Where Are We Now With Sepsis?

WHITE PAPER

Summary: The following white paper provides an overview of the history of sepsis definitions, the changes set in motion in 2016 with the publication of Sepsis-3, and the evidence surfacing since then. Special thanks to **Sam Antonios, MD, FACP, SFHM, CPE, CCDS,** for authorship. This white paper was reviewed by the ACDIS advisory board in February 2017 and serves as a companion piece to New Definitions of Sepsis and Septic Shock: Response from the ACDIS Advisory Board. You can access that here: *https://acdis.org/resources/new-definitions-sepsis-and-septic-shock-response-acdis-advisory-board*

FEATURES

Introduction: Administrative vs. clinical data

Hardly a week goes by without a mention of sepsis in the medical literature, whether peer-reviewed scientific journals or non-peer-reviewed medical publications. Recently, more evidence has surfaced that seems to support the importance of Sequential Organ Failure Assessment (SOFA) in the risk assessment of sepsis patients. The recent publication of new sepsis and septic shock management guidelines has added even more uncertainty to reconciling a clear set of criteria that enables early detection, while avoiding overdiagnosis or immature diagnoses that may lead to unnecessary care. All this is occurring as U.S. hospitals continue to struggle with tracking and measuring severe sepsis and septic shock bundles as part of the Inpatient Quality Reporting (IQR) program mandated by the Centers for Medicare & Medicaid Services (CMS).

Sepsis remains a concern for clinicians, payers, policymakers, researchers, academics, and patients, while initiatives around sepsis seek to reduce its impact and patient mortality. However, to truly move the needle on sepsis care and measure quality improvement, the industry requires accurate data on sepsis prevalence, characteristics, and outcomes, with everyone operating on the same page and applying the same rules. This is where the problems arise, since to date, clear definitions with definitional criteria are still evolving. To some degree, we are in this situation due to an overreliance on administrative data for research, which has created a picture of the world through the prism of hospital discharge codes. ICD-9 and ICD-10 codes are widely used by researchers because the data is available, cheap, and used worldwide. In reality, these codes paint a parallel reality to a more subtle clinical universe. Hospitals need a mechanism for fair payment in relation to the consumption of resources, associated costs, and application of financial tools. That mechanism is code assignment. However, when code assign-

ment is used as a vehicle to drive research, the research impacts policy. From an academic standpoint, the medical community is constantly in search of ways to improve diagnosis, disease management, and algorithms to reduce the burden of disease and mortality.

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Research has shown that the use of administrative data has led to very different sepsis rates (for example, using codes for severe sepsis or septic shock, or concurrent codes for infection and organ dysfunction, etc.). It's worth noting that sepsis codes were introduced to ICD terminology in 2002, despite the previous existence of sepsis as a disease. The discussion about coding disease is relevant because, at least in part, it has played a role as a catalyst for constant changes in the sepsis definitions. One of the weak points of research using inpatient ICD codes is that diagnosis coding can be based on suspicions and likelihood, and not on certainty. In the U.S., coding is also used to measure the degree of reimbursement a hospital is entitled to, based on resource usage. Hospital discharge coding is thus mostly geared toward determining payment, and is not always best suited to delivering reliable epidemiological sources of disease prevalence and incidence. Just like in sepsis,

SIRS, sepsis, severe sepsis, and septic shock, 1991-2015

Systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock were initially defined in 1991 by a consensus panel convened by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) (first definitions). The definitions were revisited in 2001 (second definitions) during the International Sepsis Definitions Conference, which included members from ACCP, SCCM, the American Thoracic Society (ATS), the European Society of Intensive Care Medicine (ESICM), and the Surgical Infection Society (SIS). For the sake of ease, SIRS was defined by four variables:

1. Temperature
2. Heart rate
3. Respiratory rate
4. White blood cell count

These simple clinical criteria allowed researchers to identify patients, with a goal of enrolling them in trials. It is not surprising that the criteria were quickly adopted by clinicians, who needed help in selecting the patients that needed attention early.

