Commentary

# More challenges around sepsis: definitions and diagnosis

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Sepsis is a complex and challenging syndrome, which can present in many ways and change quickly over time. Early recognition and timely management are key to help reduce its high associated morbidity and mortality (1). Zhang and colleagues recently published a guideline as part of The Society for Translational Medicine, entitled 'clinical practice guidelines for diagnosis and early identification of sepsis in the hospital' (2).

This review article highlights the difficulties associated with early and accurate diagnosis of sepsis in the clinical setting. There are numerous definitions and the development of new evidence means the diagnosis is constantly changing. One of the Survive Sepsis Campaign goals from the 2012 Consensus Conference was to improve outcomes in sepsis (1). Early identification of sepsis is key in fulfilling this goal.

There is no one specific test to diagnose sepsis, and a number of different screening tools and biomarkers have been used. This paper looked at evidence, in the form of randomised controlled trials (RCTs) and observational studies. The GRADE (Grade of Recommendation Assessment, Development and Evaluation) system was used to assess the usefulness of biomarkers and screening tools in the early diagnosis of sepsis. The limitations of using such tests as diagnostic tools in a resource limited setting are discussed.

The earliest definition for sepsis is now over twenty years old. This included SIRS (systemic inflammatory response syndrome) plus suspected or documented infection (sepsis-1) (3). This easy to recall definition can be utilised at the bedside, however a retrospective analysis by Kaukonen *et al.* suggested that SIRS is not specific and lacks sensitivity for defining sepsis and septic shock (4). Sepsis-2, a newer and more complex definition, reflects 'heterogeneity' of the disease process. Sepsis-2 lacks specific diagnostic criteria, and can be difficult to remember at the bedside (1).

Sepsis-3, developed from the ESICM-SCCM sepsis redefinitions task force, is the most recent definition based on SOFA (sequential organ failure assessment) scoring alongside infection (5). In this definition sepsis is defined as life-threatening organ dysfunction due to dysregulated host response to infection. Sepsis-3 can help identify patients requiring second line treatment, and a quick SOFA (qSOFA) can be useful for rapid patient reassessment. The data set of patients for sepsis-3 was quite specific and it may not apply to the broader range of clinical settings in which sepsis is found. The lack of a reliable definition for sepsis makes assessment, and changes in outcomes difficult to measure. Ideally one definition should be developed which is useful to clinicians and researchers alike.

Sepsis-2 classified sepsis into: sepsis, severe sepsis and septic shock (1). Severe sepsis is sepsis with organ dysfunction and septic shock is sepsis with persistent hypotension without another cause. Sepsis-3 views sepsis as a life threatening condition and has removed severe sepsis from the definition. Both classifications have limitations and the clinical usefulness of sepsis-3 remains unclear (5).

Newer scoring systems discussed in this article include PIRO (predisposition, infection, response and organ dysfunction) (6,7). Some evidence does suggest it outperforms SOFA scoring in predicting mortality in patients presenting with septic shock in the Emergency Department. PIRO was not superior to SOFA scoring in numerous studies according to Zhang *et al.* and there are no randomised trials looking at PIRO and outcomes including mortality to date (8,9).

Zhang *et al.* discuss biomarkers and scoring systems for use in the early detection of sepsis, whose clinical

usefulness has not yet been established. As sepsis is a dynamic condition, the diagnostic criteria may not all be present at one point in time. Sepsis should be considered in any patient who develops organ dysfunction and treatment implemented early. Patients should be reassessed regularly and diagnostic tests should be used in the clinical context. Some problems with biomarkers in the detection of sepsis include: differentiating between colonisation and infection, and limited specificity and sensitivity, which means they cannot be used in isolation. A highly sensitive screening test would be valuable in early detection of the disease and a specific test to confirm the diagnosis. Thus far no single diagnostic test has evidence to support its use.

This review carried out a literature review using a PubMed search. This looked at evidence in the form of RCT's and observational studies for use of biomarkers and screening tools in the early detection of sepsis. The authors found 62 studies. Search criteria including 'severe sepsis' and 'septic shock', although not currently used in the latest definitions of sepsis, may have found more articles. The authors found no randomised trials fulfilled their inclusion criteria.

A flow diagram [the 1st figure from Zhang *et al.* (2)] was used to assess evidence for the usefulness of a diagnostic test. RCT's being the gold standard, looked at patient outcomes when comparing a control and intervention group, for example the use of a biomarker such as PCT (procalcitonin) to guide treatment in sepsis. A recent randomised trial found no evidence for PCT as a guide for stopping antibiotics (10). PCT is a more useful to guide treatment rather than to diagnose sepsis. There is some evidence to suggest it may help differentiate sepsis and SIRS from other causes (8,9).

Observational studies were assessed [the 1st figure from Zhang *et al.* (2)] for evidence for tests used in diagnosing sepsis such as biomarkers and screening tools. A judgement was made on the impact of each test on patient outcomes. The diagnostic performance of which was assessed using the GRADE framework. This looked at test results and their effect on patient outcomes in terms of benefit and harm [the 3rd table from Zhang *et al.* (2)]. Early detection of sepsis (true positive results) may help reduce negative outcomes including mortality (11). However false positives will result in patients being exposed to an unnecessary intervention and false negatives will results in patients receiving treatment delays. True negatives can help decrease treatment costs.

Evidence reviewed in this article included: observational studies, meta-analysis, a systematic review and a retrospective study. The diagnostic performance of different tools was extracted from the research and displayed in the 4th table from Zhang *et al.* (2). There was no data for the sTREM-1 biomarker study and the lipopolysaccharide protein biomarker study did not have sensitivity or specificity recorded. The screening tool study, although small and prospective, had a high sensitivity and specificity. The infection probability study had a low sensitivity and specificity, and the study using a screening tool involving lactate had a low sensitivity.

Newer research involving electronic screening systems may help in accurate sepsis diagnosis in the future, however there is not enough current evidence to support their use. Limitations to the use of biomarkers and certain screening tools in the diagnosis of sepsis include their availability in limited resource settings, as highlighted by the authors. In developing countries, it is sensible to take a pragmatic approach, and use cost-effective alternative tests wherever possible. Causative organisms may vary, and different sources of infection may be associated with different outcomes.

This extensive review highlights the lack of a standard definition for sepsis and stresses the importance of early disease detection. Biomarkers and screening tools are assessed for their clinical application. These can be used to aid in the diagnosis however there remains no gold standard for diagnosing sepsis.

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## Footnote

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