very early point, the task force reached consensus on a number of important issues. First, it was agreed not to attempt to provide definitions or guidelines regarding just what constitutes "infection." The task force members did not believe that this activity was part of their charge and felt that such an exercise would require the full expertise of the infectious disease and microbiologic community. In addition, it was agreed universally that sepsis is more than just infection plus two or more SIRS criteria. Rather, it was noted that SIRS criteria were present in virtually all cases of infection and indeed were also present in noninfectious inflammation (e.g., surgery, trauma). Kaukonen et al. found that one in eight septic patients in Australian ICUs did not meet the requirement for two of the four SIRS criteria.[11] Conversely, a study by Churpek et al. demonstrated that up to 50% of ward patients met two or more SIRS criteria despite not being critically ill.[12]

However, difficulties with identifying septic patients reflected more than issues with the use of SIRS criteria. In a particularly important investigation, Giaeski et al. sought to determine the incidence of and mortality from sepsis by querying a nationally representative sample database using four different administrative approaches to identify affected patients.[13] Depending on the method used, the estimated annual incidence of sepsis varied between 800,000 and 3.1 million. Similarly, the estimated annual mortality attributed to sepsis ranged between 250,000 and 375,000. An additional concern is that the mortality attributed to septic shock differs markedly from one country to the next.[14] The previously mentioned study by Kaukonen et al. noted that mortality from septic shock was about 22%, similar to studies in the United States.[11] However, mortality in excess of 40% has been noted in patient populations in Germany, Italy, France, Spain, and the Netherlands, whereas the United Kingdom reported rates that were intermediate between the United States and the aforementioned European countries.[14] Indeed, even the cutoffs used to denote an abnormal physiologic measurement are problematic. For example, hypotension has been described as a systolic arterial pressure (SAP) below 90, a mean arterial pressure (MAP) below 60 or 70, and a fall in SAP of more than 40.[14] Each of these issues highlights the need to revisit the definitions of sepsis.

In the initial deliberations, members of the task force noted that the literature identified several key factors that differentiate sepsis from infection. Thus, in sepsis, the host response is perhaps of greater importance than the infection and the nature, extent, and modulation of the host response differed from that noted in infection alone. Further, the studies indicated that, when compared with infection, the outcome from sepsis was poor: mortality was higher,

TABLE 86.1

Definitions and Clinical Criteria in Sepsis-1 and Sepsis-2

	DEFINITIONS	DIAGNOSTIC/CLINICAL CRITERIA
Sepsis-1([8])	Sepsis; infection-induced systemic inflammatory response syndrome (SIRS) Severe sepsis; Sepsis + Organ dysfunction Organ dysfunction Septic shock; sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities Multiple organ dysfunction syndrome (MODS); presence of altered organ dysfunction in an acutely ill patient such that homeostasis cannot be maintained w/o intervention	SIRS: temp < 36°C > 38°C, HR > 90 beats/min, RR > 20 breaths/min or $PaCO_2$ < 32 mm Hg, WBC count < 4000 cells/mm^2, > 12,000 cells / mm^2, >10% immature forms
Sepsis-2([9])	Sepsis: unchanged Severe sepsis: unchanged Organ dysfunction: SOFA ([21]), PELOD in children ([22,23]) Septic shock: persistent hypotension	SIRS: unchanged Additional criteria 1. Infection, documented or suspected 2. General variables: fever, hypothermia, tachycardia, tachypnea, altered mental status, significant edema or positive fluid balance, hyperglycemia 3. Inflammatory variables: leukocytosis, leukopenia, >10% immature forms, C-reactive protein > 2 SD above normal; procalcitonin > 2 SD above normal 4. Hemodynamic variables: SBP < 90 mm Hg, MAP < 70 mm Hg, or SBP decrease > 40 mm Hg in adults or <2 SD below age normal in children, SVO_2 > 70%, cardiac index > 3.5 L/min/m^2 5. Organ dysfunction variables: PaO_2/FiO_2 < 300, UOP < 0.5 mL/kg/min for at least 2 hours or creatinine increase > 0.5 mg/dL, INR > 1.5 or aPTT > 60 seconds, absent bowel sounds, Plt count < 100,000/uL, bilirubin > 4 mg/dL 6. Tissue perfusion variables: lactate > 1 mmol/L, decreased capillary refill or mottling Septic shock: hypotension, need for vasopressors, lactate > 2.0 mmol/L

morbidity more extensive, resources were consumed at a greater rate, and sequelae were more profound and debilitating. In effect, sepsis constitutes "bad" infection. In particular, "bad" reflected abnormalities of organ function, even those that are seemingly insignificant. Therefore organ dysfunction is an essential component of sepsis per se, and the term "severe sepsis" was redundant and unhelpful and should be eliminated.

