Editorial

qSOFA—welcome to the sepsis alphabet soup

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Sepsis-3 has generated a significant amount of debate and controversy since its introduction. Specifically, Sepsis-3 introduced qSOFA as a new terminology for identifying at risk patients for sepsis. In light of the recent updated sepsis guidelines and growing controversy, we read with great interest the manuscript entitled, "Systemic inflammatory response syndrome, quick sequential organ function assessment, and organ dysfunction: insights from a prospective database of ED patients with infection" by Williams *et al.*, that was just published in the March issue of *Chest* (1). We applaud the authors for conducting this study. The Sepsis-3 task force used mostly data from US databases to validate qSOFA and proposed that prospective validation with data from non-US settings are greatly needed. The authors had three aims: (I) to determine the prognostic impact of systemic inflammatory response syndrome (SIRS); (II) to compare the diagnostic accuracy of SIRS and quick Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score (qSOFA) for organ dysfunction; and (III) to compare standard Sepsis-2 and revised Sepsis-3 definitions for organ dysfunction—in ED patients with suspected infection (2-5).

The authors' aims stemmed from key findings of "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)" (3). The task force found limitations of previous definitions including inadequate specificity and sensitivity of the SIRS criteria. The expert consensus unanimously considered the current use of two or more SIRS criteria to identify sepsis to be unhelpful. Interestingly later in the same article, "*the task force wishes to stress that SIRS criteria may still remain useful for the identification of infection" and "nonspecific SIRS criteria such as pyrexia or neutrophilia will continue to aid in the general diagnosis of infection*". However, it was not within the task force's agenda to examine the definition(s) of infection even though sepsis fundamentally requires a trigger from infection. In an accompanying article to assess the clinical criteria for sepsis, the qSOFA model (altered mental status, respiratory rate greater than or equal to 22 breaths/min and systolic blood pressure less than or equal to 100 mmHg) was derived and supported as a tool to identify sepsis in patients with suspected infection outside of the ICU (6). As a response to Sepsis-3, the Surviving Sepsis Campaign stated that in patients who have screened positive for infection, qSOFA with at least two out of three elements may be used as a secondary screen to identify patients at risk for clinical deterioration (7). Lastly and of importance regarding the face validity of the populations used to establish the evidence for these criteria, Sepsis-3 utilized a combined supra cohort of 5 large observational cohorts with three different definitions of suspected infection. The three largest cohorts defined suspected infection by using a mandatory paired combination of body fluid culture and nonprophylactic antibiotic administration as recorded in the electronic health record. Specifically, patients were included if an antibiotic was followed by any culture within 24 hours or any culture was followed by antibiotic ordering within 72 hours, and the "onset" of suspected infection was defined as the time when initial antibiotic or culture was ordered or

sampled, respectively. Recognizing that data collected from 99.9% of the patients with suspected infections in the supra cohort was retrospective and mostly extracted from extracted US databases, the task force strongly encourages prospective validation in multiple US and non-US health care settings to validate the proposed qSOFA criteria (7).

Hence per the Sepsis-3 task force's call to action, Williams *et al.* tackled several important aims by utilizing an existing prospective, observational database that was a priori designed to enroll ED patients admitted with suspected infection (8). This robust registry was a priori designed to study the performance of SIRS and SOFA-based organ dysfunction as originally described for Sepsis-2 and was expanded retrospectively to include analysis of the new Sepsis-3 definition and qSOFA as a potential tool to identify patients with sepsis (8).

This registry enrolled patients from the ED of a tertiary, university-affiliated Australian hospital with annual census over 72,000 adult presentations during two discrete time periods, October 2007—December 2008 and June 2009—May 2011. On a daily basis, ED patients admitted the day before were screened and only those patients that were adjudicated to have infection as the most likely cause for their admission according to both the treating ED senior medical officer and the admitting team were enrolled in the registry. To adjust for local practice and laboratory reference range, a modified SOFA score was used to quantify organ dysfunction. Data were collected to sufficiently calculate SIRS, qSOFA, SOFA, comorbidity, and mortality.

In total, 8,871 ED patients with suspected infection were included for analysis. After applying appropriate statistical methods to account for re-admissions within 90 days, stratifications for age and Charlson comorbidity index, discrimination, and sensitivity and specificity analyses, the authors' findings to the three aims were: (I) SIRS was associated with increased risk of organ dysfunction (RR 3.5, 95% CI: 3.1–3.8) and mortality in patients without organ dysfunction (OR 3.2, 95% CI: 2.2–4.7); (II) SIRS ≥2 and qSOFA ≥2 showed similar discrimination for organ dysfunction (AUROC 0.72 *vs.* 0.73). qSOFA ≥2 was highly specific (96.1%) for but insensitive (29.7%) to organ dysfunction, whereas specificity and sensitivity for SIRS ≥2 were 61.1% and 72.3%, respectively; (III) comparing Sepsis-2 and Sepsis-3 with organ dysfunction, mortality was similar at 30 days [12.5% (95% CI: 10.8–14.2%) *vs.* 11.4% (95% CI: 10.1–12.8%)] and at 1 year [25.5% (95% CI: 23.3–27.7%) *vs.* 26.3% (95% CI: 24.4–28.2%)].

