



# SIRS in the Time of Sepsis-3

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Severe sepsis is a common, deadly, and diagnostically vexing condition. Recent recommendations for diagnosing sepsis, referred to as consensus guidelines, provide a definition of sepsis and remove the systemic inflammatory response syndrome (SIRS) as a component of the diagnostic process. A concise definition of sepsis is welcomed. However, the approach to developing these guidelines, although thorough, had weaknesses. Emphasis is placed on mortality prediction rather than on early diagnosis. Diagnostic criteria are recommended to replace current criteria without evidence of any effect that their use would have on mortality. SIRS is a prevalent feature of patients with sepsis, should remain an important component of the diagnostic process, and remains a valuable term for discussing patients with life-threatening organ dysfunction caused by infection. CHEST 2018; 153(1):34-38

**KEY WORDS:** diagnosis; organ dysfunction quality improvement; sepsis; SIRS

Sepsis has vexed physicians for as long as there have been physicians, since before it had a name, and before any notion about microbes or infection. Five hundred years ago, the political writer Niccolo Machiavelli<sup>1</sup> gave testament to that fact, *“As the physicians say of hectic fever, that in the beginning of the malady it is difficult to detect but easy to treat, but in the course of time, having been neither detected nor treated in the beginning, it becomes easy to detect but difficult to treat.”* Little has changed about that assessment in half a millennium. There remains no single unifying pathophysiological feature or biomarker that indicates when sepsis is definitively present. We are left to evaluate patients based on their history and our physical and laboratory examinations, and we attempt to understand from those data when the elusive syndrome is present. Yet, it remains true after all this time that decisive action and earlier

treatment, at stages when we are uncertain of the diagnosis or when we cannot definitively say it is present, is much more successful than late treatment.

It has now been 1½ years since a group of intensivists sponsored by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine published what they called the Third International Consensus Definitions for Sepsis and Septic Shock, or Sepsis-3.<sup>2</sup> The new definition and the diagnostic criteria for sepsis and septic shock that the conference proposed seek to reclassify the terminology of sepsis, and the definition’s authors would have us believe that what we have called sepsis for the past 25 years is actually not sepsis at all. To be clear, systemic inflammatory response syndrome (SIRS) induced by infection, which since 1992 has been recognized as sepsis, is considered by these authors to be

**ABBREVIATIONS:** qSOFA = Quick SOFA; SIRS = systemic inflammatory response syndrome; SOFA = Sequential Organ Failure Assessment

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“an appropriate host response that is frequently adaptive.”<sup>2</sup> In other words, infection with SIRS is just infection.

The Sepsis-3 authors proposed the word sepsis to mean life-threatening organ dysfunction caused by a dysregulated host response to infection.<sup>2</sup> As a concise definition of an immense public health problem with many manifestations, this definition serves nicely to encapsulate the essence of the phenomenon. In fact, since the first International Consensus Conference, organ dysfunction has been considered the hallmark of severe sepsis, although before now a concise overall definition had not been proposed.<sup>3</sup> The classifications of sepsis, severe sepsis, and septic shock were proposed as definitions, even though they may be better characterized as diagnostic criteria. This concise definition, if used appropriately, is a welcomed addition to the sepsis lexicon.

The Sepsis-3 authors propose new diagnostic criteria to accompany the definition based on a thorough retrospective analysis of several large data sets.<sup>4</sup> Although the notion of a dysregulated host response is attractive, it clearly is difficult at present to specify just when dysregulation has occurred and which components of the response have become poorly regulated. For practical reasons, the Sepsis-3 authors sought features of organ dysfunction that would be predictive of a need for prolonged ICU care and mortality. They suggest that the diagnostic criteria for sepsis should be the presence of suspected infection associated with an increase of Sequential Organ Failure Assessment (SOFA) points  $\geq 2$  for diagnosis in an ICU. Recognizing that SOFA is not used outside the ICU, they sought a simpler combination of findings to predict the same outcomes in patients being evaluated in other settings and developed the Quick SOFA (qSOFA) criteria, based on respiratory rate, mental status, and blood pressure.<sup>4</sup>

If the assignment of a new definition and diagnostic criteria were purely an exercise in taxonomy, there would be little reason for dissent. However, the very definition indicates why it is crucial from a practical standpoint that we assign practical and sensitive diagnostic criteria. Life-threatening organ dysfunction is real and it affects real people who will entrust their lives to us as our patients. In the United States alone, sepsis kills approximately 250,000 people per year, with accumulating data that it maims many who survive.<sup>5-8</sup> Moreover, the language we use to describe infection and

sepsis clearly impacts the way we think about it, which, in turn, determines our action<sup>9</sup> or our inaction. It is important that our language and terminology are structured so that they communicate the potential for deterioration and promote aggressive intervention at all phases of the septic response. In fact, the now-called Sepsis-1 participants indicate that SIRS was included in their diagnostic criteria specifically for this reason.<sup>10</sup> Numerous authors and organizations have expressed concern on various counts about the practical application of the Sepsis-3 definition through the proposed diagnostic criteria. Critiques range from the composition of the Sepsis-3 working group to the utility of the criteria in low- and middle-income nations, the appropriate use of analytic tests, and the wisdom of replacing criteria that are clearly working with criteria of unknown effectiveness.<sup>11-22</sup> These concerns are not trivial. Although there was consensus in the conference room, consensus is lacking among physicians who diagnose and treat patients with sepsis regarding the utility of the new diagnostic criteria.

