Sepsis 2.5: Resolving Conflicts between Payers and Providers

Supplemental Digital Content

Contents

INTRODUCTION

Three decades after the first attempts to define sepsis, difficulties remain. Sepsis-1, Sepsis-2, and Sepsis-3 each represented significant advances in our understanding of the disease process, yet each carried burdens as products of their times. Sepsis-1 (1991) established the Systemic Inflammatory Response Syndrome (SIRS) in the presence of infection as the cornerstone of diagnosis (1). Sepsis-2 (2001) expanded upon the initial work, introducing definitions for severe sepsis and septic shock, considering inflammatory markers or signs of organ dysfunction as further means to identify the septic patient, and proposing a model to consider sepsis as a continuum rather than a static state (2). Noting the lack of specificity of "SIRS plus infection," Sepsis-3 (2016) elucidated the first conceptual diagnosis of sepsis as a life-threatening dysregulated host response to infection with a focus on organ dysfunction, and proposed that in the presence of infection, sepsis can be identified through use of severity indices (specifically the Sequential Organ Failure Assessment, or SOFA, score) (3).

None of the current definition in circulation can be considered a "gold standard." Focusing on Sepsis-3 alone, while many critical care groups have endorsed the standards, other key players in the care of the septic patient (such as the American College of Emergency Physicians and the Infectious Disease Society of North America) have not done so (4,5). Concerns about the conceptual basis of the definition and the operational impact of Sepsis-3 are well described in the literature. Commentary reviews problems with terminology in the definition such as "life-threatening" and "dysregulated host response." The sensitivity of the new definition, and especially the use of the SOFA score, may lead to the underdiagnosis of sepsis, decreased awareness of the diagnosis in its' early stages, and untoward delays in care. A definition that requires the patients to be more severely ill may increase rates of sepsis morbidity and mortality within quality measures. These issues have led some clinicians to question or reject the new scheme (6-22). Clinicians and hospitals may vary in their real-time application of differing sepsis definitions, with implications for "sepsis flags," patient triage, care protocols, quality improvement programs, and resource use (23).

Variant definitions of sepsis also problematic for the administrative side of inpatient care. While Sepsis-3 may be the more contemporary standard, ICD-10-CM coding remains based on Sepsis-2 categories of sepsis, severe sepsis, and septic shock (24-26). The United States Center for Medicare and Medicaid Services (CMS) offers mixed messages; CMS continues to root its' SEP-1 quality measures in the Sepsis-2 definitions of severe sepsis and septic shock, but also (through the Centers for Disease Control) issues a Hospital Toolkit for Adult Sepsis Surveillance using the presence of infection and organ dysfunction to define an Adult Sepsis Event (ASE) (26-32). As hospitals report outcome and readmission rates for sepsis, comparisons become difficult as individual clinicians or institutions use inconsistent definitions.

Competing definitions of sepsis also have implications for medical coding and reimbursement (24-26, 33). While CMS recognizes the documentation of sepsis within the medical record as sufficient to code the diagnosis, other payers may require the diagnosis to be clinically validated to support coding and payment. As previously noted, the Sepsis-2 definition is non-specific and promotes a degree of overtriage; the Sepsis-3 definition is narrower, and therefore less commonly supported by the medical

record. Payers may opt to use Sepsis-3 criteria on clinical grounds, but the use of controversial criteria resulting in payment denial may be considered adversarial by clinicians and institutions; the more aggressive the pattern of denial, the more the perception that the Sepsis-3 definition is used simply as a means to avoid payment. Demographic studies of the payer status of sepsis patients suggest that safety net hospitals may be disproportionately harmed by changes in sepsis payment patterns (34). Tensions between providers and payers have become so inflamed that the State of New York has intervened to require Managed Care Organizations to recognize the diagnosis of sepsis based on Sepsis-2 criteria as sufficient for coding and reimbursement (35, 36).

The conflict between the different definitions of sepsis, and the increasing human and fiscal burden of disease (37, 38), presented us with a unique opportunity to bridge the gap between clinicians and payers by developing a collaborative, community-based definition of sepsis. In constructing this definition, we not only looked to the medical literature and expert opinion, but also focused on how clinicians identify the septic patient, local practice patterns, the ability of the medical record to illustrate the condition, and the needs to insure accuracy in payment. Our definition chooses to focus not on sepsis-linked outcomes or identifying a specific population for research efforts, but simply on recognizing the presence of sepsis as seen in the community by the bedside clinician.

CLINICAL DEFINITION OF SEPSIS

Definitions and Characteristics

It's important to differentiate between definitions and characteristics. In the clinical context, a diagnostic definition is a conceptual statement of what something is (or, conversely, is not). The defined diagnosis may then be established by the presence of specific characteristics leading to or supporting the diagnosis. If we use the Fourth Universal Definition of Myocardial Infarction as a model, we find that:

"The clinical definition of MI denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia."

The document then lists characteristics (criteria) used to establish the diagnosis. These include an acute rise and fall of cardiac troponin values along with a selection of other parameters including symptoms of myocardial ischemia, specific EKG changes, and certain findings on echocardiography or coronary catheterization (39).

The difference between a definition and its' characteristics matter because the previous sepsis literature and resultant clinical practice have confused the two. This is especially true within Sepsis-2, where sepsis is not defined as a concept, but as a set of characteristics (SIRS plus infection). Sepsis-3 does a much better job of developing a conceptual definition of sepsis as "a life-threatening organ dysfunction caused by a dysregulated host response to infection." This definition is used by parties such as the Surviving Sepsis Campaign to frame their research and recommendations (40, 41). But while the Sepsis-3 team specifically noted that the SOFA score is not intended to be used as a stand-alone measure of sepsis, in translation the conceptual definition has been confounded with the SOFA score proposed as diagnostic criteria, such that for many SOFA has become the definition for sepsis. In the community

setting, this loss of specificity of language is seen not only in clinical work, but in aspects of payment where SOFA scores are used to audit records for the presence of sepsis rather than using the definition itself as the source of truth.

