qSOFA, cue confusion

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In February 2016, the 'Sepsis-3' Task Force provided new definitions and clinical criteria for sepsis and septic shock (1). The use of the systemic inflammatory response syndrome (SIRS) criteria within these new definitions was abandoned as the prior focus on systemic inflammation was recognized to be an outdated paradigm. A '*dysregulated host response to infection leading to organ* dysfunction' (1) better suits our current knowledge base in defining sepsis, with clinical criteria of organ dysfunction (the SOFA score) being used for operational purposes. However, the Task Force were at pains to stress that the individual SIRS variables (temperature, respiratory rate/$PaCO_2$, leukocyte count and heart rate) could still be useful for suspecting infection, though acknowledging its poor specificity and high prevalence among hospitalized patients. Churpek and colleagues identified 50% of all ward patients had at least one episode of SIRS during their hospital stay (2). Many patients will fulfil ≥2 SIRS criteria as a response to trauma, surgery, drug or transfusion reactions, or even severe anxiety or pain. Attempts to use SIRS triggers as an automated screening tool for sepsis have been abandoned as multiple false positives led to alarm fatigue (3). No study utilizing SIRS criteria alone has shown an outcome benefit.

Clearly, the challenge facing health professionals is to identify patients – infected or not - at risk of deterioration and to institute timely and appropriate treatment. Calculation of SIRS requires measurement of white blood count and $PaCO_2$; this introduces delay, cost and effort, and reflects a degree of clinical concern. Bedside assessment of routinely collected clinical variables are needed to prompt the clinician to take these and other blood tests, to order further investigations, and to initiate treatment. Relevant to this, but separate from the sepsis definitions/operational criteria, the Task Force proposed the quick Sepsis-related Organ Failure Assessment (qSOFA) as a simple bedside assessment to "*rapidly identify adult patients with suspected infection in out-of-hospital, emergency department, or general hospital ward settings who are more likely to have poor outcomes typical of sepsis*."

Notably, qSOFA has been by far the most controversial and, alas, the most misunderstood. qSOFA is a two-minute assessment using two or more of respiratory rate ≥22 breaths/min, any change in mentation (fall in GCS ≥1 point from baseline) and systolic BP ≤100 mmHg to highlight patients at higher risk of worse outcomes. This rapid score was developed from an analysis of patients with suspected infection within large US hospital population databases (4) and confirmed a well-established literature base showing these were the best routinely-collected

variables for detecting patients at risk of subsequent deterioration (e.g. 5,6). In the original validation study, Seymour et al found that only 24% of infected patients had a qSOFA ≥2, but these patients accounted for 70% of the poor outcomes (4).

Crucially, qSOFA was never intended to be a 'rule out' screening tool. The Task Force recognized it would offer specificity rather than sensitivity … *"Failure to meet ≥2 qSOFA criteria should not lead to a deferral of investigation or treatment of infection or to a delay in any other aspect of care deemed necessary by the practitioners. qSOFA can be rapidly scored at the bedside without the need for blood tests, and it is hoped that it will facilitate prompt identification of an infection that poses a greater threat to life. If appropriate laboratory tests have not already been undertaken, this may prompt testing to identify biochemical organ dysfunction"* (1).

The misinterpretations surrounding qSOFA highlight the need to consider the challenge of identifying sepsis, an acute illness still without a gold-standard diagnostic test. Neither SIRS nor qSOFA are diagnostic for either infection or sepsis but do offer information on the host's inflammatory reaction to an insult and the degree of physiological perturbation. They both provide some additional information on the patient's future outcome. A test or tool could be useful for screening, diagnosis, severity scoring, prognostication, prediction of therapeutic response, or clinical decision rules to inform best therapy (Table 1). Because of similarities in the epidemiological methods for determining illness status and additional information regarding outcome, there is always overlap between studies of diagnosis and those of prognosis.

The utility of qSOFA as a clinical decision support tool needs to be established. However, an advantage over SIRS is that qSOFA does not require laboratory tests and can be assessed quickly and repeatedly. Clearly, collecting more bedside data will increase sensitivity and specificity. The UK National Early Warning Score (NEWS) collects seven bedside variables, three of which are the qSOFA criteria. While NEWS is superior to qSOFA in identifying patients who ultimately have poor outcomes (7), the workload is necessarily greater. Sadly, many hospitals struggle to routinely measure just three variables in ward patients.

