Using sepsis scores in emergency department and ward patients

ABSTRACT

Sepsis-3, published in 2016, defined sepsis as 'life-threatening organ dysfunction caused by a dysregulated host response to infection'. Instead of systemic inflammatory response syndrome (SIRS), calculating the Sequential Organ Failure Assessment (SOFA) score was recommended. The complexity of SOFA also led to the introduction of quick SOFA (qSOFA) as a bedside tool. The simultaneous removal of SIRS and introduction of qSOFA belies their significant differences, with SIRS having a high sensitivity but very low specificity, and qSOFA being very specific for a poor outcome, but having a lower sensitivity than SIRS. In the UK, the variables within qSOFA are collected on a regular and repeated basis, along with additional variables, as part of the National Early Warning Score (NEWS). A knowledge of SIRS, qSOFA and NEWS is of value in assessing patients with suspected sepsis, as discussed in this article.

The first consensus definition of sepsis was published in 1992, which defined sepsis as systemic inflammatory response syndrome (SIRS) ≥2 with infection. SIRS became common parlance in the medical world, remaining part of the sepsis definition for more than two decades. However, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) significantly changed the definition of sepsis (Singer et al, 2016), defining it as 'life-threatening organ dysfunction caused by a dysregulated host response to infection'. SIRS was abandoned, and sepsis was now recognized by a change in sequential organ failure assessment (SOFA) score of ≥2.

This change in sepsis definition was endorsed by many colleges, but it was not universally well-received and has triggered much debate (Simpson, 2016; Sartelli et al, 2018). Delaying the recognition of sepsis until organ dysfunction was established appeared contradictory to the longstanding mantra of treating sepsis quickly and aggressively, given the 6 million deaths it causes worldwide each year. Moreover, the use of SOFA in emergency department and ward patients was limited by its complex nature, with many of the variables that SOFA requires not promptly available in these settings. Owing to this limitation, Sepsis-3 also introduced quick SOFA (qSOFA) as a bedside tool 'for the rapid identification of patients who are more likely to have poor outcomes' (Singer et al, 2016). Many studies have since compared qSOFA to SIRS, as well as to the National Early Warning Score (NEWS) – which is used throughout the UK. This article discusses the merits of SIRS, qSOFA and NEWS to help inform decisions made using these tools in the emergency department and ward setting.

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Why was SIRS abandoned?

SIRS identifies an inflammatory host response through the use of three clinical parameters and one biochemical parameter (*Table 1*). An inflammatory response can occur for many reasons beyond sepsis, and this lack of specificity is seen in practice. Studies have reported that 17% of all emergency department patients and 47% of all hospital inpatients meet SIRS criteria (Horeczko et al, 2014; Churpek et al, 2015). As well as lacking specificity, SIRS has also been criticized for not being failsafe (Singer, 2016), with one study showing that 1 in 8

Table 1. Criteria of commonly used scoring systems which may be used in sepsis

Systemic inflammatory response syndrome criteria (≥2)	Body temperature >38.0 or <36.0°C
	Heart rate >90 beats/minute
	Respiratory rate >20 breaths/minute or partial pressure of carbon dioxide <4.3 kPa
	White blood cell count <4000 cells/mm3 or >12 000 cells/mm3
Quick sequential organ failure assessment score (≥2)	Respiratory rate ≥22 breaths per minute
	Systolic blood pressure ≤100 mmHg
	Altered mental state
National Early Warning Score 2 (≥5)	Respiratory rate: up to 3 points starting from >20 and <12 breaths/minute
	Systolic blood pressure: up to 3 points starting from <111 and >219 mmHg
	Level of consciousness: 3 points for V, P, or U on AVPU scale or new confusion
	Body temperature: up to 3 points starting from <36.1°C, and up to 2 points starting from temperature >38°C
	Heart rate: up to 3 points, starting from <51 and >90 beats/minute
	Oxygen saturations: up to 3 points with trigger score dependent on whether patients are at risk for type 2 respiratory failure
	Supplemental oxygen: 2 points for yes

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patients admitted to an intensive care unit with sepsis did not meet criteria for SIRS (Kaukonen et al, 2015). Clinical trials using the SIRS definition were also not successful (Singer, 2016).

