

REVIEW

Overview of the Third International Consensus Definitions for Sepsis and Shock (Sepsis - 3)

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Abstract

In 2016 new definitions of sepsis and septic shock have been published. This article summarises the new insights that have led to these changes and discusses the new definitions and clinical criteria of sepsis and septic shock.

Introduction

The new definitions of sepsis and septic shock have been recently published.^[1] The main reasons for this update were (i) to reassess current definitions in light of new insights into the underlying pathophysiological mechanisms, (ii) to clearly delineate clinical criteria used to operationalise the definitions to alleviate the existing confusion due to inconsistently applied criteria for 'organ dysfunction' and 'septic shock' and (iii) to offer healthcare practitioners an easy bedside prompt to recognise patients at risk of having sepsis. A Task Force, consisting of 19 members with expertise in the field of sepsis pathophysiology, clinical research and epidemiology, was convened by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine. This Task Force reviewed data based on large electronic health record databases and created new definitions and supporting clinical criteria by consensus meetings and Delphi processes. The recommendations were then circulated to the major professional societies covering multiple relevant disciplines in both developed and low-and-middle-income countries for peer review and endorsement. This article will provide an overview of these new insights, the new definitions and clinical criteria, and the consequences for daily practice.

New insights

The previous iteration of sepsis definitions (Sepsis-2) dates back to 2001 (*table 1a*). Apart from an additional list of signs and symptoms possibly indicating sepsis, the original sepsis definition (the Bone criteria – Sepsis-1) dating from 1991

remained practically unchanged. This original concept of sepsis was based on a model which consists of four phases in a continuum: the first phase is an infection which can progress into the second phase called sepsis (combining infection with at least two of the four systemic inflammatory response syndrome (SIRS) criteria^[2]) which can deteriorate towards severe sepsis (organ dysfunction) and, ultimately, worsen into septic shock. The underlying pathophysiological mechanism was related to an exaggerated systemic inflammatory host response.

Over the last years the concept of a systemic inflammatory response being the core mechanism has been increasingly challenged. Evidence indicates that sepsis is a syndrome triggered by an infection resulting in a dysregulated response by the host with pro- as well as anti-inflammatory components. However, not only immune-modulating mechanisms play a role; cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic and coagulation pathways are also affected. The interaction between pathogen, host factors and time is relevant and together these factors make sepsis an unpredictable syndrome.^[3-5]

The validity of the SIRS criteria has also been questioned. Retrospective data from Australasian ICUs show that one in eight ICU patients admitted with infection-related organ failure had fewer than two SIRS criteria and thus did not qualify as 'septic' under the old definition.^[6] On the other hand, a US study showed that SIRS criteria were fulfilled at least once in their hospital stay by almost half of the patients admitted to general wards, including many without infection.^[7] In other words, the sensitivity of the SIRS criteria have been challenged. They discriminate poorly between non-infective and infective causes of inflammation,^[6,7] despite the observation that the presence of SIRS criteria is associated with higher mortality in infectious

patients. This increase in mortality is linear and there is not a clear cut-off for patients with two or more SIRS criteria.^[7]

Another aspect recognised on reviewing the literature over the past 14 years is the lack of uniformity. A systematic review conducted by the Task Force^[8] found many different descriptions of septic shock had been applied in the literature resulting in a tenfold variation in incidence and fourfold variation in mortality. Not only were these descriptions dissimilar, but the severity measured by various organ failure scoring systems also differed.^[1] A recent survey by Rhee et al. highlighted the subjective and highly variable diagnoses attached to septic patients by clinicians.^[9] The authors stressed the need for 'objective criteria and standardised reporting to enhance consistency and comparability in sepsis research, surveillance, benchmarking, and reporting.'

New definition and clinical criteria of sepsis

The new definition states that sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. (*table 1b*) An important aim of this change was to differentiate sepsis ('bad infection') from uncomplicated infection. Three new aspects are thus added to the previous definition. First, sepsis is life-threatening, implying the need for prompt recognition and intervention. Second, there is a dysregulated host response which underlines the importance of both pro- and anti-inflammatory and other processes. Third, sepsis is more severe than an uncomplicated infection, meaning that organ dysfunction needs to be present. New 'sepsis' (infection with organ dysfunction) thus makes the old term 'severe sepsis' redundant. Such patients should urge a physician to be alert and consider greater levels of monitoring and intervention.