The systematic review by Fernando and colleagues (8) in this issue of *Annals* that compares the prognostic accuracy of qSOFA and SIRS underlines this confusion. Figure 1 of their paper reveals

sensitivities and specificities for qSOFA ranging from 0.12-0.98 and 0.19-0.96, respectively. For SIRS the respective ranges are 0.51-0.99 and 0.05-0.68. Aside from differences in patient populations altering pre-test probability, we note that most of the cited studies relied on retrospective analyses of databases. The 14 studies they deemed 'prospective cohort studies' were mostly analyses of historical data prospectively collected for other reasons; only three of these were performed specifically to assess qSOFA. The degree of data completeness and the extent to which these analyses are skewed by indication bias is unknown. Critically, the time window relating to scoring of SIRS and qSOFA relative to culture-taking and commencement of antibiotics is not described for these studies. In the original derivation (4), Seymour et al used the maximum qSOFA and SIRS criteria within a 72-hour time window (48 hours before to 24 hours after the first suspicion of infection) and found similar results when undertaking sensitivity analyses using smaller time windows (including 3 hours before to 3 hours after).

The holy grail is to have rapid early warning systems in place that accurately flag up all patients – infected or non-infected - at risk of deterioration, without escalating care or expending effort unnecessarily, inappropriately or dangerously. Such patients should be prioritized for treatment. qSOFA and the SIRS criteria should be viewed as complementary rather than competing.

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Table-1:

Rationale for test or tool	**Key epidemiological principles**	**qSOFA versus SIRS misinterpretation and explanations**
Hospitalised patient's illness status		
- Screening tool for sepsis	Used to detect pre-clinical disease or risk factors for disease Should have high sensitivity to avoid missing potential disease Simple, cheap, easy to implement on a large scale, rapidly performed and acceptable to patients Target population is at risk individuals	SIRS variables require laboratory testing and extremely high SIRS prevalence in ward patients makes it impractical as a screening tool. qSOFA was developed in symptomatic patients, thus it is not a screening tool for 'sepsis'.
- Diagnostic test for sepsis	Establishes presence or absence of disease Should have high specificity Higher cost and lower patient acceptability is justified ability to confirm diagnosis Target populations are either patients with symptoms or asymptomatic patients with a positive screening test	Diagnosis of sepsis requires confirmation of organ dysfunction. SIRS negative sepsis is common, even in critically ill patients. None of the SIRS variables are direct markers of organ dysfunction. Therefore, SIRS criteria are not diagnostic test for sepsis. qSOFA negative sepsis is likely. Acute change in consciousness and hypotension are markers of organ dysfunction. However, only two organ systems are represented in qSOFA. Therefore, qSOFA is also not a diagnostic test for sepsis. However, qSOFA will have greater specificity compared to SIRS criteria when considering sepsis diagnosis.
- Severity score for sepsis	In patients with the disease, increase in severity score increases the risk of bad outcomes	In patients with sepsis, presence of increasing numbers of SIRS variables and qSOFA variables increase the risk of death. However, as qSOFA variables include organ dysfunction variables, the risk of death would be higher in qSOFA positive patients. This is not because of 'late diagnosis of sepsis' but because of higher illness severity in qSOFA positive sepsis patients.
- Clinical decision rules for sepsis	In patients with suspected disease, the presence or absence of a set of clinical features makes clinicians take a particular course of action to avoid bad outcome	Neither SIRS nor qSOFA were derived to function as clinical decision rules. However, likelihood of worse outcomes with increasing SIRS or qSOFA points makes clinicians consider antibiotic therapy.
Additional information on future outcome		
- Prognostic value in sepsis patients	Patients with a positive test are likely to have greater risk of bad outcomes	SIRS cut offs were derived unencumbered by data.

		qSOFA analyses was performed using two key principles – Bayesian Information approach and logistic regression models with mortality and intensive care unit length of stay as outcomes. Thus, qSOFA could be considered as a tool that provides additional prognostic value in sepsis patients.
- Responsiveness to treatment in sepsis patients	Patients with a positive test are likely to benefit from an intervention	Neither SIRS nor qSOFA were derived to ascertain responsiveness to treatment. This could be tested in a randomised controlled trial.