In developing a community-based definition of sepsis, unpacking the terms within Sepsis-2 and Sepsis-3 is a reasonable place to start.

Systemic Inflammatory Response Syndrome (SIRS)

SIRS in the presence of infection has defined sepsis within Sepsis-1 and Sepsis-2. However, over time it has become clear that SIRS criteria lack specificity for the patient who is clinically considered as "septic." It would seem reasonable to move away from SIRS as a diagnostic criteria in favor of other descriptors which may demonstrate similar sensitivity but higher specificity. In addition, we view definitions as conceptual. While specific physiologic parameters may support the definition, they may not belong in the definition itself. The use of SIRS within the definition of sepsis contradicts this principle.

Life-Threatening

The Sepsis-3 definition includes the term "life-threatening" as an integral concept. We would reject this term as part of our operational definition, as the wide range of subjective interpretation of this phrase minimizes it's impact and relevance. For example, the Sepsis-3 definition is based on an assumption of a baseline mortality rate of 10% in patients diagnosed with sepsis. But is sepsis not "life-threatening" until it hits that designated mortality rate? One might well argue that a mortality rate of 5%, or 1%, is also "life-threatening."

Specifying that sepsis is "life-threatening" also suggests that outcome validity takes precedence over construct validity. Construct validity is the reliability of a data point or a set of characteristics to identify the presence of disease, and can be assessed by measures such as specificity, sensitivity, and positive/negative predictive values. A focus on outcomes drives one to identify characteristics that may or may not be fundamental to the diagnosis, but which are instead associated with a specific presumed outcome (42, 43). The Sepsis-3 group acknowledged this bias as they describe comparing different critical care outcome scores to actual mortality rates, identifying the SOFA score as most closely matching these presumptions.

(Construct validity is certainly subject to similar biases. The characteristics identified as hallmarks of a diagnosis will generally be led by the conceptual definition. But eliminating outcome measures from the definition of sepsis itself keeps focus on the presence of condition at hand.)

One might argue that there needs to be some way within the definition itself to indicate that sepsis is a serious illness, representing a level of severity above that of a simple localized infection. We consider that the term "sepsis" carries with it the inherent implication for severe illness. The goal is to ensure that the clinical definition sets forth a physiologic construct that reflects that level of severity.

Organ Dysfunction

The concept of organ dysfunction as a sign of severe sepsis is introduced in Sepsis-2, and it becomes the linchpin of Sepsis-3. We agree that organ dysfunction over and above that which might be anticipated from infection alone is consistent with the systemic illness we label as sepsis.

The difficulty here is trying to differentiate the degree of organ dysfunction that might be expected from a localized infection for those of a more generalized one. Sepsis-2 references scoring systems such as SOFA as possible indicators of organ dysfunction; Sepsis-3 codifies that severity scoring (specifically SOFA) is the preferred means to demonstrate organ dysfunction.

We strongly disagree with the use of the SOFA score in this manner. The SOFA score was not designed as a diagnostic marker, nor an outcome predictor. In its' original form it was simply intended as a means to track the impact of therapeutic interventions upon the critically ill patient; further study noted that SOFA scores may be predictors of patient discharge from the ICU, but not of overall patient mortality(44-46). It's use as a diagnostic marker within Sepsis-3 is a result of matching the presumption of life-threatening illness with a standardized acuity measurement which shows the greatest association with mortality between measures explored within the studied population. Work which "validates" the use of the SOFA score in patients with sepsis do so by noting the predictive effects of higher SOFA scores on mortality rather than explore the relationship of SOFA to the actual diagnosis of sepsis. SOFA does not reflect any particular specificity, focus, or relevance to the diagnosis of sepsis; it only suggests who might die in any setting of critical illness or injury (46,47). The score itself does not require that abnormal findings (seen as "points") are related to the pathophysiology of sepsis; instead, they simply reflect the overall status and mortality risk of the patient, whether from acute, chronic, or acute disease superimposed upon chronic illness. While the Sepsis-3 document indicates that changes in SOFA score must be related to sepsis, the degree of certainty of attribution, and the magnitude of the changes required within each parameter, remains inherently subjective.

It is also of note that the Sepsis-3 document advocates use of the Quick SOFA (qSOFA) score, a SOFA derivative consisting of respiratory rate, systolic blood pressure, and altered mental status to be used as a screening tool for patients likely to be diagnosed with sepsis. However, the literature notes that at best, qSOFA is equivalent to or even less sensitive than the well-accepted SIRS criteria for the early identification of patients with sepsis. These findings have resulted in groups such as ACEP and ISDA to neither endorse nor recommend qSOFA as a single screening tool, but also casts doubt upon the application of the SOFA score more broadly within this patient cohort (39, 48-51).

Given these limitations and concerns, we feel it is imperative to move away from use of the SOFA score to characterize sepsis. We believe that focusing on the concept of organ dysfunction independent of any particular scoring system gets closer to the conceptual definition of sepsis as infection with organ dysfunction at the core of Sepsis-3.

We would instead propose a location-based approach to demonstrating organ dysfunction. First, we look for signs of systemic illness external to the seat of infection. For example, if a patient with pneumonia also exhibited acute kidney injury, AKI may represent organ dysfunction outside of the seat

of disease (in this case, the lung). We also recognize that even in localized infections, more severe symptoms specific to the organ system may be present and suggest sepsis. A patient with localized pyelonephritis may develop AKI as a reflection of organ dysfunction.