What is qSOFA?

The use of SOFA as a bedside tool is restricted by its complexity. It consists of many variables: the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2), platelet count, bilirubin, mean arterial pressure and use of dobutamine, adrenaline or noradrenaline, Glasgow Coma Scale score, creatinine, and urine output over 24 hours. Many of these variables will not be promptly available for emergency department and ward patients. Owing to this limitation, qSOFA was also introduced as a bedside tool to 'raise suspicion of sepsis on the regular floor' (Vincent et al, 2016).

The parameters for qSOFA were chosen using a data-driven approach, with large databases of predominantly non-intensive care unit patients analysed to identify which variables were most predictive of two outcomes: an intensive care unit stay of ≥3 days or mortality. From this, three clinical parameters were chosen (*Table 1*), and it was suggested that a qSOFA score of ≥2 should prompt clinicians to investigate further for organ dysfunction, consider escalation of therapy and evaluate for referral to critical care.

Studies comparing qSOFA and SIRS

While it has been stressed that qSOFA does not substitute for SOFA in defining sepsis and is not a replacement for SIRS (Vincent et al, 2016), the simultaneous introduction of qSOFA and abandonment of SIRS has led to direct comparisons. A brief literature search was conducted by electronically searching PubMed for articles with qSOFA, SIRS, and/or NEWS in the title and/or abstract, and conducting a Web of Science search on all relevant papers.

Meta-analyses have shown that qSOFA has a much higher specificity for mortality than SIRS, but at the cost of a lower sensitivity (especially in non-intensive care unit patients) (Fernando et al, 2018; Jiang et al, 2018; Maitra et al, 2018). To investigate the optimal balance between sensitivity and specificity, many studies make use of a receiver operating characteristic curve.

> **"...in the cases in which qSOFA is positive, there is concern that this occurs late... when the disease process is less reversible and there is less time for intervention."**

In a receiver operating characteristic curve, 'sensitivity' (the true positive rate) is plotted against '1 minus specificity' (the false positive rate). The area under the receiver operating characteristic curve (AUROC) is often reported to quantify the discrimination of the test. A test with an AUROC of 0.5 performs no better than guessing at random. A test with perfect discrimination (detecting all true positive with no false positives) generates an AUROC of 1.0 (Sedgwick, 2015).

Studies published around the time of Sepsis-3 reported positively on qSOFA because of its superior AUROC. For predicting mortality in 152 patients (67% emergency department, 33% hospital wards) with suspected infection who eventually required intensive care unit admission, Finkelsztein et al (2017) reported that qSOFA (AUROC=0.74; 95% confidence interval=0.66–0.81) 'had a greater accuracy' than SIRS (AUROC=0.59; 95% confidence interval=0.51–0.67). In addition, Freund et al (2017), in a prospective multicentre study of 879 adult emergency department patients with suspected infection, concluded that their findings 'supported the use of qSOFA in the emergency department setting', with qSOFA demonstrating a superior AUROC (0.80; 95% confidence interval=0.74–0.85) compared to SIRS (0.65; 95% confidence interval=0.59–0.70).

These studies were not alone in reporting a superior AUROC for qSOFA, but other studies raised concerns regarding the especially low sensitivity of qSOFA. In some studies, more than half of patients who died or required critical care intervention never scored a qSOFA of ≥2 by the time of the event (Moskowitz et al, 2017; Goulden et al, 2018; van der Woude et al, 2018). Moreover, in the cases in which qSOFA is positive, there is concern that this occurs late (Churpek et al, 2017), when the disease process is less reversible and there is less time for intervention.