These results were both surprising and not surprising. For aim 1, the authors found that SIRS was prognostic, which is in contrast to Shapiro *et al.*'s findings from his cohort of patients with suspected infection (9). Similar to Sepsis-3 cohorts, Shapiro used blood culture as a surrogate to suspected infection. For aim 2, both SIRS ≥2 and qSOFA ≥2 showed adequate discrimination. It was expected that qSOFA will be more specific as it is derived from the revised definition for sepsis, but how shall we deal with its insensitivity? Interestingly to note that from Kaukonen's study's supplementary Table 1, there was significantly more SIRS positive than SIRS negative severe sepsis in the first 24 hours after ICU admission from the ED as the source (10). For aim 3, the study showed that Sepsis-2 and Sepsis-3 mortality for organ dysfunction was comparable between Sepsis-2; however, more prognostic and clinical information was conveyed using Sepsis-2 regarding number of organ dysfunctions. As suggested, the SOFA score may require recalibration because it was originally not designed to prognosticate (4).

However, we do not agree with some of the authors' conclusions. The authors stated that qSOFA is inferior to SIRS due to its relative insensitivity and overstated the clinical importance of SIRS ≥2. If we just examine the crude data from this paper, we can see how qSOFA still likely has an important role as the Sepsis-3 task force had intended. In this study 18.1% (164/905) of patients with qSOFA ≥2 died at 30 days, while only 2.0% (163/7,966) of qSOFA <2 patients had died at 30 days. Of patients with SIRS ≥2, 6.1% (253/4,176) had died at 30 days, while 1.6% (74/4,695) of patients with SIRS <2 had died at 30 days, while patients with SIRS ≥2 without organ dysfunction as defined by Sepsis-3 only had a 30-day mortality of 2.0%. We feel that these data further validate the Sepsis-3 findings and recommendations and favor qSOFA over SIRS. Goals of the Sepsis-3 were to differentiate sepsis from uncomplicated infection and to provide updated definitions for the severity of infection. One simplified conclusion from Sepsis-3 is that sepsis should be defined as patients with infection that have a high morbidity and mortality. We do acknowledge that this study has demonstrated that overall, patients with suspected infections with SIRS ≥2 were sicker than patients with SIRS <2. But after accounting for organ dysfunction, SIRS did not offer additional clinical prognostication for these patients. With that in mind, it is unclear what SIRS has to offer over qSOFA and clinician judgment. In this study, the qSOFA ≥2 population was very ill with a high 30-day mortality, while the qSOFA <2 population had a similar 30-day mortality as the SIRS <2 group and the SIRS

≥2 without organ dysfunction group. Also in this study, SIRS <2 patients with organ failure had a mortality of 9%. If one relied purely on SIRS, this was a very sick subgroup of patients that could have potentially been missed from early sepsis recognition and treatment. Finally the Sepsis-3 taskforce had not intended qSOFA or SOFA to be a stand-alone definition of sepsis, and it was not their intention that lack of qSOFA criteria should lead to deferral of testing or treatment. The main findings of this study can be summarized as patients with infections with SIRS ≥2 were sicker than patients without SIRS ≥2, except in the setting of organ dysfunction and shock, when SIRS did not contribute much information to clinical outcomes. After reading this paper we are still left with the unsettling question: what is the role of SIRS in sepsis care now?

After William *et al.*'s online release on November 19, 2016, many more investigations of qSOFA in the non-ICU and ED populations with suspected infection have been published and there are some mixed results and conclusions (11-14). As Rothman contends that sepsis has two problems regarding identification at admission and predicting onset during hospitalization, we agree that sepsis screening models need to be developed to tailor to different settings (15). Because sepsis prevalence and mortality are different among populations of different settings, clinical criteria and prediction and prognostication models need to become more sophisticated dynamically and perhaps machine learning will help all of us in the near future (16). Even though a natural history of sepsis does exist, time zero on sepsis onset has yet to be defined. As a bottom line for the annual estimate of more than 500,000 ED patients with sepsis in the US and moreover across the world, the ED providers need both robust screening and prognosticating tools in order to deliver the best care in a timely and resource appropriate fashion for the patients they are caring (17). Until then, the SSC international guidelines will continue to state, "*we recommend that hospitals and hospital systems have a performance improvement program for sepsis*, *including sepsis screening for acutely ill*, *high-risk patients* (18)."

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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