Dysregulated Host Response

Sepsis-3 also introduced the concept of a dysregulated host response as integral for the definition of sepsis. While we understand the rationale for the concept, it remains uncertain how exactly a dysregulated host response might present and what marker(s) we might use to distinguish it from other pathophysiologic responses to infection. As a result, we cannot see how this phrase adds meaning to a clinically-based definition meant for use at the bedside. In the community context, we would contend that a dysregulated host response is clinically synonymous with manifestations of organ dysfunction. Retaining the term "dysregulated host response" does not contribute to the clarity of the definition.

Severe Sepsis

Sepsis-2 characterizes "severe sepsis" as sepsis (SIRS plus infection) with accompanying organ dysfunction. As we wish to move away from using SIRS as definitional criteria for sepsis and focus on organ dysfunction as the clinical hallmark of sepsis, we do not believe that the diagnosis of severe sepsis has further utility.

Septic Shock

Both Sepsis-2 and Sepsis-3 have promulgated definitions for septic shock. As opposed to the criteria-based definition of sepsis within the same work, Sepsis-2 turns to a conceptual definition of septic shock as a "state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes." Criteria supporting the diagnosis include decreased systolic or mean arterial pressures despite "adequate volume resuscitation."

Sepsis-3 also offers a conceptual definition of septic shock as a "particularly profound circulatory, cellular, and metabolic abnormalities are associated with an increased risk of mortality than sepsis alone." In Sepsis-3, septic shock is characterized by a requirement for vasopressor use to support a minimum mean arterial pressure (MAP) of 65 mmHg, accompanied by evidence of hyperlactatemia.

In reviewing the competing definitions, we find the Sepsis-3 phrasing problematic. "Profound" becomes a subjective term, and the definition is focused on progression and outcomes rather than on early identification of septic shock itself. We also consider that as a measure of hypoperfusion, lactate itself can be considered a measure of shock and may be seen in the septic patient prior to the onset of frank hypotension requiring vasopressor use. In contrast, the Sepsis-2 definition appears more focused on recognizing the presence of septic shock.

Both the Sepsis-2 and Sepsis-3 definitions of septic shock cite specific values for blood pressure within their criteria. We feel that this reliance of specific numbers or ratios limits the utility of these indicators given variances in "normal" values with differences in age and underlying medical conditions. We consider that the response to treatment of hypotension as described in Sepsis-2 may be a better measure of the presence of septic shock.

Revised Definition of Sepsis and Septic Shock

Based on the discussion above, we propose the following conceptual definition of sepsis:

"Sepsis is present when a patient with infection exhibits evidence of organ dysfunction at a site external to the seat of infection, or what is routinely expected from the localized infection." .

"Septic shock is present when a patient with sepsis exhibits persistent hypotension following initial fluid resuscitation."

For purposes of discussion, we call this definition "Sepsis 2.5," as we believe it incorporates the best concepts of Sepis-2 and Sepsis-3.

CHARACTERISTICS AND CRITERIA

With the conceptual definition in hand, attention now turns to identifying those characteristic that identify sepsis. We suggest the cardinal signs of sepsis are an ill-appearing patient, documented or suspected infection, and evidence of organ dysfunction.

Clinical Appearance

Experienced clinicians recognize that much of their diagnostic intuition is based on the appearance of the patient, and it's likely that most would consider the septic patient to "look sick." However, neither Sepsis-2 nor Sepsis-3 include any reference to patient appearance or condition as part of their diagnostic criteria. This is understandable as the assessment of patient appearance and acuity of illness is a purely subjective measure. This leads to a conundrum most often seen in patients diagnosed under Sepsis-2, who qualify for the diagnosis of sepsis as "SIRS plus infection" but look quite well.

Patient appearance is a key driver of clinical diagnosis in the real-time community setting, and we believe it is reasonable to expect that the patient with sepsis appears clinically unwell. Documentation in the medical record should reflect a clinical appearance consistent with acute illness. Such documentation may describe the patient as toxic, septic, acutely ill, appearing uncomfortable, in mild, moderate, or severe distress, or similar terminology.

We also recognize that there is a subset of patients who will not be able to manifest a robust pathophysiologic response to infection, and in whom the clinical appearance may mask indications of sepsis. These patients include those undergoing chemotherapy, on immunosuppressive agents, or at the extremes of age. In these circumstances, we consider that the clinician should include a description of sepsis risk factors to support the clinical assessment of sepsis in atypical presentations.

Documented or Suspected Infection

The presence of infection remains a mainstay of the diagnosis of sepsis. Where problems arise, it tends to be in the identification of the specific source of the septic state, especially when the original insult is a non-focal systemic viral illness or when the patient has bacteremia without identification of a specific source. We would consider clinical documentation of any infectious state, be it localized or systemic, as supportive of the diagnosis of sepsis.

Organ Dysfunction

We've previously reviewed the meaning of the term "organ dysfunction" in our proposed definition for sepsis. Identifying clinical parameters demonstrating organ dysfunction incorporates the experience of Sepsis-2, Sepsis-3, and clinical practice. We would consider the following presentations consistent with the organ dysfunction of sepsis when identified as related to infection and not attributable to another concurrent or chronic condition:

Acute encephalopathy

Acute encephalopathy may be diagnosed in the patient experiencing organic stress on the central nervous system as manifested by alteration of the patient's baseline level of cerebral function. Documentation should support the nature of change from baseline mental status, care for any underlying cause, and any improvement or resolution.