Time before treatment

Time has been a major issue in the SIRS *vs* qSOFA debate. Early goal-directed therapy has been a mantra of sepsis care for many years, and there is evidence that this improves outcomes (Seymour et al, 2017). The Surviving Sepsis Campaign guidelines recommend administration of effective intravenous antibiotics within the first hour of recognition. With sepsis causing 52 000 deaths in the UK (The UK Sepsis Trust, 2019), affecting all age groups, Sartelli et al (2018) argued that the cost of false negatives (delayed or missed treatment) are more severe than those of false positives (unnecessary antibiotics and fluid, use of resources). Earlier recognition also facilitates more appropriate triage (home *vs* ward *vs* intensive care unit) (Simpson, 2016), with evidence for worse outcomes when admission to intensive care is delayed compared to direct admission (Escarce and Kelley, 1990; Cardoso et al, 2011).

Others have suggested that discerning the impact of early goal-directed therapy on mortality from that of the broader definition of sepsis incorporating less severe disease is difficult (Vincent et al, 2016). The value of antibiotics in the absence of organ dysfunction has also been questioned (Singer, 2016), and even in patients with sepsis (but without shock), it has been suggested that it may be safe to take time to gather data to inform whether antibiotics are necessary, as the harmful effects of antibiotics are complex and often underappreciated (Klompas et al, 2018). While SIRS may detect more patients who will have a poor outcome, with a high false positive rate Foëx (2018) argued that it is a poor discriminator for identifying patients in whom greater support may be needed. qSOFA is much more specific for a poor outcome, but the literature suggests that this will be negative in a significant proportion of patients who may also be appropriate for escalation. To meet this clinical need, other tools may be useful.

The National Early Warning Score

NEWS was developed in the 1990s with the purpose of detecting patients who were deteriorating, and was introduced nationwide in 2012, endorsed by the Royal College of Physicians. Its use nationally has helped to standardize the detection and treatment of

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CURRICULUM CHECKLIST

This article addresses the following requirements from the general internal medicine training curriculum:

- Delivering effective resuscitation and managing the acutely deteriorating patient.
- Managing an acute unselected take.

deteriorating patients, and it is considered an important advance in the care of acutely ill patients.

Many studies assessing NEWS have deemed it superior to qSOFA and SIRS for predicting mortality or intensive care unit admission in patients with sepsis, with NEWS demonstrating a similar AUROC to qSOFA, but without its very low sensitivity (*Figure 1*). This strong performance is not entirely surprising as it contains similar parameters to qSOFA, but with the addition of oxygen saturations, level of supplemental oxygen, temperature and heart rate (*Table 1*). Unlike qSOFA and SIRS, it is collected routinely and repeatedly for inpatients in the UK, with the interval between scores being determined by the magnitude of the preceding score.

It was most recently updated in December 2017 (NEWS2), and a consideration in this update was determining how NEWS could be used to better identify patients likely to have sepsis who were at immediate risk of serious clinical deterioration and required urgent clinical intervention. The efficacy of NEWS2 appears similar to NEWS but data are limited (Pimentel et al, 2019).

Biomarkers

Biomarkers have been suggested as a way of further improving the identification of high-risk patients. One possible marker is serum lactate levels. These are rapidly available through point-of-care testing and is highly specific for an increased risk of mortality for patients with sepsis in a curvilinear fashion (Puskarich et al, 2014), with the association being strongest when the lactate measurement is >4 mmol/litre (Shapiro et al, 2005). This increased mortality is observed even without hypotension (Puskarich et al, 2014), and it is supported by an abundance of literature.

Serum lactate forms part of the Sepsis-3 septic shock definition (i.e. 'sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥65 mmHg and having a serum lactate level >2 mmol/litre (18 mg/dl) despite adequate volume resuscitation'). Serum lactate was also assessed for inclusion in qSOFA, but although value was seen in patients with a borderline qSOFA (qSOFA=1), in whom an elevated lactate level was suggestive of an increased mortality similar to that of qSOFA=2, it was not included in the final model, with one of the issues being that it could not be measured in all health-care systems. In UK populations, lactate is routinely collected as part of the 'Sepsis Six' and thus it may be beneficial for patients with borderline qSOFA scores. Studies have not shown a benefit of adding lactate to NEWS (Abbott et al, 2016).

Other biochemical parameters have also been suggested – including procalcitonin, C-reactive protein, a lactate:albumin ratio, and neutrophil–lymphocyte count ratios (Ljungström et al, 2017) – but none of these are in routine use in sepsis scores.

