# The new international sepsis guidelines (Sepsis-3): the central message remains

**In February the international consensus definitions for sepsis and septic shock were updated to reflect current understanding of the syndrome. A new scoring system was also released (qSOFA) to aid early identification of organ dysfunction in sepsis.**

February saw the publication of the long-awaited and controversial third international consensus definitions for sepsis and septic shock (Sepsis-3), which replace the 2003 definitions (Levy et al, 2003). Published as a trio of articles in *JAMA* (Seymour et al, 2016; Shankar-Hari et al, 2016; Singer et al, 2016), the high-profile guideline committee reminds us of the unacceptable and continued burden of sepsis to public health. As such, the consensus definitions, which contain much that is new, must be seen as an opportunity for all to embrace and implement the recommendations contained therein (Schorr and Dellinger, 2014).

Since the last guidelines were published, much has changed in our understanding of what exactly constitutes sepsis; great emphasis has been placed on early recognition and detection as well as rapid initiation of treatment protocols. This has resulted in an urgent need for these new international sepsis guidelines.

## What is sepsis?

Sepsis refers to a clinical syndrome caused by infection and its pathophysiological sequelae, which presents in a highly heterogeneous manner.

Physiological, pathological and biological abnormalities produce a constellation of signs and symptoms that are correlated with each other rather than producing a specific disease in itself (the word syndrome derives from the Greek word for concurrence). This makes the task of defining sepsis troublesome.

In 1991, the first consensus definition reflected the then prevailing view that sepsis consisted of suspected infection plus the systemic inflammatory response syndrome (SIRS). This approach to defining sepsis has remained at the heart of most definitions and diagnostic criterion developed since, and remains strongly embedded in the psyche of the medical community as a result. Over the past 30 years, critical care management, while still mostly supportive, has become more widely available and possibly more effective (Kaukonen et al, 2014). Advances in understanding of the underlying pathophysiological mechanisms leading to sepsis, and an increasing clinical understanding that not all septic patients demonstrate SIRS, have led to an urgent need for a new definition of sepsis that reflects these and promotes the development of therapies specifically targeted at underlying mechanisms.

Sepsis-3, convened and funded by the European Society of Intensive Care Medicine and the US Society of Critical Care Medicine, saw a task force of 19 specialists, from a variety of disciplines from basic science to critical care, engage in a series of iterative discussions resulting in a new definition of sepsis based on current understanding of the pathobiology of the syndrome. The resultant definition emphasizes that sepsis is organ dysfunction secondary to a dysregulated host response to infection. The inclusion of the word 'dysregulated' is integral to the conceptualization of the pathobiology of the syndrome.

The loss of SIRS from the new definition of sepsis is perhaps the biggest conceptual leap for most clinicians involved in the care of critically ill patients. Large database analysis and clinical experience tells us that not all septic patients mount an aggressive systemic inflammatory response to infection; however, the clinical manifestations of a common cold, i.e. SIRS plus infection, would, under previous definitions, have

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**Table 1. Systemic inflammatory response syndrome**

| To diagnose systemic inflammatory response syndrome (SIRS) requires two or more of the following: |
|---|
| Temperature >38°C or <36°C |
| Pulse >90 beats per minute |
| Respiratory rate >20/min or $PaCO_2$ <32 mmHg (4.2 kPa) |
| White cell count >12 x $10^6$ or >10% immature band forms |

**Table 2. The Sequential (Sepsis related) Organ Failure Assessment score (SOFA)**

| System | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Respiration ($PaO_2/FiO_2$, kPa) | ≥53.3 | <53.3 | < 40 | <26.7 (with respiratory support) | <13.3 (with respiratory support) |
| Coagulation (platelets, x$10^3$/ul) | ≥150 | <150 | <100 | <50 | <20 |
| Liver (bilirubin; umol/litre) | <20 | 20–32 | 33–101 | 102–204 | >204 |
| Cardiovascular (mean arterial pressure; mmHg)* | ≥70 | <70 | <70 + dobutamine (any dose) | <70 + epinephrine ≤0.1 μg/kg/min or norepinephrine ≤0.1 μg/kg/min | <70 + epinephrine >0.1 μg/kg/min or norepinephrine >0.1 μg/kg/min |
| CNS (Glasgow Coma Score) | 15 | 13–14 | 10–12 | 6–9 | <6 |
| Renal (creatinine; umol/litre) | <110 | 110–170 | 171–299 | 300–440 | >400 |
| or urine output (ml/day) | | | | <500 | <200 |