Claims data showed a strong increase in the rate of hospitalizations for sepsis, and interestingly, the same data showed stable or decreasing rates of hospitalizations for the infections that most usually cause sepsis—in other words, more sensitive coding was suspected to be capturing a wider, but less severely ill group of patients over time.

However, since the release of the second definitions, research began to appear on the inadequacy of SIRS criteria in the risk assessment or definition of sepsis. On the other hand, severe sepsis, defined as SIRS with end-organ failure, continued to have decent supporting evidence. Not surprisingly, SIRS criteria were found to be too sensitive. SIRS can have many non-infectious causes, such as trauma, burns, pancreatitis, ischemic diseases, and neurological diseases. Research into biochemical markers began to show that activation of inflammatory, coagulation, microbial clearance, and other pathways leads to a host response that eventually results in end-organ damage, but the research could not distinguish whether such activations were started by bacteria or some other non-infectious insult.

From an epidemiological perspective, things were getting even more interesting. According to the Centers for Disease Control and Prevention, sepsis rates doubled between 2000 and 2008. Sepsis became the 11th leading cause of death in the United States in 2010, and it was the most expensive condition treated in U.S. hospitals in 2011. Claims data showed a strong increase in the rate of hospitalizations for sepsis, and interestingly, the same data showed stable or decreasing rates of hospitalizations for the infections that most usually cause sepsis—in other words, more sensitive coding was suspected to be capturing a wider, but less severely ill group of patients over time. Several studies by Rhee et al. (2016) tend to support the rise in administrative cases of sepsis as a result of changes in the MS-DRG system and the reimbursement impact from those cases. However, Bouza et al., looking at the increase in sepsis coding rates in Spain, note that that country's rate increase is probably not driven by financial incentives (Spain has a universal healthcare system) but rather by the many campaigns to improve sepsis awareness and recognition, as well as by hospitals' due diligence to improve the reliability of coding. These results are not surprising, given the inherent subjectivity associated with bedside clinical assessment. An interesting study distributed five case vignettes of patients with suspected or confirmed infection and organ dysfunction to a sample of practicing intensivists. The results showed significant variability.

The rise in sepsis incidence ignited an abundance of initiatives to promote earlier recognition and better treatment. In a very short period of time, bundles and early goal therapy became standard. Following the death of a 12-year-old patient,

New York state started requiring all its hospitals to adopt sepsis protocols. By 2015, CMS had decided to adopt the National Quality Forum measure for public reporting of sepsis, now known as SEP-1. SEP-1 defined severe sepsis and septic shock according to the 2001 sepsis definitions. This meant it used the presence of SIRS and organ dysfunction (described in detail in the SEP-1 specification manual) as the triggers for initiation of the three-hour and six-hour care bundles.

SIRS, sepsis, severe sepsis, and septic shock, 2016-present

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In February 2016, the *Journal of the American Medical Association (JAMA)* included three articles from the Sepsis Definitions Task Force that updated the definition of sepsis and presented the validation studies done to support the revised definition. In their definition article, Singer et al. (2016) described the available evidence, along with its relevance and related findings, from which the third iteration of consensus conference definitions for sepsis and septic shock was developed. Thirty-one medical societies listed in the acknowledgment section of the article endorsed the proposed definition, which was referred to as Sepsis-3. The authors decided to look at clinical factors in electronic records and find the best factors predictive of mortality as a surrogate for the definition of sepsis. Specifically:

- The task force defined sepsis as **"life-threatening organ dysfunction caused by a dysregulated host response to infection."** For the clinical setting, the task force recommended that organ dysfunction be represented by an increase in the SOFA score of two points or more, which is associated with in-hospital mortality greater than 10%.
- The task force defined 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 with sepsis alone."** Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and a serum lactate level greater than 2 mmol/L (> 18 mg/dL) in the absence of hypovolemia.

Most people focus too much on the clinical criteria, the SOFA score, as a prerequisite for defining or diagnosing sepsis. In reality, the proposed definition of sepsis is a single phrase: **a life-threatening organ dysfunction caused by a dysregulated host response to infection.** This implies that the elements needed for diagnosis are (a) an infection that the physician suspects, associated with (b) a dysregulated host response (which all too often is not reliably measurable). This leads to **(c), life-threatening organ dysfunction.** How much organ dysfunction? The definition does not specify. However, the articles attempt to propose a tool to quantify organ dysfunction by an increase of two or more points in the SOFA score. Why SOFA?

