



## Editorial

# To have sepsis or to be septic—is the difference between these clinical conditions important?




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**Keywords:**

Sepsis  
 Septic  
 Critical care  
 Definition  
 Bacteria  
 Viruses

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The past three decades has seen various controversies over definitions and approaches to managing the patient with sepsis. The recent proposal for a new definition of ‘sepsis’ arising from the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)<sup>1</sup> has created further confusion, and a lively debate has followed its publication, with calls for a re-assessment of the definitions.<sup>2–4</sup> The key point of confusion seems to be that the clinical condition referred to as ‘sepsis’ is being confused with the patient ‘being septic’.

Accurate definition of a disease entity should help facilitate immediate clinical action through instituting relevant diagnostic procedures and appropriate management. The recent proposal of sepsis does not do that,<sup>1</sup> because a septic patient may be ill due to a range of other infections such as severe malaria, influenza, or Ebola virus disease, and will still be labelled as having sepsis. The new definition, or should we call it the ‘so-called definition’, is based on a set of organ-specific predictors of outcome and is not a definition of a clinical entity that could usefully help the clinician to manage septic patients rationally.

‘Sepsis’, to the infectious disease physician, is an illness caused by the presence of bacteria in the body tissues or bloodstream, i.e., an ill patient for whom blood culture is positive or is expected to be positive. Thus the word ‘sepsis’ immediately informs the physician that here is someone with a potentially life-threatening bacterial infection that requires treatment with appropriate antibiotic cover, and that the identification of the focus or source of the bacterial infection via appropriate investigations, including microbiological and imaging diagnostic procedures, may be required.

‘Septic’ is a very different term from ‘sepsis’ to the infectious disease physician; the patient being septic means that the patient has the same symptomatology as a patient with sepsis, but the bacterial diagnosis may not be obvious and a range of other pathogens need to be considered much more broadly, so that appropriate, pathogen-specific therapy can be instituted. For instance, a patient with severe influenza, malaria, or viral

haemorrhagic fever may be septic on presentation, but does not have sepsis as per the definition.

The initial definition of sepsis from 1992 defined sepsis as “a clinical response arising from infection” without clearly defining ‘infection’ (whether it meant bacterial, viral, fungal, or parasitic) as the underlying cause.<sup>5</sup> The paper then introduced the concept of ‘systemic inflammatory response syndrome’ (SIRS), to include non-infectious clinical conditions that show a sepsis-like presentation. The authors argued that it is likely that a common pathophysiology underlies SIRS, and that this justified the use of the term ‘SIRS’ no matter what the underlying aetiology. Now, 25 years later, we question this key assumption behind the introduction of the ‘SIRS’ concept. The paper also defined sepsis, severe sepsis, and septic shock, and it is obvious that the authors were focused on bacterial infections throughout – and not viral, fungal, parasitic, or other non-infectious causes.

The next major attempt to revise the definitions of sepsis was in 2001.<sup>6</sup> This paper discussed the possibility of defining sepsis based on biochemical parameters alone. It was stated that sepsis is “a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms”. The paper concluded that “the current concepts of sepsis, severe sepsis, and septic shock seem to be robust definitions and should remain as described 10 years ago”. The major difference between the 1992 and 2001 definitions is the detailed listing of biochemical markers for use in patients with sepsis. The definition did not specifically distinguish between viral, parasitic, and other causes, and yet again the authors must have primarily been thinking of invasive bacterial infection.

The recent attempt to define sepsis has focused on organ dysfunction.<sup>1</sup> In this paper, sepsis is defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection”. The definition does not distinguish between bacterial, viral, and parasitic infections, and it is suggested that the concept of ‘severe sepsis’ be abandoned. Furthermore, a detailed scoring system with five levels for dysfunction of respiration, coagulation, liver, cardiovascular, central nervous system, and renal functions is introduced (see Table 1 in Singer et al.<sup>1</sup>). The scoring system predicts severity and thus outcome and is useful when performing studies where it is important that the patient meets certain inclusion criteria and important when comparing outcomes between different units.

But is a scoring system predicting outcome a definition of a clinical entity? Certainly the proposed scoring system improves

predictions of mortality and stages the severity of the patient's condition, but it does not help the physician in planning a rational strategy for management, because it entirely ignores the specific microbial (bacterial, viral, fungal, or parasitic) or non-microbial aetiology of the condition. Thus it does not help map out a rational management strategy (specific choice of antibiotics, antimalarial, antivirals, steroids) and does not discuss the appropriate diagnostic tests to be used in a patient with 'sepsis'.

In all three definitions (the 1992, 2001, and 2016 definitions) it is stressed that common definitions and criteria are needed in order to perform comparable research studies on well-defined patient populations. This is critical, but existing definitions of 'sepsis' and 'being septic' will challenge a scoring system for predicting outcomes that allows patients with bacterial blood stream infections, malaria, and influenza to be pooled. Studies will need to include patients with a common microbial aetiology to be comparable and rational.

It is important that we return to the 1992 definition and define 'sepsis' as a response to bacterial infection, and that we consider other microbial aetiologies when using the term 'septic'. This will help the attending clinician to think more broadly and to work out the most appropriate management strategy based on considerations of probabilities for different diagnoses.

The definition of sepsis presented by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)<sup>1</sup> fulfils the criteria for US hospitals to bill the insurance system for a patient with 'sepsis' and also satisfies the US health care system requirement for a single diagnosis to classify patients with fever and organ dysfunction. However, the confusion and debate it has created requires global consensus to be obtained in defining 'sepsis' and 'septic' so that the definitions are universally acceptable. For low- and middle-income countries where there are limited resources for intensive investigations, a new paradigm should include practical guidelines with management algorithms, so that all specific aetiologies of the septic patient can be considered and treated. This will also assist in achieving common research protocols.

*Conflict of interest:* None.

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18 April 2016