Many clinical criteria may direct towards the possible presence of sepsis in an infectious patient. The Task Force evaluated those which best identify organ dysfunction in patients with an infection. The electronic healthcare record of 1.3 million patient encounters in the 12 hospitals of the University of Pittsburgh Medical Center conglomerate was used as the discovery database. A total of 148,907 patients were identified with suspected infection on the basis of having cultures taken and antibiotics commenced. Four other databases (three US, one non-US) consisting of a further 700,000 infectious patients were used for validation. To characterise the possibility of sepsis in these patients, three different scores were evaluated: the SIRS criteria, the LODS (Logistic Organ Dysfunction System) and the SOFA (Sequential Organ Failure Assessment) score. The main outcome was to identify the score that offered the best discriminative validity for predicted mortality or other poor outcomes such as a prolonged ICU stay. For non-ICU patients SIRS and the SOFA score offered comparable discriminative value. However, for patients in the ICU, SOFA and LODS

were superior to SIRS. A SOFA score ≥ 2 was associated with a 10% risk of hospital mortality in the patients with suspected infection; these patients had a 2-25-fold increased risk of dying compared with patients with a SOFA score < 2 . As the SOFA score is integrated in daily critical care practice to a greater extent than LODS, the Task Force recommended that an acute change in total SOFA score ≥ 2 characterises organ dysfunction. If a previously healthy patient is admitted to hospital, the baseline SOFA score can be assumed to be zero. Past medical history, or prior blood tests in already hospitalised patients would identify those with a higher baseline score.

QuickSOFA score to identify patients at risk of sepsis

Clearly, blood tests are indicated in any patients with infection who are suspected of having organ dysfunction. This would enable the SOFA score to be calculated. However, not every patient with a mild infection requires blood tests. To aid the clinician in identifying patients at risk of having sepsis, the Task Force designed a 'quick SOFA score' (qSOFA – *table 2*) which consists of three variables: abnormal mentation (i.e. new-onset agitation, altered mentation with GCS ≤ 14 , drowsiness, confusion or coma), respiratory rate (≥ 22 /minute) and systolic blood pressure (≤ 100 mmHg). These variables were identified from a list of 21 variables frequently recorded in ward and ED patients as having the greatest predictive validity for a poor outcome. qSOFA was less useful in ICU patients in whom sedation, pressors and mechanical ventilation may affect the values. When two of the three variables were present in a ward or ED patient with suspected infection, this equated to a risk of dying of approximately 8%, whereas having all three equates to a mortality risk in excess of 20%. By contrast, having 0 or 1 qSOFA criteria was associated with a mortality risk $< 3\%$.

The advantage of qSOFA is that it can be assessed within a few minutes at the bedside. The Task Force suggested that ≥ 2 qSOFA criteria should trigger, if not already done, any necessary treatment escalations and investigations. This includes blood tests to assess organ dysfunction that would not only aid clinical management but also allow SOFA scoring to see whether the patient fulfils the organ dysfunction criteria to qualify for the new definition of sepsis. Importantly, even if the patient does not have ≥ 2 qSOFA criteria yet the clinician is concerned, e.g. by hypoxaemia or oliguria, the Task Force recommended active intervention and investigations as the patient may still have organ dysfunction.

The addition of serum lactate to the qSOFA is an important parameter that has been investigated. It is a very common blood test to identify unwell patients and their response to treatment. Adding different levels of lactate to qSOFA post hoc statistically increased the predictive validity of qSOFA. However, the clinical relevance was questioned as the predicted mortality of qSOFA

Table 1a. Previous definitions and clinical criteria of sepsis and septic shock

	Definition	Clinical criteria	Substituted by new definition of
Sepsis 2.0	SIRS with confirmed or presumed infection	SIRS: - Temperature >38°C or <36°C - Heart rate >90/min - Respiratory rate >20/min or PaCO ₂ <32 mmHg - WCC 12 or >10% immature band forms	• Infection or sepsis
Severe sepsis 2.0	Sepsis with organ failure	Organ dysfunction: - Systolic blood pressure <90 mmHg or MAP <65 mmHg or lactate >2.0 mmol/l (after initial fluid challenge) - INR >1.5 or a PTT >60 sec - Urine output <0.5 ml/kg/h for 2 h - Creatinine >177 µmol/l - Platelets <100 x 10 ⁹ /l - SpO ₂ <90% on room air	- Sepsis
Septic shock 2.0	Sepsis with refractory hypotension	Hypotension: - Systolic blood pressure <90 mmHg or MAP <70 mmHg Refractory: hypotension persisting after 30 ml/kg crystalloid	- Septic shock