DEFINITIONS VERSUS CLINICAL CRITERIA

Early in the process, the task force came to a somewhat startling realization: what we have long considered "definitions," for example, what have been so labeled in Sepsis-1 and Sepsis-2, were, in fact, not definitions. Per *Merriam-Webster's Dictionary of English Usage,* a definition is "a statement expressing the essential nature of something" or, more generically, "a statement that describes what something is." Implicit in this formulation is a sense of completeness that is not reflected in definitions using clinical criteria such as SIRS. Sepsis cannot be identified by a specific biologic substrate—a pathology specimen or a laboratory or imaging study—in the way that is possible for many other diseases and syndromes. Indeed, there is a substantial gap between our pathobiologic understanding of sepsis and our ability to translate this understanding into something clinically tangible. It was felt that the best course was to generate a definition that incorporated the most up-to-date scientific understanding of the disorder and to use a data-driven, epidemiologically based approach to generate clinical criteria that would be of value to the bedside practitioner. The hope was that it would be possible to generate a relatively simple, user-friendly set of measures that could be used to determine which patients in whom infection was suspected were at risk for sepsis and thus may require urgent or emergent attention.

SEPSIS-3 DEFINITION OF SEPSIS

An updated definition was generated based on contributions from individuals with substantial records of sepsis investigation (Table 86.2). This group included individuals with expertise in sepsis pathobiology, clinical trials, and/or epidemiology. Further, the group included expertise in various aspects of sepsis-induced organ dysfunction. Several important concepts were delineated during the consensus process that culminated in the new definition. Discussions clearly indicated that the hallmark of sepsis is organ dysfunction. However, current clinical approaches to identifying and quantifying organ dysfunction are insensitive and inaccurate. In some cases research approaches currently under development have uncovered more accurate indices that can detect dysfunction at an earlier time point. In addition, our enhanced understanding of the host response

to something perceived as a threat ("danger") strongly suggests that, in sepsis, normal protective mechanisms break down. To some extent they become overactive, attacking not just the danger but also the host. However, there are also data indicating that normal protective responses become inadequate. For example, immunosuppression is present early in sepsis.[15–18] The results, reached using a consensus process, now define sepsis as *life-threatening organ dysfunction caused by a dysregulated host response to infection*. The new definition emphasizes the preeminent role of the host response, and the inclusion of organ dysfunction differentiates sepsis from simple infection or inflammation. Importantly, subsequent work by Seymour et al. suggested that even low levels of organ dysfunction were associated with a substantial mortality.[19]

SEPSIS-3 DEFINITION OF SEPTIC SHOCK

Generating an updated definition for septic shock proved to be somewhat more problematic. At the core was a difference of opinion regarding the very nature of the disorder (see Table 86.2). Some task force members believed that septic shock was really sepsis, in which the dysfunctional organ was the cardiovascular (CV) system, and argued that the definition should reflect that reality. Two arguments against this conceptualization were discussed. The first posited that, if septic shock is sepsis with CV dysfunction, there was no compelling reason to differentiate it from sepsis with dysfunction in any other system. However, data using previous definitions that compared severe sepsis to septic shock reveal that mortality is substantially higher in the latter.[14] A more compelling line of discussion noted that septic shock involves cellular and metabolic abnormalities that are either absent in sepsis, or, if present in sepsis, occur at a level that is substantially lower than what is seen in septic shock. This line of reasoning suggests that the pathobiology underlying septic shock differs from that precipitating sepsis, a hypothesis that cannot be tested at this time. Ultimately, a middle course embracing CV and cellular/metabolic abnormalities and emphasizing the mortality difference was chosen. Thus Sepsis-3 defines septic shock as *a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone*.

TABLE 86.2

Definitions and Clinical Criteria: Sepsis- 3

	DEFINITIONS	CLINICAL CRITERIA
Sepsis-3([11])	Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection Organ dysfunction: based on SOFA score Septic shock: a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone	Sepsis: 1. SOFA ≥ 2 () 2. 2/3 qSOFA criteria – SBP < 90 mm Hg, RR: 22 breaths/min, altered mental status Septic shock: hypotension, need for vasopressors, lactate > 2.0 mmol/L

CLINICAL CRITERIA TO IDENTIFY PATIENTS LIKELY TO HAVE SEPSIS

Although the new definition of sepsis is consistent with the most up-to-date knowledge regarding the pathobiology of the disorder and is a better example of a definition, it lacks clinical utility (see Table 86.2). Specifically, organ dysfunction, especially in early stages when intervention is most likely to be effective, is difficult to identify. Similarly, the exact nature of a "dysregulated host response" is incompletely understood in animal models, let alone patients. In fact, what constitutes a "regulated host response" is obscure.