We are presented with numerous difficulties in using this new definition and its proposed criteria for diagnosis. The first is that in the proposed diagnostic criteria, the authors have assigned a literal, or stipulatory, interpretation of the new definition.<sup>10</sup> At the heart of sepsis lies infection, and without infection there is no sepsis. All infections in any host have the potential to result in life-threatening organ dysfunction, depending on the virulence of the organism and the host's response to it. Although it would be difficult to prove experimentally, it is reasonable to assert that all infections begin asymptotically with an inoculum of microorganisms. Only when there has been a host response, at least locally, to that inoculum does the infection produce symptoms that prompt a patient to either treat themselves or seek treatment. At some time, the local response becomes a system-wide response. This system-wide response has been recognized as SIRS.<sup>3</sup> Subsequently, or simultaneously, organ dysfunction, multiple organ dysfunction, and shock may result. The literal interpretation of “sepsis” as being a problem only when life-threatening organ dysfunction is already present fails to recognize the spectrum of the illness, minimizes the importance of infection to its evolution and as its principal driver, and devalues systemic host response as a harbinger of the onset of organ failure.

Mounting evidence indicates that timing is important to sepsis treatment and that the relatively simple maneuvers of early antibiotic and fluid administration

are effective in reducing mortality. Kumar et al<sup>23</sup> first demonstrated this potential of early antibiotic administration in patients with septic shock, but recent analyses in patients with severe sepsis have demonstrated positive effects both on the development of shock and on mortality.<sup>24,25</sup> Both the volume and the early administration of IV resuscitation fluids are associated with improved survival in patients with severe sepsis.<sup>26,27</sup> These findings underscore the need for diagnosing patients with sepsis as early as possible in the continuum of illness and initiating treatment as soon as possible. There is little question that the Sepsis-3 SOFA criteria identify patients with severe sepsis and septic shock. Subsequent prospective observational analyses, along with additional retrospective analyses, corroborate that SOFA and qSOFA have better predictive ability for mortality than does infection with SIRS.<sup>28-30</sup> However, the data suggest that they do so by an increased specificity that comes at the cost of early detection.<sup>28</sup>

The Sepsis-3 authors are off the mark in their assertion that their proposed diagnostic criteria represent the first such criteria based on evidence. It has been known since the time of Hippocrates that tachypnea, tachycardia, and fever are associated with life-threatening illness.<sup>31</sup> The recognition of SIRS as systemic manifestations of infection, distinct from local signs, was not made by the Sepsis-1 authors in a vacuum but represented a distillation of clinical knowledge accumulated from the age of Koch and Pasteur up to and including the studies evaluating the clinical utility of SIRS and organ dysfunction.<sup>32</sup> Since the publication of the Sepsis-1 criteria, myriad publications, ranging from epidemiologic studies to clinical trials to performance improvement studies, have demonstrated that the categories of infection, sepsis, severe sepsis, and septic shock have clinical utility, as evidenced in part by increasing risk of mortality across the spectrum.<sup>33-36</sup> The Sepsis-3 criteria are indeed the first to be formally derived from and tested in specific data sets; however, only their predictive ability for mortality and prolonged ICU stay have been evaluated, not their utility in reducing mortality.

Because there is no single biomarker that clearly identifies sepsis, the proposed shift in diagnostic criteria represents the substitution of one clinically defined syndrome for another. Although the Sepsis-3 definition represents the first succinct definition proposed by a consensus conference, it adds nothing to the understanding of sepsis that we have had since the Sepsis-1 conference. The diagnostic criteria we have

used for 25 years implicitly recognize that organ dysfunction is the key factor associated with critical illness and mortality, even though the mortality attributed to infection with SIRS is not at all negligible at 7% to 9%.<sup>33</sup> The essence of what physicians hope to prevent and to treat remains the same. The question is whether SIRS aids physicians and other providers in identifying patients who either have or are acquiring life-threatening organ dysfunction due to infection. The historical answer is clearly yes.