Because the data showed that such an increase is a bad prognosticator. Are there better organ dysfunction prognosticators? Potentially. The medical literature is attempting to identify them, as will be mentioned below. The authors of Sepsis-3 compared SOFA criteria, SIRS criteria, and LODS (Logistic Organ Dysfunction System) criteria, in terms of predicting mortality, before ultimately recommending SOFA.

It is important to note that such criteria are not diagnostic of sepsis since specific criteria for the identification of infection are not included. Sepsis-3 leaves clinicians with the challenge of determining whether a given patient is infected, and whether organ dysfunction is attributable to such infection.

It is important to note that such criteria are not diagnostic of sepsis since specific criteria for the identification of infection are not included. Sepsis-3 leaves clinicians with the challenge of determining whether a given patient is infected, and whether organ dysfunction is attributable to such infection. Often, these are difficult determinations. It is also important to note that a culprit organism is not identified in up to 50% of patients who present with sepsis, and a positive culture is not required to make a diagnosis of sepsis.

In short, the new definition generated more questions than answers. It was critiqued as being too narrow, as it was calibrated to predict the worst outcomes of sepsis, meaning that early interventions could be delayed or that other outcomes could be ignored. Furthermore, many have worried about the ability to operationalize the newer definitions and maintain the momentum on early identification of septic patients.

CMS responded with a publication in JAMA asserting that the existing sepsis definitions, including the use of SIRS criteria, had been instrumental in training clinicians and nurses on how best to identify the earliest stages of sepsis. As such, they have helped clinicians identify, diagnose, and treat sepsis early, before a patient's condition worsens. CMS expressed concern that the proposed Sepsis-3 definitions could precipitously delay the diagnosis of sepsis rather than help identify the diagnosis early. The article concluded by reporting that, prior to changing the widespread and understood SEP-1 definitions, rigorous clinical investigation of the task force's proposed definition is required, and that CMS will track the forthcoming related research and field testing.

Since the publication of Sepsis-3, more evidence has surfaced in support of the predictive accuracy of SOFA (and sometimes the quick SOFA score, or qSOFA) compared to SIRS to predict severe adverse outcomes. French research published in *JAMA* in January 2017 found that among patients presenting to the emergency department with suspected infection, the use of qSOFA resulted in greater prognostic accuracy for in-hospital mortality than SIRS or severe sepsis.

Another study in the same publication showed that among adults with suspected infection admitted to an ICU, an increase in the SOFA score of two or more points had greater prognostic accuracy for in-hospital mortality than SIRS criteria or the qSOFA score. These findings were noted to suggest that SIRS criteria and qSOFA may have limited utility for predicting mortality in an ICU setting. On the other hand, in a study published in the *American Journal of Respiratory and Critical Care Medicine in September 2016,* the Modified Early Warning Score (MEWS) and National Early Warning Score (NEWS) showed better discrimination than qSOFA in that comparison. MEWS has potential to be a better prognosticator of poor outcomes and will likely be studied further.

New sepsis treatment guidelines

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The most recent development in sepsis is the January 2017 publication of new guidelines from the Surviving Sepsis Collaborative. The Surviving Sepsis Guidelines were first published in 2004, with revisions in 2008 and 2012. In January 2017, the fourth revision of the guidelines was presented at the 46th annual SCCM meeting and published online jointly in *Critical Care Medicine and Intensive Care Medicine.* The updated Surviving Sepsis Guidelines were generated by 55 international experts representing 25 international organizations involved in the care of patients with sepsis, and provided 93 recommendations on early management of sepsis and septic shock. From a clinical perspective, some of the changes involve the use of early goal-directed therapy, which is no longer recommended. The guidelines also recommend the use of hemodynamic assessment for further fluid administration after the initial fluid bolus, including available physiological variables but also hemodynamic monitoring (invasive or noninvasive) to determine the type of shock.