WCC = white cell count; MAP = mean arterial pressure; INR = international normalised ratio; PTT = partial thromboplastin time

Table 1b. New definitions and clinical criteria of sepsis and septic shock

	Definition	Clinical criteria	Major differences compared to previous definitions
Sepsis 3.0	Life-threatening organ dysfunction caused by a dysregulated host response to infection	- Suspected or documented infection and an acute increase of ≥2 SOFA points - Patients with a suspected infection with an increased risk of mortality or ICU stay can be identified outside the ICU using the quick SOFA (qSOFA)s	- Dysregulated host response - Life threatening - SOFA score
Septic shock 3.0	A subset of sepsis patients in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality	- Sepsis and vasopressor therapy needed to elevate MAP ≥65 mmHg and - Lactate >2 mmol/l following adequate fluid resuscitation	- Circulatory abnormalities together with cellular abnormalities

including lactate level >2 mmol/l was similar to a qSOFA without the lactate. Also comparing lactate and qSOFA, qSOFA was superior to identify higher-risk patients with different levels of lactate. In summary, lactate did not add clinical value to the qSOFA.^[10]

Table 2. Quick SOFA

Quick SOFA (2 out of 3)
- Respiratory rate ≥22 per minute - Altered mentation GCS ≤13 or ≤14 with new onset agitation - Systolic blood pressure ≤100 mmHg

New definition and clinical criteria of septic shock

Septic shock is newly defined as a subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are profound enough to substantially increase mortality.^[1] (*table 1b*) Using the Surviving Sepsis Campaign database, the combination of circulatory failure and cellular metabolism abnormalities added significantly to increased mortality risk than either alone. This is the major difference compared with the 2001 definition in which a poorly described ‘circulatory failure’ was the only criterion. For operationalisation of the definition, patients need to be vasopressor-dependent to maintain a mean arterial pressure ≥65 mmHg AND have a lactate >2 mmol/l despite adequate fluid resuscitation.

To correlate cellular metabolism abnormalities with clinical criteria proved challenging. Final consensus was reached that lactate was the most reflective regularly collected clinical variable, acknowledging it is not always available and that the blood lactate level is influenced by multiple factors, such as insufficient tissue oxygen delivery, impaired aerobic respiration, accelerated aerobic glycolysis, and reduced hepatic clearance.

Three clinical criteria were tested in cohort studies: hyperlactatemia, hypotension and vasopressor therapy. Together they carried a hospital mortality risk of 42% using a cut-off lactate level of >2 mmol/l. Hyperlactataemia alone (without hypotension) carried an in-hospital mortality risk of 26% while fluid-resistant hypotension requiring inotropes/vasopressors but without an increase in lactate levels carried a mortality risk of 30%. As the combination of hypotension with an inotrope/vasopressor requirement plus hyperlactataemia was associated with a higher risk-adjusted mortality, the majority of the Task Force voted that both parameters should be present to characterise septic shock. Patients with hyperlactataemia or hypotension alone should still be actively managed, but to improve consistency such patients do not qualify as being in ‘septic shock’.

Discussion

The Task Force considers that the new definitions better reflect the current understanding of sepsis pathophysiology. Full consensus was not reached for every aspect, reflecting the ongoing challenge presented by a syndrome for which no gold-standard diagnostic test exists. Pragmatic compromises were thus reached and a minimum of a two-thirds majority had to be attained. Clearly, sepsis is still not fully understood; areas of

uncertainty and points of discussion still remain, obstructing a completely unambiguous description.

However, the new clinical criteria of sepsis and septic shock are pragmatic to use, do not require invasive diagnostics and are available to use for scientific goals such as research, epidemiology and coding. The quickSOFA score is an easy bedside tool but it is important to realise that this is based on retrospective data predominantly culled from US patient populations. It requires prospective validation in varied healthcare settings. SIRS criteria may still remain useful as a screening tool to identify patients with infection.

