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Sepsis early warning scoring systems: The ideal tool remains elusive!☆

Sepsis is one of the most common reasons for hospitalization. Sepsis, defined as life threatening organ dysfunction caused by a dysregulated host response to infection, affects an estimated 31.5 million patients a year worldwide, resulting in 5.3 million deaths [1]. In the United States, sepsis accounts for nearly $24 billion in annual healthcare costs [2]. Although prior research has focused largely on patients with sepsis in the intensive care unit (ICU) or emergency department (ED), up to 50% of septic patients are treated on hospital wards [3]. Longitudinal trends from randomized controlled trials and observational studies suggest that outcomes in patients with sepsis are improving [4-8]. However, mortality remains over 45% for those with septic shock [9]. Early diagnosis and intervention are essential to improve patient outcomes from sepsis. The Surviving Sepsis Campaign is focused on raising sepsis awareness and decreasing sepsis-related mortality, yet early recognition and treatment of sepsis remains challenging [10]. Physiologic derangement often precedes the recognition of clinical deterioration, and this concept has led to the development of diagnostic tools to accurately identify patients with sepsis or those at high risk for decompensation. Some early warning scoring systems (EWS) have been developed which have utility in screening patients with abnormal physiologic signs, while others can play a role in risk stratification. Unfortunately, sepsis remains a complex syndrome with no gold standard for its detection.

1. Scoring systems

The Sepsis-3 Definitions task force of the Society of Critical Care Medicine and European Society of Intensive Care Medicine used multivariable logistic regression to develop qSOFA - a quick Sequential Organ Failure Assessment (SOFA) score to assist clinicians identify, among patients with suspected infection, those who are at risk of death and morbidity from sepsis. The qSOFA consists of three components that are each allocated 1 point: respiratory rate ≥22/min, systolic blood pressure ≤100 mm Hg and altered mental status [11]. A qSOFA of ≥2 points suggests organ dysfunction and had high predictive validity for in-hospital mortality or prolonged ICU stay, especially among patients with infection outside the ICU. When compared to the systemic inflammatory response syndrome (SIRS) criteria, qSOFA was superior (area under the receiver operating characteristic curve (AUROC) of 0.81 vs 0.76), and slightly better than the traditional SOFA score (AUROC 0.79) in ED and ward patients. Freund et al. similarly showed that among patients presenting to the ED with suspected infection, the qSOFA had greater prognostic accuracy for in-hospital mortality than did either the SIRS or severe sepsis (i.e., addition of elevated lactate) criteria (AUROC 0.80 vs. 0.65 for both SIRS and severe sepsis) [12].

In 2012, the Royal College of Physicians of London released a standardized National Early Warning Score (NEWS) to identify acutely ill patients, including those with sepsis, in hospitals in England. This score has been highly effective and is widely adopted [13]. The NEWS allocates points in a weighted manner, based on the derangement of patient vital signs from an agreed "normal" range - respiratory rate, oxygen saturation, systolic blood pressure, pulse rate, mental status and temperature. This tool was designed for repeated measurement to track patients during their clinical trajectory and to trigger an alert at predefined thresholds. The sum of the allocated points is used to indicate a patient's severity of illness, and to inform the need to increase the patient's physiological monitoring or deliver expert help to the bedside.

In December 2017, the latest version of the NEWS called NEWS2 was launched as an update to include a new section for scoring oxygen saturation for patients with hypercapnic respiratory failure, to ensure the most appropriate prescription of extra oxygen if required and recognition of new confusion (or delirium) as a sign of potentially important clinical deterioration [13]. A NEWS2 score of ≥5 identifies a patient at serious risk of clinical deterioration and a poor clinical outcome.

Churpek et al. evaluated the difference between early warning systems including NEWS, modified early warning system (MEWS), and qSOFA in predicting death or prolonged ICU stay in 30,677 ED and hospital ward patients with suspected infection [14]. MEWS is a simple physiological scoring system validated in medical and surgical patients based on 5 bedside parameters including systolic blood pressure, heart rate, respiratory rate, temperature, and level of consciousness. Churpek et al. revealed that discrimination for in-hospital mortality was higher for NEWS (AUROC 0.77) and MEWS (AUROC 0.73) than for qSOFA (AUROC 0.69) and SIRS criteria (AUROC 0.65). However, given the differences in AUROCs among these scoring systems, one wonders whether these differences are clinically relevant and what their true impact is.

Table 1 shows a comparison of the sensitivity and specificity for mortality of SIRS, qSOFA, MEWS, and NEWS in non-ICU patients with suspected infection, all displayed with their normally used cutoff values [14]. The table suggests that at the currently used cutoffs, SIRS ≥2 has a higher sensitivity and a very low specificity for in-hospital mortality than other proposed diagnostic criteria.

2. The search for an ideal screening tool

Data indicate that early identification and initiation of treatment of sepsis is associated with reduced mortality, but there is no ideal

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Table 1
Sensitivity and specificity for mortality of diagnostic criteria for sepsis in non-ICU patients. Data adapted from Churpek et al. [14].