Sepsis-Associated Encephalopathy is thought to result from the complex interactions of neurotransmitter dysfunction, microglial activation, inflammation and ischemia of the brain, and dysregulation of the blood-brain barrier. As SAE is associated with increased morbidity and mortality, its' presence in the septic patient would represent organ dysfunction of specific clinical significance (52,53).

Definitions of acute encephalopathy within the literature span the range of presentations from drowsiness, lethargy, somnolence, and disorientation to frank confusion, delirium, stupor, and coma (54-56). SOFA uses the Glasgow Coma score as a key component; in contrast, the CDC Hospital Toolkit does not feature changes in mental status as a sign of organ dysfunction. We prefer a functional definition of acute encephalopathy to one based on measurement to promote proper assessment of patients who do not evidence a normal mental status at baseline, but are nonetheless at risk for sepsis, such as those with developmental delay, chronic dementia, or prior head injury or stroke.

Arterial hypotension

Systolic blood pressure $\leq$90 mm/Hg; OR mean arterial pressures (MAP) $\leq$65; or a decrease in systolic blood pressure by $\geq$40 mm/Hg from baseline; OR initiation of a new vasopressor infusion.

The majority of sepsis documents (including Sepsis-2, Sepsis-3, the SOFA score, and the CDC Hospital Toolkit) use arterial hypotension and/or the initiation of vasopressor therapy as a marker of organ dysfunction, especially with reference to the diagnosis of severe sepsis and septic shock. SOFA begins to assign "points" to arterial hypotension below a MAP 70 mmHg, while Sepsis-2 defines hypotension associated with septic shock as a MAP of $\geq$ 60 mmHg. The value of 65 mmHg selected for use appears to be a reasonable compromise between these endpoints.

Acute kidney injury

Increase in serum creatinine by 0.3mg/dL or more within 48 hours; OR increase in serum creatinine to 1.5 times baseline or more within the last 7 days; OR urine output less than 0.5 mL/kg/h for 6 hours

Acute kidney injury (AKI) in sepsis may result from microvascular dysfunction, inflammation, and metabolic reprogramming of renal tubules (57). Circulating cell-free hemoglobin released from red blood cells damaged during a sepsis episode have also been implicated in the development of AKI (58).

Our criteria for AKI is based on the Kidney Disease Improving Global Outcome (KDIGO) document. This 2012 work re-evaluates and supercedes prior classification schemes for AKI such as that proposed by the Acute Kidney Injury Network (AKIN) and the Acute Dialysis Quality Initiative (RIFLE) (59). The SOFA score gives "points" for elevated creatinine values, but these values may reflect baseline renal status and not acute changes related to infection and organ dysfunction. The CDC Toolkit uses the older RIFLE criteria to establish renal dysfunction in an ASE. We feel the KDIGO criteria represents the current "gold standard" for the diagnosis of AKI.

Acute respiratory failure

Signs and symptoms or respiratory distress (dyspnea, tachypnea, retractions, decreased ability to speak, altered mentation, abnormal or quiet lungs sounds, et al) AND EITHER room air oxyhemoglobin saturation < 90%; OR room air PaO2 < 60 mmHg; OR P/F ratio < 300 if the patient is not on supplemental oxygen, or acute decrease in P/F ratio with known underlying pulmonary disease, OR PaO2 decrease of 10 mmHg over baseline values (baseline can be defined as the patient's most recent blood gas as an outpatient or at the end of an inpatient stay); OR Need for supplemental oxygen therapy > 2 liters/minute over baseline; OR HFNC, NIPPV, or mechanical ventilation in order to achieve target oxyhemoglobin saturation > 94%

Finding a uniform concise and comprehensive definition of acute respiratory failure (ARF) remains elusive. Many works have contributed elements to what we consider as a more global description of ARF. Our proposed definition encompasses measures of acute hypoxia or hypercarbia with clinical signs and symptoms of respiratory distress and appropriate oxygen delivery systems and content. We also integrate newer concepts such as the use of the P/F ratio to indicate hypoxia, the use of high-flow oxygen per nasal cannula as an oxygen delivery system, and target oxyghemoglobin saturations to determine oxygen content needs (60-67).

Hyperglycemia

Serum glucose measurement ≥ 200 mg/dL in the absence of a diagnosis of diabetes mellitus, or specific notation of exacerbation of diabetic hyperglycemia related to infection, that significantly improves with treatment of sepsis.

The etiology of hyperglycemia in sepsis is likely related to a stress response within the neuroendocrine axis leading to increased release of catecholamines, cortisol, and glucagon (68). Variability of insulin levels coupled with decreased sensitivity to insulin may play a role as well (69).

The literature demonstrates that septic patients with hyperglycemia ($\underline{\geq}$ 200 mg/dl) have worse outcomes than those with lower glucose levels in patients both with and without a known history of diabetes (68). We are comfortable using this value as a marker of organ dysfunction in patients with no prior history of diabetes. However, given the clinical reality that many patients with diabetes have poor control and routinely have blood glucose values above 200 mg/dl, and that no specific value has been established for an abnormally exaggerated hyperglycemic response to infection, we must rely on the clinical judgement of the physician to make this determination.

Coagulation abnormalities

INR >1.5 or aPTT >60 sec in the absence of an intrinsic coagulation disorder or the use of exogenous anticoagulants.

