Using Sepsis-3 to identify infected patients with high mortality risk

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Title: Population-Based Evidence Supporting SEPSIS-3 to Identify Infected Patients at Higher Risk of Mortality

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In February 2016, “The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)” made a splash in the fundus of critical care medicine. In Altmetric.com’s stylized world of impact metrics, this article scores in the top 99th percentile of publications of similar age, not surprising since the Consensus recommended the most substantive changes to the definition and clinical criteria for sepsis since the original 1992 description. Despite this consumption, the clinical criteria may have been ill-absorbed by some given their retrospective derivation from large inpatient datasets encompassing ICU and hospital wards but not emergency departments and clinical criteria that perhaps confusingly differed by setting. For those awaiting further commentary and study, 2016 was gluttonous: 129 scientific articles, 57 reviews and 52 editorials cited the original publication. However, for those looking to separate the wheat from the chaff, the current article from Donnelly et al. presents classic descriptive, population-based epidemiology.

To contextualize the findings of any epidemiological study, we start with clarifying the study sample and the case definitions. The study by Donnelly et al. samples from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study that enrolled >30,000 community-dwelling Americans ≥ 45 years of age from 2003-2007. The REGARDS sample emphasized geography and race. Specifically, the strategy aimed to recruit 30% of its participants from the Stroke Belt and 20% from the Stroke Buckle of the southeastern US, with Blacks oversampled to comprise 50% of participants within each region. From this specific cohort, Donnelly et al. screened those with participant-reported, investigator-confirmed hospitalizations, sampling and adjudicating those hospitalizations that met the most encompassing Angus et al. ICD-9 criteria for serious infections as the reason for hospitalization. From this sample, the worse combination of physiologic data from the first 28 hours of the first infection hospitalization was used to classify participants into 3 separate but overlapping groups defined as those that had ≥2 qSOFA, SOFA or SIRS criteria.

This design has several implications on the generalizability of the results. REGARDS oversampled in areas that are hot spots of sepsis in the US. Specifically, counties in the Mississippi Valley, Middle Georgia and Central Appalachia areas demonstrate a high degree of clustering of sepsis mortality and have an age-adjusted sepsis mortality incidence of 93 per 100,000 person-years compared to the national average of 60. While this gives ample cases for the present analysis, it will also tend to bias towards overestimating national averages of sepsis incidence when not accounting for the stratified sample strategy in the analysis. Additionally, as intended by the authors the present study only captures community-acquired sepsis with early manifestations of sepsis during hospitalization. Participants whose physiologic signs of sepsis manifest outside the first 28 hours would remain in the ‘serious infection’ category, while those with later hospital-acquired sepsis would be classified into the ‘no infection’ denominator. This would tend to bias towards underestimating the total burden of sepsis on the US population.

With this in mind, the study demonstrates varying incidences of the different sepsis syndromes with 820, 580 and 200 cases per 100,000 person-years of the sepsis-SIRS, sepsis-SOFA and sepsis-qSOFA syndromes, respectively. For comparison, over a similar time period of 2004-2009 among national, administrative hospital discharge data in the US, different ICD-9 case definitions of sepsis have demonstrated incidences between 300-1,000 cases per 100,000 person-years. The study also demonstrates different temporal trends for these syndromes.
While the age-adjusted incidences of all infections and sepsis-SIRS increased 45% and 32%, sepsis-SOFA and sepsis-qSOFA incidences increased 200% and 300%, respectively. This observation echoes others that have demonstrated greater upward trends of sepsis coding relative to more modest upwards trends in coding for infections or objective evidence of bacteremia\textsuperscript{10,11}. This suggests that some component of the temporal increases in sepsis are due to increases in infections and potentially larger increases in the incidence, capture and coding of organ dysfunction.

In addition to this descriptive epidemiology, Donnelly et al. examine the associations between each of the syndromes with mortality at various time points. Across in-hospital, 28-day and 1-year end-points, sepsis-qSOFA was associated with the highest mortalities, followed by sepsis-SOFA, sepsis-SIRS and non-sepsis infections. Furthermore, qSOFA and SOFA were similar and uniformly better than SIRS in regards to discriminating those with infection at high risk of death. In general, these findings support the original findings of SEPSIS-3 but with a few important caveats\textsuperscript{12}. We think this study in particular supports the use of a dichotomous SOFA score to identify a more narrow patient population at a higher risk of death than that identified by SIRS. While SOFA and qSOFA had very similar associations and predictive characteristics with mortality, qSOFA identified a smaller patient group and may potentially have been a more biased group (of unknown direction) given that much of the data for 1 of the 3 qSOFA components, \textit{mentation}, was missing and assumed to be normal.

Finally, for readers looking to apply this study to the individual care of patients entering the emergency department, we echo the study authors’ words of caution. The retrospective analysis of hospital data may be more clinically applicable to the ‘Monday morning’ provider reviewing the last days’ worth of data rather than the emergency provider needing to make rapid decisions using available data. Furthermore, an experienced provider may be more likely to gather these data sequentially, use data in a non-dichotomous fashion and make decisions using all available data rather than choosing to look at one criteria at the exclusion of others. Despite the above hypothetical concerns, a recent prospective observational study of patients admitted to the emergency department with infection provides reassurance, demonstrating similarly enhanced clinical characteristics of dichotomous qSOFA and SOFA over SIRS in predicting those at risk for death\textsuperscript{13}. If last year’s publication record can predict the future, there will likely be more science to come to help us appropriate the use of sepsis-3 for research and clinical practice.
References