However, because sepsis represents a major public health problem, the task force felt that it was imperative to provide clinicians with clinical criteria that were data driven, simple to measure, and easily obtained. Thus Seymour et al. reported on the results of a perusal of several large datasets in search of an approach that could reliably identify patients suspected of having infection who were likely to have or develop sepsis.[19] These investigators were searching to identify patients *likely to have sepsis*. Because there is no gold standard by which to identify sepsis reliably, the study followed a framework outlined by Angus et al. and used proxies for sepsis.[20] It was surmised that infected patients with sepsis would be more likely to spend a prolonged period in the ICU or succumb to the syndrome. These proxies have *face validity*, that is, they are logical choices that make sense. Seymour et al. then sought to identify clinical measures (or combinations of measures) that predict which patients are most likely to die or require an extended ICU stay, an approach commonly said to provide *predictive validity*.[19] They first examined the predictive validity of several composite "scores" that were already in use clinically. In particular, the SIRS criteria and the sequential organ failure assessment (SOFA) score were tested using receiver-operator characteristic analysis. SOFA has been used in ICUs for some time and has some known predictive validity for mortality.[21] The initial assessment was performed on data from the electronic health record (EHR) at the University of Pittsburgh Medical Center (UPMC), a multihospital system containing large university hospitals and small (some with fewer than 100 beds) private facilities. Use of receiver-operating characteristic (ROC) analysis in approximately 150,000 patients with suspected infection demonstrated that SIRS had predictive validity that was superior to a simple comorbidity composite index but inferior to a SOFA score of at least 2. Thus a relatively small change in SOFA was highly predictive of poor outcome. Because of the use for which SOFA was designed, it is deemed a useful proxy for organ dysfunction. Multivariate analysis then was applied to the 21 variables that composed Sepsis-2. On hospital wards and in the emergency department, a combination of an SAP less than or equal to 100 mm Hg, a respiratory rate equal to or exceeding 22 breaths/min, and altered mentation, termed quick SOFA (qSOFA), had predictive validity equivalent to SOFA and superior to that of SIRS. Of particular importance, qSOFA failed to identify many of the patients falsely classified as potentially septic by the use of SIRS. The analysis was repeated and the results were confirmed in four additional databases containing EHRs from more than 1 million patients with suspected infection. Although the derivation set and three of the four validation datasets were based in the United States, one small dataset was from Germany.

The analysis also worked when the predictive validity for other end points, for example, a discharge diagnosis of

severe sepsis or septic shock, was tested. The entire analysis was retrospective, and thus future prospective validation is essential. Extension to non–US-centric populations, especially those in resource-limited locales, is equally important. Finally, the SOFA score, which was derived nearly 20 years ago, contains elements that are no longer relevant and never have been validated prospectively.

CLINICAL CRITERIA FOR SEPTIC SHOCK

The new definition of septic shock identifies three key characteristics: circulatory abnormalities, cellular/metabolic dysfunction, and a risk of mortality exceeding that for sepsis alone (see Table 86.2). However, the approach to identifying clinical criteria for septic shock differed from that used for sepsis in part because there are no lists of potential criteria or ready-made scores to test. Therefore a Delphi approach was used. The first objective was to arrive at a task force consensus on a few clinical measures that have face validity as proxies for circulatory and cellular/metabolic abnormalities. It was agreed that the appropriate variables to test using a data-driven approach were hypotension despite adequate fluid resuscitation, an ongoing requirement for vasopressors to maintain blood pressure, and an elevated serum lactate level. It also was determined that the standard for predictive validity should be the ability of these variables to predict a significantly higher mortality than that of sepsis alone. Using all possible combinations six possible cohorts were identified (Table 86.3).

The first data set to be tested was the Surviving Sepsis Campaign (SSC) database, chosen for several reasons. Inclusion requires that a patient meet old criteria for severe sepsis or septic shock. In addition, among the included entries were a number that were classified as having septic shock, providing another target for predictive validity. In this dataset, the mortality in patients who met all three criteria—hypotension (MAP < 65 mm Hg per SSC criteria), an ongoing vasopressor requirement, and an elevated serum lactate (>2 mmol/L per SSC criteria)—was significantly different than that in the other five groups. The crude hospital mortality in this group was 42%. These findings were verified in datasets from University of Pittsburgh Medical Center and from electronic medical record data obtained from Kaiser-Permanente Northern California. The caveat that the analysis was retrospective and must be verified prospectively, as identified in the clinical criteria for sepsis, applies here as well. Use of the SSC database, which contains entries from around the world, especially Europe and South America, provides some assurance regarding non-US populations. Also, all patients entered into the SSC database met 2001 criteria for either severe sepsis or septic shock. Therefore, in addition to their predictive validity for mortality exceeding 40%, the predictive validity of the combination of all three parameters (hypotension, pressors, and hyperlactatemia) to differentiate severe sepsis from septic shock was verified in the derivation dataset. In the validating datasets, the three parameters had significant predictive validity for a discharge diagnosis of septic shock.