Sepsis-induced coagulopathy (SIC) results from deregulation of the coagulation cascade and fibrinolytic systems. Coagulopathy in patients with sepsis may be mild or progress to overt disseminated intravascular coagulation. Sepsis-associated DIC differs from that of other causes, in that systemic bleeding is not a common finding and the coagulopathy results in organ dysfunction via decreased tissue perfusion. As a result, changes in fibrin-related markers are not associated with sepsis, while lower platelet counts and a prolonged prothrombin time (PT) are linked to increased sepsis mortality (70,71). The best reference values indicate a PT ratio of > 1.4 as suggestive of SIC. We have chosen a more conservative value of > 1.5, and a roughly correlated activated partial thromboplastin time of > 60 seconds, to more firmly establish the presence of SIC.

Thrombocytopenia

Platelet count <100K cells/µL AND ≥ 50% decline from baseline (baseline must be ≥100K cells/µL.)

Thrombocytopenia in sepsis may result from multiple factors including decreased platelet production, abnormal platelet function, platelet sequestration, and consumptive coagulopathy (DIC) (72,73). The SOFA score uses a platelet value of < 150k/uL as a marker for thrombocytopenia; the CDC Toolkit suggests the criteria noted above. Others suggest a platelet count between 100-150k/uL as consistent with SIC, with a value of < 100k /uL indicating more severe dysfunction. We have opted to use the more conservative values.

Hyperbilirubinemia

Total bilirubin ≥ 2.0 mg/dL and increase by 100% from baseline unrelated to known underlying disease of the liver or biliary system

Elevated serum bilirubin is a sign of liver dysfunction, and higher levels may contribute to an imbalanced immune response in the septic patient (74). SOFA begins to assign severity "points" at bilirubin levels $\geq$ 1.2 mg/dL, while the CDC Toolkit uses the values noted above as criteria to aid in recognition of the Adult Sepsis event. We believe the CDC Toolkit definition is preferred as it accounts for baseline elevations in bilirubin from underlying hepatic or biliary disease, and requires any acute changes in bilirubin values to be ascribed to the presumed infection and/or the septic state.

Hyperlactatemia

Acute elevation of serum lactate ≥ 3.0 mmol/L (27.0 mg/dL)

Lactic acid (lactate) has been found to be prognosticator of mortality in patients with sepsis (75-77). Hypotension, redirection of blood flow to the central circulation, increased capillary permiability, and cardiopulmonary collapse may result in decreased tissue perfusion and elevated levels of serum lactate. Hyperlactatemia is a required component of the definition of septic shock within Sepsis-3; both this document and the CDC Toolkit suggest a value of $\geq$ 2 mmol/L as indicative of significant hyperlactatemia

in the patient with sepsis. Other work previously cited suggests a higher value of ≥ 4 mmol/L as a marker of increased mortality. We have adopted a level of ≥ 3 mmol/L as a reasonable compromise.

Cardiac dysfunction

Non-ischemic acute myocardial injury attributed to the septic state; OR new-onset atrial fibrillation; OR the syndrome of Sepsis-Induced Cardiomyopathy (SICM) characterized by acute and reversible myocardial dysfunction (acute global biventricular dysfunction or acute left ventricular dilation, diminished response to fluids and catecholamines, and the absence of acute ischemic myocardial event as the etiology of cardiac dysfunction).

Myocardial dysfunction in the septic patient may result from the release of pathogen- and damage-associated molecular patterns, cytokines, and nitric acid that together contribute to an escalating cycle of myocardial compromise (78). The Fourth Universal Definition of Acute Myocardial Infarction suggests that an acutely elevated troponin in the absence of objective signs or symptoms of cardiac ischemia represents a non-ischemic myocardial injury (NIMI). In the proper clinical context, high-output states such as sepsis may be the root cause of an acute rise in troponins consistent with acute myocardial injury (39).

New-onset atrial fibrillation in septic patients is also recognized as associated with increased morbidity and mortality (79,80). Work has also recognized a specific sepsis-induced cardiomyopathy (SICM) as evidence of organ failure in the septic patient (81).

The reader will note that several of these elements are consistent with SOFA scoring in Sepsis-3. The main difference here is that the parameters carry no specific "weight" in determining the diagnosis. If we follow the logic that we're looking to identify sepsis and not to predict mortality, there seems to be no reason to require the patient exhibit any particular number of "organ dysfunctions" to qualify for the diagnosis; indeed, notations of "organ dysfunction" within the Sepsis-2 and Sepsis-3 documents do not use or specify the plural.

Septic Shock

We consider that septic shock may be diagnosed when the above three cardinal criteria are met *and* the patient exhibits age-appropriate hypotension unresponsive to initial fluid administration. Appropriate initial fluid therapy is characterized by a clinically appropriate, age- and weight-adjusted crystalloid fluid bolus. Septic shock can be diagnosed by continuing resuscitative fluid administration following the initial bolus, and/or the use of intravenous vasopressors to maintain adequate mean arterial pressure, cardiac output, and peripheral perfusion.

Pediatric and Other Special Patient Populations

We believe that a definition of sepsis must be applicable to all patient populations, with appropriate variances for age (pediatrics) and condition-appropriate (ex. pregnancy) physiologic differences. Prior work with both Sepsis-2 and Sepsis-3 have focused on adapting SIRS and/or SOFA criteria to the pediatric population. For example, the 2005 International Pediatric Sepsis Consensus Conference definition mandates that either temperature or white blood cell count abnormalities must be present to

establish the diagnosis of SIRS; SIRS cannot be confirmed through tachycardia and tachypnea alone (82-84).

We believe that by focusing on the concept of organ dysfunction, and by eliminating the use of specific scoring systems, our definition is applicable to a wider spectrum of patient populations. Values for physiologic parameters describing organ dysfunction may require adjustment to account for age and weight-based differences in pediatric patients, gravid females, the elderly, and other populations.