The use of lactate in shock has several disadvantages. Lactate measurements are not available everywhere, in which case other alternatives reflective of tissue hypoperfusion, such as capillary refill, should be evaluated. It is important that such tests be reproducible and validated. Lactate is not specific for shock or cellular dysfunction. However, the combination of hyperlactataemia and hypotension does select a very high-risk group of septic patients. This will hopefully improve identification of suitable patient populations for future research studies. For example, only 15-20% of patients enrolled into the three Early Goal-Directed Therapy studies had the combination of vasopressor-dependent hypotension and hyperlactataemia and this accounts in part for the low reported mortality.

Some have voiced concerns about the new definitions and clinical criteria, for example, introducing delay in intervening by using qSOFA over SIRS (which still has a sensitivity for sepsis of 88%⁽⁶⁾), or that those patients who do not fulfil the more rigid septic shock criteria would be neglected. These points can be readily rebutted. SIRS may be present in patients with a bad cold though this should not mandate administration of antibiotics. On the other hand, the Australasian study mentioned earlier highlighted that 1-in-8 patients with infection-related organ dysfunction did not have the necessary two SIRS criteria yet they had still been identified, transferred to intensive care and were being actively treated. Exactly the same applies to qSOFA which provides a simple and rapid risk stratification (indeed, faster than SIRS which requires laboratory testing), in much the same way that any Early Warning Score highlights those patients at increased risk of doing badly. Patients generating clinical concern should be actively managed regardless of whether they meet a particular label of 'sepsis' or 'septic shock'. Clinicians should not delay treatment simply because ≥ 2 qSOFA criteria are not met. Symptomatic hypotensive patients should still be treated actively even if their lactate is normal.

It will take some considerable effort to implement the new definitions and clinical criteria. Coding systems will need to be changed and educational programs adjusted. Mortality rates will

need to be recalibrated to determine whether currently claimed improvements in outcomes are being unduly influenced by variable reporting. Is this hard work justified? The view of the Task Force and, judging by the extensive peer review feedback, most people in the sepsis community, is that change is necessary in view of the marked inconsistency currently surrounding the diagnosis and epidemiology of sepsis and the negative impact on research, such as underpowering clinical trials by enrolling less sick patients. The use of qSOFA also offers the possibility of improved identification of those infected patients at risk of doing badly. Prospective evaluations do need to be performed in multiple healthcare settings to confirm the utility of the new definitions and criteria, and qSOFA. Sepsis-3 is not the final word but the next step of an iterative process that hopefully is an improvement over the current flawed definitions.

Conclusion

The new sepsis criteria (Sepsis-3) reflect a better understanding of sepsis, although acknowledging this condition still remains incompletely understood. They are hopefully an improvement on previous iterations and will offer greater consistency, but are by no means perfect. They will nevertheless trigger more studies to enhance our knowledge of sepsis and to develop more specific markers.

Disclosures

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References

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock. *JAMA*. 2016;315:801-10.
2. Levi MM, Fink MP, Marshall JC, et al 2001 SCCM/ESICM/ACCP/ATS/SIS International sepsis definitions conference. *Intensive Care Med*. 2003;29:530-8.
3. Van der Poll T, Opal SM. Host-pathogen interactions in sepsis. *Lancet Inf Dis*. 2008;8: 32-43.
4. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369:840-9.
5. Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T. Host innate immune response to sepsis. *Virulence*. 2014; 5:36-44.
6. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med*. 2015;372:1629-38.
7. Churpek MM, Zdravetz FJ, Winslow C, Howell M, Edelson DP. Incidence and prognostic value of the systemic inflammatory response syndrome and organ dysfunctions in ward patients. *Am J Respir Crit Care Med*. 2015;192:958-64.
8. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *J Am Med Assoc*. 2016 315:775-87.
9. Rhee C, Kadri SS, Danner RL, et al. Diagnosis sepsis is subjective and highly variable: a survey of intensivists using case vignettes. *Crit Care*. 2016 20:89.
10. Seymour CW, Liu V, Iwashyna TJ, et al. Assessment of clinical criteria of sepsis. *J Am Med Assoc*. 2016;315:762-74.