**Catecholamine dosage for at least 1 hour. Patients are assumed to have a baseline score of 0 indicating no organ dysfunction. $FiO_2$ = fractional concentration of inspired oxygen; $PaO_2$ = partial pressure of oxygen (arterial). From Vincent et al (1998)*

satisfied the criteria for diagnosis of sepsis. The tipping point here is that with a common cold, organ dysfunction is absent and therefore the risk of mortality is low (Levy et al, 2003) (*Table 1*).

As is to be expected from a consensus definition, the final product forms a balance between expert opinion and evidence. Understanding exactly what constitutes organ dysfunction and what precisely is a regulated host response to infection still eludes us, yet the new definition promotes an approach to sepsis that encourages these core concepts to be addressed.

## How to recognize sepsis

Pending the introduction of an accepted highly sensitive and specific biomarker for sepsis that reflects both mortality risk and the individual host response to infection, diagnosis still rests upon clinical suspicion and observations.

Singer and colleagues took a novel quantitative 'big data' approach to the development of the new diagnostic guidelines through the retrospective analysis of predictors of mortality in large cohorts of patients. The approach taken was to assess the predictive validity of the sequential (Sepsis related) Organ Failure Assessment score (SOFA) (*Table 2, Figure 1*), SIRS criteria and the more complex Logistic Organ Dysfunction System (LODS) score in a primary cohort consisting of 148 907 patients (Le Gall et al, 1996; Vincent et al, 1998).

Among 7932 intensive care unit admissions with suspected infection, both SOFA and LODS performed similarly in terms of predictive validity for in-hospital mortality and better than SIRS. An acute change in SOFA score of 2 points or greater was therefore taken as the clinical representation of life-threatening organ dysfunction.

For possible sepsis outside of the intensive care unit, the authors developed a new bedside clinical score for individuals with suspected infection who are more likely to have the poor outcomes typical of sepsis (quick SOFA or qSOFA; *Table 3*), derived from readily available clinical observations that again performed better than SIRS at predicting mortality.

New clinical criteria for identifying septic shock in adults were also developed. These were arrived at through systematic review and meta-analysis, which informed a Delphi process resulting in the new definition. The new definition was then tested in several cohort studies (Seymour et al, 2016) (*Table 4*).

**Figure 1. The Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score. From Vincent et al (1998).**

The SOFA score is used to determine the extent and/or rate of an individual's organ dysfunction secondary to sepsis. It is based on six separate values, scoring the level of dysfunction in each of the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems. SOFA was designed for simplicity, using readily available bedside clinical variables, and to focus more on organ dysfunction and morbidity than on mortality prediction.

The score is calculated on admission and every 24 hours until discharge. Both the mean and the worst score recorded during that period can be used as predictors of outcome. The scores can be summated in a number of ways: individual scores for individual organs to determine progression of organ dysfunction, as the sum of scores on one single intensive care unit day or as the sum of the worst scores during the intensive care unit stay.

The minimum possible score is 4 and the maximum is 24. Despite sequential daily calculation, the SOFA score is not intended to indicate success or failure of treatment or to influence clinical management.

Mortality prediction is limited to intensive care unit stay only; scores of 0–6 predicting <10% mortality, 13–14 around 50% mortality and greater than 15 90% mortality.

**Table 3. The Quick Sequential (Sepsis related) Organ Failure Assessment score (qSOFA)**

| |
|---|
| Hypotension: systolic blood pressure <100 mmHg |
| Altered mental status |
| Tachypnoea: respiratory rate >22/minute |
| A score of ≥2 criteria suggests a greater risk of poor outcome |

## KEY POINTS

- New definitions for sepsis and septic shock have been formulated.
- Systemic inflammatory response syndrome has been removed as a criteria for diagnosing sepsis.
- A new screening tool to identify patients with sepsis who are at high risk of deterioration (qSOFA) has been described.
- Some criticism has been levelled at the new definitions for potentially identifying patients too late in the septic process and for not being applicable to patients from low or middle income environments.
- Sepsis remains a major cause of long- and short-term morbidity and of mortality.