SEPSIS 2.5: A COMMUNITY-BASED MODEL

Sepsis 2.5 is designed to be flexible and responsive to changes in our understanding of sepsis. It may expand to encompass additional measures of organ dysfunction, or narrow as we identify key elements specific or unique to the diagnosis. It is intended as a bedside tool designed to allow all parties caring for the septic patient to recognize the presence of sepsis in a rapid and consistent fashion, facilitating early and aggressive care to prevent excess morbidity and mortality.

We noted at the outset of this work that this definition of sepsis is not an academic exercise nor a research effort, but a response to clinical and administrative pressures in community practice. It was designed to set forth clinical parameters that can be easily recognized, documented, reviewed, and audited. We would highly encourage our academic colleagues to assess this concept in a more rigorous fashion for both construct and outcome validity, but also to understand that our purpose in this work was to add community-based functionality and clarity to a contentious academic debate.

We fully expect that as the medical community gains a better understanding of sepsis (and especially as we learn more about biomarkers that may help distinguish the septic response) (85), definitions will be refined, updated, and kept current with evolving knowledge. But for today, Sepsis 2.5 is proposed as a useful tool for the bedside clinician.

REFERENCES

1. Bone RC, Balk RA, Cerra FB, et al. Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. Chest 1992; 101:1644-55.

2. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATIS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003; 29:530-8.

3 Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315(8):801-10.

4. Osborn TM. ACCEP endorses Latest Surviving Sepsis Campaign Recommendations. ACEP Now, March 14, 2017. http://www.acepnpow.com/article/acep-endorses-latest-surviving-sepsis-campaign-recommendations

5. Slesinger TL, Dubensky L. Sepsis-3, A New Definition. Solutions or New Problems? ACEP Newsletter, online at https://www.acept.org/content.aspx?id=105419

6. Sartelli M, Klugert Y, Ansaloni L, et al. Raising Concerns about the Sepsis-3 Definitions. World Journal of Emergency Surgery 2018; 13:6 dio: 10.1186/s13017-018-0165-6

7. Peach BC. Implications of the New Sepsis Definition on Research and Practice. Journal Crit Care 2017; 38:259-62.

8. Hernandez G, Machado F, Ospina-Tascon G. To the Editor: Defining Septic Shock. JAMA 2016; 316(4): 454-5.

9. Fang X, Wang Z, Yang J, et al. Clinical Evaluation of Sepsis-1 and Sepsis-3 in the ICU. Chest 2018; 153(5):1169-1176.

10. Osuchowski MF, Thiemermann C, Remick DG. Sepsis-3 on the Block: What Does it Mean for Preclinical Sepsis Modeling?. Shock 2017; 47(5):658-60.

11. Giamarellos-Bourboulis EJ, Tsaganos T, Tsangaris I, et al. Validation of the New Sepsis-3 Definitions: Proposal for Improvement in Early Risk Identification. Clin Microbial Infect 2017; 23:104-9.

12. Cohen J. Current Clinical Controversies in the Management of Sepsis. J R Coll Physician Edinb 2016; 46:263-9.

13. Carneiro AH, Povoa P, Gomes JA. Dear Sepsis-3, We Are Sorry to Sayt that We Don't Like You. Rev Bras Ter Intensive 2017; 289(1):4-8.

14. Simpson SQ. SIRS in the Time of Sepsis-3. Chest 2018; 153 (1):34-38.

15. Simpson SQ. New Sepsis Criteria: A Change We Should Not Make. Chest 2016; 149(5):1117-8.

16. Driessen RGH, van de Poll MCG, Mol MF, et al. The Influence of a Change in Septic Shock Definitions on Intensive Care Epidemiology and Outcome: Comparison of Sepsis-2 and Sepsis-3 Definitions. Infectious Disease (Lond) 2018; 50(3):207-13.

17. Sterling SA, Puskaricjh MA, Glass AF, et al. The Impact of the Sepsis-3 Septic Shock Definition on Previously Defined Septic Shock Patients. Crit Care Med 2017; 45(9):1436-42.

18. Marshall JC. Sepsis-3: What is the Meaning of a Definition? Crit Care Med 2016;44(8):1459-60.

19. Fernando S, Rochwerg B, Seely Aje. Clinical Implications of the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3_0> CMAJ 2018; 190:E1058-9.

20. Braun D. A Retrospective Review of the Sepsis Definition After Publication of Sepsis-3. Am J Med 2019; 132(3):382-4.

21. Schlapbach LJ, Berger C, Aebi C, et al. SIRS in the Time of Sepsis-3. Chest 2018; 153(6):1512.

22. Verboom DM, Frencken JF, Ong DSY, et al. Robustness of Sepsis-3 Criteria in Critically Ill Patients. J Intensive Care 2019; 7:46.:

23. Machado FR, Nsutebu E, Abduk-Aziz S, et al. Sepsis-3 from the Perspective of Clinicians and Quality Improvement Initiatives. J Crit Care 2017; 40:315-7.

24. "Septicemia and SIRS." In Bernard SP, Risk Adjustment Documentation and Coding, American Medical Association, 2018, p. 252-5.

25. Association of Clinical Documentation Improvement Specialists (ACDIS). "Where Are We Now With Sepsis?" ACDIS White Paper, March 2017. Online at https://acdis.org/system/files/resources/37163%20Where%20Are%20We%20Now%20With%20Sepsis%20WP.pdflink???

26. Chapman S. Redefined Sepsis Affects Coding, Documentation. For The Record 2016; 10-13, available at www.fortherecordmag.com

27. Pepper DJ, Jaswai D, Sun J, et al. Evidence Underpinning the Centers for Medicare and Medicaid Services' Severe Sepsis and Septic Shock Management Bundle (SEP-1): A Systematic Review. Annals of Internal Medicine 2018; 168(8):558-568.