It is not at all clear that prolonged ICU stay or mortality are the correct end points on which to base diagnostic criteria. Death and prolonged ICU stay are end points that all physicians should be striving to prevent, and the clear purpose of diagnostic criteria is to prompt physicians to intervene, not merely to classify disease. Given that sepsis does exist on a continuum of disease severity, it is an odd step to settle on a diagnostic system that fails to recognize or even attempt to recognize the condition at its earlier phases when it is most treatable. This is equivalent to stating that angina pectoris is an unimportant feature of coronary vascular disease because it is less predictive of short-term mortality than is acute ST segment-elevation myocardial infarction. The analogy is especially poignant given that with steady effort we have reduced the incidence of myocardial infarction and the risk of death in patients who have angina by recognizing it as an important, if less than specific, sign of an underlying pathologic condition and intervening before the onset of infarction. Similarly, successful efforts to save the lives of patients with sepsis focus on organized surveillance, early detection, and early intervention.<sup>34,35,37</sup>

SOFA and its derivative, qSOFA, are severity of injury scores, and initial validating descriptions of SOFA related an increasing score to mortality.<sup>38-40</sup> It is, therefore, not surprising that the Sepsis-3 team found these scores to more reliably predict mortality and prolonged ICU stay in patients with presumed infection than did SIRS, which does not specifically involve organ dysfunction. The more germane comparison would be with patients who had evidence of severe sepsis, as previously defined.<sup>3</sup> The receiver operating characteristic curves for predictive ability used by the Sepsis-3 authors can be useful in two ways: (1) to show which test (eg, SIRS, SOFA, or qSOFA) has better overall predictive capability for mortality and (2) to help choose the best cutoff point for a given test. However, neither the receiver operating characteristic curve nor the area under it is a useful tool for actually diagnosing patients.

Once the cutoff has been established, the important issue becomes the sensitivity and specificity of that cutoff point for making the sepsis diagnosis. The sensitivity and specificity of severe sepsis criteria (Sepsis-1 and Sepsis-2) are superior to either of the Sepsis-3 diagnostic criteria for predicting mortality.<sup>41</sup> Finally, qSOFA predicts clinical deterioration late, being present a median of 5 hours before ICU transfer or death, whereas SIRS, albeit less specific, precedes that combined outcome by 17 hours.<sup>28</sup> This last point is important, because the human enterprise of diagnosing and mobilizing treatment for patients with severe sepsis is both time-sensitive and time-consuming.

In the United States, at least, the proposed change in diagnostic criteria has left clinicians in a quandary for several reasons. First of course is that nearly all physicians recognize the components of SIRS as indicating that an infection has become something more serious than a localized process. A cognitive dissonance arises from being told that features known to portend increased risk for organ dysfunction and mortality are simply normal and adaptive. Second, the Centers for Medicare & Medicaid Services has related that public reporting measures for US hospitals will continue to be based on our current schema of sepsis, severe sepsis, and septic shock.<sup>17</sup> For the Sepsis-3 criteria to be used in this country would mean that every hospital and every provider maintain two separate means for diagnosing and tracking patients, an unlikely scenario. Finally, although International Classification of Diseases, tenth revision codes and Centers for Medicare & Medicaid Services reporting measures have not changed, some insurance companies have denied payment for sepsis, basing their decisions on the Sepsis-3 criteria. The author has consulted with numerous hospitals facing this last challenge. Unless some adjustments are made to the diagnostic criteria proposed by the Sepsis-3 authors, there is unlikely to be a resolution to these quandaries soon.

The lexicon of sepsis is one of our most important tools in the fight to have more providers at every level engaged in keeping infected patients alive, and this is the most compelling reason for SIRS to remain a part of that lexicon. The language we use shapes the way we think and the way we act.<sup>9</sup> If the term SIRS is relegated to the “infection” category, it assumes the importance of a common cold, an impacted tooth, a cystitis. If, conversely, it is placed in the “possible sepsis” or “possible severe sepsis” bin, the presence of SIRS prompts rapid evaluation for the worst of its potential

consequences, and there is ample evidence for it to remain in the “possible sepsis” category. The most appropriate use for SIRS is that its presence prompts an immediate search for both infection, as its possible source, and organ dysfunction, as its possible companion. This is the way that the Sepsis-1 authors intended it to be used.<sup>10,14,42</sup> Contrary to the Sepsis-3 authors’ unanimous opinion that SIRS is “unhelpful” in the diagnosis of sepsis, using such an approach to prompt therapy is effective in reducing mortality.<sup>27,34-36</sup> That fact, alone should command the retention of SIRS in the diagnosis and language of sepsis.

Fever, tachypnea, tachycardia, and increased WBC count are consistent features of critical illnesses, including those induced by infection. The odds of at least two of them being present when infection causes life-threatening organ dysfunction are more than seven to one.<sup>43</sup> These are facts, and they will remain facts, regardless of how we manipulate our language and our approach. We serve our patients best if we use all the facts available to diagnose their sepsis early, when our treatment is most likely to be of use to them.

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