From a definition perspective, the new guidelines address Sepsis-3 carefully but directly. The introduction starts by listing the definition of sepsis **as a life-threatening organ dysfunction caused by a dysregulated host response to infection and a reference to the Sepsis-3 article.** The new sepsis and septic shock management guidelines point out that although the Sepsis-3 definition proposed clinical criteria to operationalize the new definitions, the studies used to establish the evidence for the new guidelines and patient populations were primarily characterized by the previous definition of sepsis, severe sepsis, and septic shock stated in the 1991 and 2001 consensus. The new recommendations state that hospitals and hospital systems should develop a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients. The recommendations explain that sepsis performance improvement programs can aim for earlier recognition of sepsis via a formal screening effort and improved

management of patients once they are identified as being septic. Because lack of recognition prevents timely therapy, sepsis screening is associated with earlier treatment.

A limitation of Sepsis-3 definitions is that they cannot identify patients whose organ dysfunction is secondary to an underlying infection. Thus, a constellation of clinical, laboratory, radiologic, physiologic, and microbiologic data is typically required for the diagnosis of sepsis and septic shock.

According to a review by Neviere et al, sepsis exists on a continuum of severity ranging from infection and bacteremia to sepsis and septic shock, which can lead to multiple organ dysfunction syndrome and death. A limitation of Sepsis-3 definitions is that they cannot identify patients whose organ dysfunction is secondary to an underlying infection. Thus, a constellation of clinical, laboratory, radiologic, physiologic, and microbiologic data is typically required for the diagnosis of sepsis and septic shock. The diagnosis is often made empirically at the bedside upon presentation, or retrospectively upon the availability of follow-up data.

Clearly, there is continued clinical need to identify sepsis and at-risk patients early. All patients with infection or bacteremia are at risk of developing sepsis and represent early phases in the continuum of sepsis severity. The lesson here is that SIRS may have been nonspecific in identifying early sepsis, but qSOFA is more promising. However, qSOFA score performance has been variable in predicting mortality and cannot be used empirically without clinical judgment. Further, SOFA does not consider other patient risk factors, such as age or underlying comorbidities like splenectomy or immunodeficiency.

Summary and takeaways

To sum up what this paper has demonstrated:

- Sepsis was originally defined as SIRS with infection.
- Studies emerged reporting the non-specificity of this definition, and there was a call for an update.
- Administrative claims of sepsis have spiked, creating the perception of a sepsis epidemic, although data suggests the jump might stem from a change in coding practices around the globe.
- Due to sepsis' risk of mortality, early intervention initiatives were created and became part of regulatory compliance directives under CMS' SEP-1.
- In February 2016, the proposed Sepsis-3 definition framed sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection.
- A proposed tool for quantifying organ dysfunction was an increase in SOFA score of 2 points or more as a threshold that predicts high risk of dying from sepsis. SOFA is an organ dysfunction score and not a diagnosis of sepsis score.
- Another proposed tool for quantifying organ dysfunction (in the absence of SOFA) is qSOFA. qSOFA is easy to obtain; however, it demonstrated poor performance in the ICU. qSOFA may also be used as an early detection tool.

A physician's clinical judgment is needed to discern whether the condition is caused by an infection, whether that infection has caused a dysregulated host response, and whether the resulting host response amounts to a life-threatening organ dysfunction.

- SOFA and qSOFA are not diagnostic tools. They are prognosticators of poor outcomes that would support the organ dysfunction component of the Sepsis-3 definition (which itself has several components).
- Since the publication of Sepsis-3, more evidence is surfacing in support of SOFA's predictive abilities.
- New guidelines for management of sepsis and septic shock were published in January 2017. The new guidelines confirm the definition of sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection.
- The new guidelines continue to emphasize the importance of early recognition, and the medical literature still supports the concept of early sepsis recognition in order to avoid delays in care and poor outcomes.
- ICD-10 coding guidelines are still unchanged and do not reflect any of the changes proposed.
- CMS-defined triggers for initiation of severe sepsis and septic shock bundles are still based on use of SIRS with organ dysfunction and do not incorporate SOFA (SEP-1 quality measure).