28. Faust JS, Weingart SD. The Past, Present, and Future of the Centers for Medicare and Medicaid Services Quality Measure SEP-1: The Early Management Bundle for Severe Sepsis/Septic Shock. Emerg Med Clin North Am 2017; 35(1):21931.

29. Townsend SR, Rivers E, Tefera L. Definitions for Sepsis and Septic Shock: To the Editor. JAMA 2016;316(4):457-8.

30. Kalantari A, Mellemat H, Weingert SD. Sepsis Definitions: The Search for Gold and What CMS Got Wrong. West J Emerg Med 2017; 18(5):951-56.

31. Rhee C, Chiotos K, Cosgrove SE, et al. Infectious Disease Society of American Position Paper: Recommended Revisions to the National Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) Sepsis Quality Measure. Clin Infec Dis 2021; 72:54152.

32. Centers for Disease Control, United States Department of Health and Human Services. Hospital Toolkit for Adult Sepsis Surveillance. March 2018. Available at: https://www.cdc.gov/sepsis/pdfs/Sepsis-Surveillance-Toolkit-Mar-2018_508.pdf

33. Baldawi M, Al-Jubouri M, Watson J, et al. The Potential Financial Consequences of the New Sepsis-3 Sepsis Definition. Crit Care Med 2016; 44(12): Supplement.

34. O'Brien JM, Lu B, Ali NA, et al. Insurance Type and Sepsis-Associated Hospitalizations and Sepsis-Associated Mortality Among US Adults: A Retrospective Cohort Study. Critical Care 2011; 15:R130.

35. New York State Department of Health. Article 44 MCO Sepsis Guidelines, July 15, 2019. Online at https://health.ny.gov/health_care/managaged_care/plas/2019-07-15_article44_gudiance.html,

36. New York State Department of Health. Sepsis Regulations: Guidance Document 405.4(a)(4). Online at https://www.health.ny.gov/regulations/public_health_law/section/405

37. Buchman TG, Simpson SQ, Sciarretta KL, et al. Sepsis Among Medica Beneficiaries: 1. The Burdens of Sepsis, 2012-2018. Crit Care Med 2020; 48(3):276-288.

38. Rhee C, Klompas M. The Eye-Popping Costs Associated with Sepsis Diagnoses among Medicare Beneficiaries. Crit Care Med 2020; 48(3):420-1.

39. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction. JACC 2018; 72 (18): 2231-64.

40. Evans L, Rhodes A, Alhazzani W, t al. Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock 2021. Intensive Care Med https://doi.org/10.1007/s00134-021-06506-y

41. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock 2016. Crit Care Med 2017;45(3):1-67.

42. Deutschman CS. Imprecise Medicine: The Limitations of Sepsis-3. Crit Care Med 2016; 44(5):857-8.

43. Deutschman CS. Sepsis-3: of Love and Bliss. Crit Care Med 2017; 45(4):739-40.

44. Vincent JI, Morena R, Takala J, et l The SOFA Score to Describe Organ Dysfunction/Failure. Intensive Care Med 1996; 22:707-10.

45. Hewett JN, Rodgers GW, Chase JG, et al. Assessment of SOFA Score as a Diagnostic Indicator in Intensive Care Medicine. IFAC Proceedings Volumes 2012; 45(18):467-72.

46. Lambden S, Laterre PF, Levy MM. The SOFA Score – Development, Utility, and Challenges of Accurate Assessment in Clinical Trials. Crit Care 2019; 23;374.

47. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for sepsis. JAMA 2016; 315(8):762-774.

48. 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.

49. Dykes LA, Heintz SJ, Heintz H, et al. Contrasting qSOFA and SIRS Criteria for Early Sepsis Identification in a Veteran Population. Federal Practitioner 2019; Special Issue; S21-4.

50. Mignot-Ever L, Raaijmakers V, Buunk G, et al. Comparison of SIRS Criteria and qSOFA Score for Identifying Culture-Positive Sepsis in the Emergency Department: A Prospective Cross-Sectional Multicenter Study. Study. BMJ Open 2021; 11:e041024. doi: 10.1136/bmjopen-2020-041024

51. Yealy DM, Mohr NM, Shapiro NI, et al. Early Care of Adults with Suspected Sepsis in the Emergency Department and Out-of-Hospital Environment: A Consensus-Based Task Force Report. Annal Emerg Med 2021; 78(1):1-19.

52. Mazeraud A, Righy C, Bouchereau E, at al. Sepsis-Associated Encephalopathy: A Comprehensive Review. Neurotherapeutics 2020; 17:392-403.

53. Huang Y, Chen R, Jiang L, et al. Basic Research and Clinical Progress of Sepsis-Associated Encephalopathy. Journal of Intensive Medicine 2021; (1):90-95.

54. Chalela JA. Acute Toxic-Metabolic Encephalopathy in Adults. Up-to-Date, current to June 16, 2020.

55. Dobbs MR. Toxic encephalopathy. Semi Neurol. 2011;31:184-193 [PubMed] [Google Scholar]

56. Erkkinen MG, Berkowitz AL. A Clinical Approach to Diagnosing Encephalopathy. Am J Med 2019; 132:1142-47

57. Peerapornratana S, Manrique-Caballero CL, Gomez H, et al. Acute Kidney Injury from Sepsis: Current Concepts, Epidemiology, Pathophysiology, Prevention, and Treatment. Kidney Int 2019; 96(5):1083-1099.

58. Kerchberger VE, Ware LB. The Roe of Circulating Cell-Free Hemoglobin in Sepsis-Associated Acute Kidney Injury. Seminars in Nephrology 2020; 40(2):148-159.