**Table 4. History of definitions of sepsis**

| | |
|---|---|
| 1992–2016 definition of sepsis | Sepsis is the systemic inflammatory response to infection |
| 1992–2016 sepsis clinical criteria | Suspected infection plus systemic inflammatory response syndrome |
| 2016 definition of sepsis | Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection |
| 2016 sepsis clinical criteria | Suspected infection plus organ dysfunction as defined by an increase of 2 points or more in the Sequential Organ Failure Assessment (SOFA) score |
| | Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality |
| 2016 septic shock clinical criteria | Sepsis and (despite adequate volume resuscitation) both of: |
| | Persistent hypotension requiring vasopressors to maintain mean arterial pressure ≥65 mmHg, and |
| | Lactate ≥2 mmol/litre |
| | Where these criteria are present, hospital mortality is predicted to be over 40% |
| | The term 'severe sepsis' is no longer in use |

## Difficulties with the new definition and diagnostic criteria

The population of patients with infection and organ dysfunction is heterogeneous. The new definition and diagnostic criteria for sepsis is therefore unsurprisingly particularly broad-brush and cannot allow precise categorization of patients according to underlying pathobiology or demographic. As a result, the definition does not help in directing modalities of care for the individual patient towards treatment of the underlying condition. This is a global weakness of the concept of sepsis itself, and not necessarily of the new criteria.

Both SOFA and SIRS can be viewed as global readouts of organ dysfunction and mortality indicators, but do not in themselves diagnose the cause of the dysfunction. qSOFA, retrospectively derived from databases with large omissions in terms of non-intensive care unit patients, while clearly applicable to all environments, will need prospective validation before being widely adopted into clinical practice. Furthermore, the necessity for the development of organ dysfunction in order to meet criteria may delay important therapy until too late in the development of sepsis (Simpson, 2016).

Perhaps the most important omission is a gold standard method to define or detect infection. This may not exist, but must surely be the most difficult question to answer. SIRS may therefore linger in clinical use as a diagnostic prompt towards suspicion of infection.

The patient data used to create the new consensus definitions came exclusively from adults in high-income countries, the majority being from the USA. This may limit the applicability to middle and low-income countries and to the paediatric population. Indeed the inclusion of lactate in the definition of septic shock may be problematic in resource-poor settings where this test may not be readily available.

## The future

The removal of SIRS from the diagnostic criteria for sepsis was one of the greatest strengths of this work, despite the disquiet caused. Sharpening the edge of the definition encourages both clinicians and scientists alike to focus on cutting down to the bare bones of what exactly the syndrome of sepsis is.

The next consensus definition will inevitably be developed in the context of an explosion of basic science research into the changes that define the early stages of the development of sepsis. The hope is that this will yield the answers to definitively identifying not only when an individual is infected, but also whether a patient is developing the organ dysfunction characteristic of sepsis, allowing tailored targeting of therapy to the precise phenotype of the individual patient. This could, and probably should, result in the definition of sepsis as a group of diseases characterized by their myriad clinical causes linked to individual pathobiological patterns of development and presentation.

## What now? How to apply the new definitions to your clinical practice

Screening for, early identification and timely treatment of patients with sepsis remain the cornerstones of management. First, infection should be suspected using established signs and symptoms, bloods and cultures taken and antibiotics administered while obtaining appropriate laboratory tests (i.e. lactate) to evaluate for sepsis-related organ dysfunction.

In patients with suspected infection, qSOFA can now be used to help identify organ dysfunction as a secondary screen to help identify patients at higher risk of deterioration. If organ dysfunction is identified then it should be ensured that sepsis management bundles have been initiated.

The Surviving Sepsis Campaign has produced a useful overview of how to integrate the new definitions into clinical care, available at survivingsepsis.org.

Sepsis-3 is a landmark in the continuing battle to reduce preventable deaths from sepsis and a renewed opportunity to focus on quality care of the septic patient. **BJHM**

*Conflict of interest: none.*


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