Criteria	Sensitivity (%)	Specificity (%)
SIRS ≥2	93.8	12.3
qSOFA ≥2	68.7	63.5
MEWS ≥5	71.4	65.0
NEWS ≥7	86.6	47.5

screening tool to facilitate early detection. Sepsis is complex and patients may become septic at any point during their hospital stay. Screening should ideally be performed longitudinally over time. Until recently, majority of EWS studies have focused on mortality prediction in patients with sepsis, rather than on identifying a process which should be reversed rapidly and to recognize a patient with a suspected infection who requires immediate attention. Certainly, this ideal system will require additional resources and costs and could potentially be a burden on caregivers and challenging to implement without clinician buy-in.

All currently employed sepsis EWS have limitations. In the case of qSOFA, only three clinical manifestations of sepsis (respiratory, cardiovascular and neurological) are being assessed. However, sepsis can be present in patients without a qSOFA score ≥2, as demonstrated by the limited sensitivity of qSOFA to detect organ dysfunction [15]. Moreover, a qSOFA of ≥2 can also be present in infected patients who are not septic. A qSOFA ≥2 also identifies patients with a mortality risk of 10%, which remains quite high. Williams et al. compared the diagnostic accuracy of SIRS and qSOFA for organ dysfunction among 8871 ED patients [15]. SIRS was present in 47% of patients and was associated with an increased risk of organ dysfunction and mortality in patients without organ dysfunction. Additionally, SIRS and qSOFA revealed similar discrimination for organ dysfunction (AUROC 0.72 vs 0.73, respectively). qSOFA was specific but poorly sensitive for organ dysfunction (96.1% vs 29.7%, respectively). Thus, although a qSOFA ≥2 shows high specificity, it has very poor sensitivity, thereby limiting its utility as a bedside screening tool and a potential trigger for intervention.

Arguably, the ability of EWS to detect sepsis earlier relates to the number of variables being monitored, since the underperforming qSOFA has three boundary levels, whereas MEWS and NEWS have 13 and 19 boundaries, respectively. An abnormality in one parameter can be associated with an abnormality in others, possibly rendering some responses to be redundant, such as in patients with respiratory failure requiring oxygen administration. Additionally, while NEWS has a higher sensitivity trigger which can lead to earlier identification of patients and prompt earlier interventions, this could potentially also lead to trigger fatigue and over work and distraction of providers in non-septic patients. With regards to the updated NEWS2, there are no new studies to evaluate its potential benefits over the original NEWS.

Future EWS are currently being devised using machine learning algorithms. Preliminary data suggest that these algorithms may be more accurate than MEWS [16], or assist in predicting sepsis [17,18]. However, additional larger prospective studies are needed to confirm these findings.

Recognizing infection before sepsis occurs is vital, yet the early diagnosis of sepsis remains very challenging and there is no single ideal screening tool. For the goal of early detection and facilitating early intervention, a high sensitivity tool may be more appropriate than a tool with lower sensitivity and higher specificity as the "cost" of missing sepsis may be devastating to the patient. Ultimately, these sepsis EWS are not universally exclusive and could in fact be complementary. NEWS, MEWS, and SIRS have the potential to trigger further close monitoring and evaluation of the patient, as they can be utilized for screening patients. An elevated EWS may be associated with organ dysfunction in some patients, but an abnormal score does not necessarily define the presence of organ dysfunction. The utility of these EWS is in their call to action of the medical team. After careful evaluation, work-up, and prompt management of the patient, a scoring system such as qSOFA could then be used as a tool for risk stratification, as it can be utilized in predicting death or prolonged ICU stay. Our suggested approach to screening for sepsis outside of the ICU is shown in Fig. 1. Abnormal physiologic signs should trigger a cascade of events to ensure that patients are adequately evaluated and managed. However, an absence of qSOFA or NEWS criteria should not prevent a clinician from engaging in the immediate investigation and management of a patient with suspected sepsis, indicating that experienced clinical judgement remains vital.

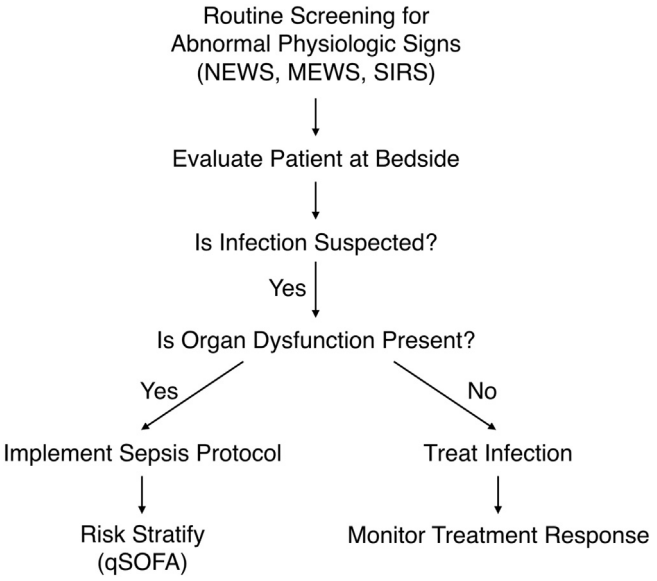

Fig. 1. A suggested approach to screening for sepsis outside of the ICU.

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