CONCERNS, CONTROVERSIES, AND LIMITATIONS

In the initial paper, in subsequent discussions, and in responding to certain postpublication criticisms, the task force was able to acknowledge a number of important limitations and controversial points. Some (i.e., the need for prospective validation, extension to populations not well represented in the deriving and validation datasets, deliberately leaving certain elements [e.g., "adequate resuscitation"] vague or using nonuniform cutoffs for elements such as "hypotension" based on what was available in specific datasets) have been discussed and were addressed in the original paper. Others (e.g., the difficulty in measuring lactate in underresourced populations) can be addressed only when application of the new clinical criteria is assessed in future studies. Comments on many of these issues can be found in the original papers[10,14,19] or in responses to the comments of others.[24] Perhaps the most important limitation, and the one about which the members of the task force felt most strongly, involves the need to maintain the distinction between definitions and clinical criteria. The clinical criteria do not define sepsis. This fact has led to misunderstanding and consternation. For example, a group of emergency physicians have expressed concern that "sepsis can no longer be diagnosed in the ED." In a sense, sepsis, like many syndromes that lack a "gold standard" by which they can be unequivocally identified, cannot be "diagnosed" by anyone. Rather, the best that can be done is to determine what clinical characteristics or criteria best provide predictive validity for something that is very likely to be sepsis, for example, poor outcome. Hopefully better descriptors of "organ dysfunction" or a "dysregulated host response" will be forthcoming in the near future. However, if they spur practitioners to act, to consider additional investigations, and to escalate the level of care or institute treatment, then the clinical criteria do indeed enable practitioners to diagnose sepsis.

TABLE 86.3

Diagnostic Groups for Developing Clinical Criteria for Septic Shock in Sepsis-3 From Surviving Sepsis Campaign Database

COHORTS	NUMBER (% TOTAL)	MORTALITY	ADJUSTED MORTALITY	*p* VALUE
1. Hypotension after fluids and pressors and lactate > 2 mmol/L	8520 (45)	42%	1 (reference)	
2. Hypotension after fluids and pressors, lactate < 2 mmol/L	3985 (21	30%	0.57	<.001
3. Hypotensive after fluids, no pressors, lactate > 2 mmol/L	223 (1.2)	29%	0.65	0.009
4. No hypotension, no pressors, lactate > 2 mmol/L	3266 (17)	26%	0.71	<.001
5. No hypotension, no pressors, lactate > 2 mmol/L, < 4 mmol/L,	2696 (14)	30%	0.77	<.001
6. Hypotensive after fluids, no pressors, lactate < 2 mmol/L	150 (0.8)	19%	0.32	<.001

From Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(315):775-787.

CONCLUSION

The new definitions represent a summation of our best scientific understanding of the pathobiology underlying sepsis, whereas the new clinical criteria provide important tools that enable clinicians to suspect, recognize, and initiate treatment for patients in whom sepsis or septic shock is likely. It is fully expected that both will require revision as our understanding and clinical acumen increases.

Key Points

1. Sepsis is now defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection."
2. Septic shock is now defined as "a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone."
3. Because there is no "gold standard" test or finding that unequivocally identifies patients with sepsis or septic shock, development of clinical criteria is based on predictive validity. Specifically, clinical criteria identify patients with suspected infection who are highly likely to have proxy outcomes consistent with the presence of sepsis or septic shock in patients with suspected infection. The clinical criterion identified and validated in a retrospective analysis of more than 1 million electronic health records (EHRs) from patients with suspected infection was a sequential organ failure assessment (SOFA) score of 2 or more points.
4. From among patients with suspected infection, the proxy for sepsis was a clinical course characterized by death or by a stay of 3 or more days in an intensive care unit. From among patients meeting clinical criteria for sepsis, the proxy for septic shock was mortality in excess of 40%. The clinical criteria used were retrospectively identified and validated in the same EHRs and in patient data entered into the Surviving Sepsis Campaign database. The criteria that identified these patients were hypotension despite adequate fluid resuscitation, an ongoing vasopressor requirement, and a serum lactate in excess of 2 mmol/L.
5. A newly developed parameter, dubbed quickSOFA (qSOFA), can be used to prompt clinicians outside the intensive care unit to suspect sepsis.

Key References

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A complete reference list can be found online at ExpertConsult.com.

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