59. KDIGO Acute Kidney Injury Work Group. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. Kidney International 2012; 2 (Supplement 1): 1-138.

60. American Heart Association. Highlights of the 2015 AHA Guidelines Update for CPR and ECC. https://eccguidelines.heart.org/wp-content/uploads/2015/10/2015-AHA-Guidelines-Highlights-English.pdf

61. Beasley R, Chien J, Douglas J, et al. Thoracic Society of Australia and New Zealand Oxygen Guidelines for Acute Oxygen use in Adults. Respirology 2015; 20:1182-91..

62. Chu DK, Kim LH-Y, Young PJ. Mortality and Morbidity in Acutely Ill Adults Treated with Liberal versus Conservative Oxygen Therapy (IOTA): A Systematic Review and Meta- Analysis. Lancet 2018; 391:1693-1705.

63. O'Driscoll BR, Howard LS, Earis J,et al. BTS Guideline for Oxygen Use in Adults in Healthcare and Emergency Settings. Thorax 2017; 72:i1-i90. Doi:10.1136/thoraxjnl-2016-209729

64. Pinson RD. Revisiting Respiratory Failure. ACP Hospitalist 2013. Available at acphospitalist.org

65. Nishimura M. High-Flow Nasal Cannula Oxygen Therapy in Adults. Journal Intensive Care 2015; 3(15):1-8.

66. Sharma S, Danckers M, Sanghavi D, et al. High Flow Nasal Cannula. STAT Pearls, NCBI Bookshelf, last updated July 25,2021.

67. Maryland Hospital Association. Recommended Guidelines from Ob, Renal, and Respiratory Workgroups. Online at https://www.mhaonline.org/docs/default-source/transforming-health-care/complications/complications-work-groups/final-recommendations.pdf?sfvrsn=81c5c30d_4

68. Wernly B, Lichtenauer M, Hoppe UC, et al. Hyperglycemia in Septic Patients: An Essential Stress Survival Response in All, a Robust Marker for Risk Stratification in Some, to be Messed with in None. J Thorac Dis 2016; 8(7):E621-624.

69. Rivas MM, Nugent K. Hyperglycemia, Insulin, and Insulin Resistance in Sepsis. Am J Med Sci 2021; 361)3):297-302.

70. Samuarl J M, Moore Hb, Moore EE. Coagulopathy in Severe Sepsis: Interconnectivity of Coagulation and the Immune System. Surgical Infections 2018; 19(2):208-15.

71. Iba T, Levy JH, Raj A, et al. Advance in the Management of Sepsi-Induced Coagulopathy and Disseminated Intravascular Coagulation. J Clin Med 2019; 8:728.

72. Ghimire S, Ravi S, Budhatholki R, et al. Current Understanding and Future Implications of Sepsis-Induced Thrombocytopenia. Eur J Haematol 2021; 106:301=-5.

73. Vardpn-Bounes F, Ruiz S, Gratacap MP, et al. Platelets are Critical Key Players in Sepsis. Int J Mol Sci 20-19; 20:3494.

74. Han HS, Park C-M, Lee D-s, et al. Evaluating Mortality and Recovery of Extreme Hyperbilirubinemia in Critically Ill Patients by Phasing the Peak Bilirubin Level: A Retrospect Cohort Study. PLOS ONE 2021; https://doi.org/10.1371.journal.pone.0255230.

75. Liu Z, Meng Z, Li Y, et al. Prognostic Accuracy of the Serum Lactate Level, the SOFA score, and the qSOFA score for Mortality Among Adults with Sepsis. Scandanavian Journal of Trauma, Resuscitation, and Emergency Medicine 2019;27(1):51.

76. Gattinone L, Vasques F, Camporota L, et cal. Understanding Lactatemia in Human Sepsis. Am J Resp Crit Care Med 2019; 200(5):582-9.

77. Lee SM, An WS. New Clinical Criteria for Septic Shock: Serum Lacate Level as New Emerging Vital Sign. J Thorac Dis 2016; 8(7):1388-90.

78. Kakihana Y, Ito T, Nakahara M, et al. Sepsis-Induced Myocardial Dysfunction: Pathophysiology and Management. Journal of intensive Care 2016;4:22.

79. Bosch NA, Cohen D, Walkey A. Risk Factors for New-Onset Atrial Fibrillation in Patients with Sepsis; A Systematic Review and Meta-Analysis. Crit Care Med 2019; 47(2):280-87.

80. Xiao F-P, Chen M-Y, Wang L, et al. Outcomes of New-Onset Atrial Fibrillation in Patients with Sepsis: A Systematic Review and Meta-Analysis of 225,841 Patients. Am J Emerg Med 2021; 42:23-30.

81. L'Heureux M, Sternberg M, Brath L, et al. Sepsis-Induced Cardiomyopathy: A Comprehensive Review. Current Cardiology Reports 2020; 22:35

82. Goldstein B, Giroir B, Randolph A, et al. International Pediatric Sepsis Consensus Conference: Definitions for Sepsis and Organ Dysfunction in Pediatrics. Pediatr Crit Care Me 2005;6(1):2-8.

83. Matics TJ, Sanchez-Pinto N. Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children. JAMA Pediatr 2017;171(10):e172352 doi: 10.1001/jamapediatrics.2017.2352

84. Peshiman N, Nadel S. Sepsis in Children: State of the Art Treatment. Ther Adv Infectious Dis 2021;8:1-11.

85. Barichello T, Generoso JS, Singer M, et al. Biomarkers for Sepsis: More than Just Fever and Leukocytosis - A Narrative Review. Critical Care 2022; 26:14.