National Institute for Health and Care Excellence criteria

In the UK, an additional guideline for recognizing sepsis was produced by the National Institute for Health and Care Excellence (2017). However, this has been criticized for being overly sensitive and complex. One study identified that 69% of admissions required review within 1 hour, compared to 6% with qSOFA and 18% with previous sepsis definitions (Thompson et al, 2017). Camm et al (2018) reported that its high sensitivity was at the expense of a very low specificity, and that further research should be undertaken before widespread adoption.

Conclusions

Sepsis-3 significantly changed how sepsis was defined, emphasizing a 'dysregulated host response' and 'life-threatening organ dysfunction'. The simultaneous move away from SIRS while introducing qSOFA led to direct comparisons, but SIRS and qSOFA are very different tools. qSOFA is a simple tool that, when positive, is highly specific for patients who will have the outcome of death or prolonged intensive care unit stay. Serum lactate levels may be a useful adjunct in patients with a borderline qSOFA. However, in a very significant proportion of patients who will have a poor outcome, qSOFA will not be positive. This limitation should be considered when using this tool, especially in emergency department and ward patients.

SIRS has a higher sensitivity than qSOFA and may be of value in identifying patients not recognized by qSOFA, but the high number of patients who become 'SIRS positive' may limit its discriminatory function. NEWS, while not designed specifically for sepsis, has proven effective in identifying patients with sepsis at risk of poor outcomes, and its automated collection on a nationwide basis is of use in detecting deteriorating patients. As with all of these tools, a positive score should trigger clinicians to investigate further for organ dysfunction (SOFA score), consider escalation of therapy, and evaluate for referral to critical care. BJHM

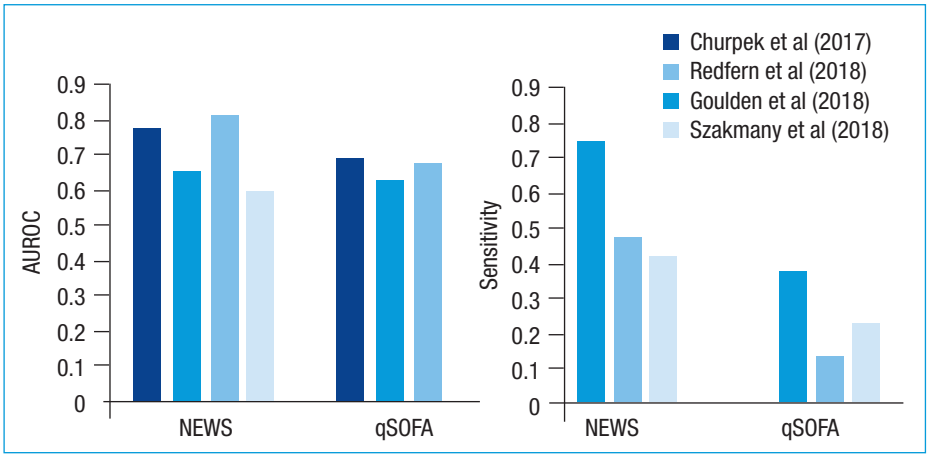

Figure 1. Sensitivity and area under the receiver operating curve (AUROC) values for quick sequential organ failure assessment (qSOFA) (≥2) and National Early Warning Score (NEWS) (≥5–6). The low sensitivity of qSOFA has been raised as a concern by many studies.

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KEY POINTS

- The definition of sepsis was significantly changed in 2016 to emphasize 'life-threatening organ dysfunction' and a 'dysregulated' host response to infection.
- To identify organ dysfunction, the Sepsis-3 task force suggest using a change in sequential organ failure assessment (SOFA) of ≥2.
- Quick SOFA (qSOFA) was introduced as a tool for the rapid identification of patients who were more likely to have poor outcomes and was created using a data-driven approach.
- While systemic inflammatory response syndrome has a high sensitivity and a low specificity, qSOFA has a low sensitivity and high specificity.
- The National Early Warning Score contains the same parameters as qSOFA but with additional variables, and in many studies it outperforms qSOFA.

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