What does this mean for documentation and coding specialists?

- The medical community has moved closer to incorporating the definition of sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection with the publication of new treatment guidelines based on this definition. In short, SIRS with infection is not enough to define a condition as sepsis, as it is unlikely to cause a life-threatening organ dysfunction.
- This means that physicians are likely to use this mindset as they treat sepsis patients. However, the definition leaves many pertinent issues unsolved. A physician's clinical judgment is needed to discern whether the condition is caused by an infection, whether that infection has caused a dysregulated host response, and whether the resulting host response amounts to a life-threatening organ dysfunction. In their discernment, physicians are likely to use the SOFA criteria (due to their predictive ability) but the definition does not restrict them to such criteria. As mentioned above, SOFA is an organ dysfunction score and not a diagnosis of sepsis score. It does not consider factors, such as age or underlying comorbidities, that may increase a patient's risk of mortality. Such risk assessment requires the clinical judgment of a physician. In other words, a physician may use his or her clinical judgment to determine whether a patient has an infection, leading to dysregulated host response, leading to life-threatening organ dysfunction. If the physician reaches such a conclusion without using SOFA, his or her documentation needs to support that conclusion as well as the factors that were considered in reaching it (patient comorbidities, for example). Since SEP-1 is still mandated in hospitals, physicians may use the combina-

tion of SIRS with multiple organ dysfunction as a supporting criterion for severe sepsis. After all, SIRS with several organs failing as a result of infection is associated with poor outcomes and may satisfy the definition. Despite being too sensitive, SIRS can still detect the manifestations of sepsis.

Recently, there have been reports of auditor denials for sepsis cases based on the Sepsis-3 definition. Several things have to be considered when reviewing those denials:

It is always recommended to discuss any questions that arise about sepsis with practicing physicians and providers.

- Physicians practicing medicine are documenting in the medical record based on their understanding of the latest clinical literature, and their views regarding issues such as sepsis need to be considered in the context of available definitions. Up until February 2016, previous definitions have guided their actions and documentation, and such time frames must be adhered to and respected.
- Even after February 2016, physicians are still required to use SIRS and organ dysfunction for defining severe sepsis and septic shock based on SEP-1, in order to comply with regulatory requirements. Hospitals looking to stay compliant with the IQR program cannot ignore such criteria.
- Since February 2016, using SIRS and infection as the sole definition of sepsis is not supported by the published literature. This may sound confusing given the previous comment, but here is a clarification: SIRS and infection, without the judgment of life-threatening organ dysfunction, cannot be used by a physician to establish a diagnosis of sepsis. However, given the continued SEP-1 measure, SIRS and organ dysfunction is a valid support for the diagnosis of severe sepsis (and sepsis) for two reasons: The first is because physicians are to comply with the SEP-1 mandate, and the second is because such cases do satisfy the definition of life-threatening organ dysfunction caused by a dysregulated host response to infection, despite the fact that SOFA may not have been used as a tool.
- Finally, physicians are adept at making complex clinical judgments. ICD-10 official coding guidelines offer a set of rules that have been developed to accompany and complement the official conventions and instructions provided within ICD-10-CM itself. The instructions and conventions of the classification take precedence over guidelines. Adherence to these guidelines when assigning ICD-10-CM diagnosis codes is required under the Health Insurance Portability and Accountability Act (HIPAA). A joint effort between the healthcare provider and the coder is essential to achieve complete and accurate documentation, code assignment, and reporting of diagnoses and procedures. It is always recommended to discuss any questions that arise about sepsis with practicing physicians and providers.
- The latest coding guidelines offer the following important reminder for CDI professionals: The assignment of a diagnosis code is based on the

provider's diagnostic statement that the condition exists. The provider's statement that the patient has a particular condition is sufficient. Code assignment is not based on clinical criteria used by the provider to establish the diagnosis. Obviously, the medical record needs to have good documentation to support the diagnoses used, but this guideline clearly identifies the physician as carrying the burden of diagnosing conditions.

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WHAT IS AN ACDIS WHITE PAPER?

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