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Predicting and Eventually Preventing the Future: Sepsis Risk in Community Dwelling Adults

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Sepsis; Severe Sepsis; Prevention; Risk; Epidemiology

Sepsis is an acute syndrome resulting from systemic inflammation occurring in the setting of a severe infection (1). The number of cases in the United States is estimated to be greater than 750,000 per year (2), representing a substantial burden to the health system. Mortality from sepsis is high and now is the leading cause of death in patients admitted to medical intensive care units in the United States (2). Despite the high mortality and morbidity of sepsis, acute sepsis treatment has improved recently (3). Early identification, prompt initiation of early goal directed therapy and antibiotics, as well as improved supportive care in the intensive care unit are likely responsible for many of these improvements. However, sepsis continues to have an unacceptably high mortality and morbidity and, despite improved outcomes, sepsis incidence appears to be rising in the United States (4-6). This experience has several similarities to early advances in acute myocardial infarction (MI) care (7). Efforts to reduce the burden of MI initially focused on early diagnosis and treatment of the acute coronary event with some success. Subsequent research has added a focused on modifiable risk factors and MI prevention leading to marked decline in heart disease mortality in recent years (8).

To date, most advancement in community-acquired sepsis care has focused on prompt treatment of the acute sepsis hospitalization. In this issue of *Critical Care Medicine*, Wang and colleagues took a different approach by developing prediction scores that estimate the long term risk of sepsis and severe sepsis in a large population of adults at their baseline health state (9). The authors utilized the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort to study the risk of sepsis in 30,239 community dwelling adults. The REGARDS cohort included adults with an age $\geq$ 45 years in a stable phase of health, from diverse regions of the continental United States (10). Baseline information was collection on all subjects and subjects were followed for a median period of 6.6 years for hospitalizations related to sepsis and/or severe sepsis. Hospitalizations for community-acquired sepsis identified by administrative data were further validated by chart review. The authors then derived risk prediction tools separately for both community-acquired sepsis and

severe sepsis. The final risk prediction tool for sepsis included 13 clinical variables and 4 biomarkers used to separate sepsis risk into 5 categories ranging from very low (2.3 events/1,000 person years) to very high risk (21.1 events/1,000 person years). The authors also derived a prediction tool for severe sepsis that included the same variables, with both models demonstrated good discrimination and calibration. The most influential factors in the prediction models were chronic lung disease, age ≥ 75 years, peripheral artery disease, and elevations in the biomarkers Cystatin-C, C-reactive protein, and albumin-to-creatinine ratio.

Prior studies have identified individual baseline risk factors for infection and sepsis, including chronic diseases, age, sex, race, and individual genetic background (2, 11, 12). Additionally, therapies are used in select populations to prevent sepsis, such as immunizations for certain infections or antibiotics for neutropenic fever in patients undergoing chemotherapy. Wang and colleagues' approach is novel by estimating the annual risk of sepsis and severe sepsis in outpatients with an ultimate goal to use this information to prevent sepsis in a broad population (9). The authors present a compelling argument suggesting that future research should focus on reducing the long-term likelihood of sepsis, similar to the paradigm shift from acute treatment in favor of myocardial infarction and stroke prevention. The study they conducted is the first step towards achieving this goal by providing a tool to estimate long-term sepsis risk and identify those at highest risk using easily available clinical variables and easily measured biomarkers of renal function and inflammation.

There are several limitations to the sepsis risk prediction scores derived from the REGARDS cohort, most importantly, the use of a patient cohort designed to study stroke risk rather than sepsis risk. The initial design of REGARDS resulted in the absence of some clinical variables and biomarkers that may be important in estimating sepsis risk (e.g. liver disease and biomarkers of endothelial dysfunction) and if included may have improved the predictive ability of the sepsis risk prediction score. However, subjects enrolled in the large REGARDS population cohort had extensive clinical information collected regarding a number of chronic conditions relevant to sepsis, as well as biomarkers hypothesized to be associated with sepsis risk. The authors also used a validated approach to identify sepsis hospitalizations with the added step of reviewing medical records to ensure correct classification of the sepsis diagnosis.

Once validated and refined, the sepsis and severe sepsis risk prediction scores have several possible utilities. First, information provided by a risk prediction tool would offer an estimated long-term risk of sepsis for individual patients, potentially allowing for earlier interventions at the first signs of infection in those at highest risk. Second, the sepsis prediction score identified several potentially modifiable risk factors for sepsis hospitalization. Future research may identify modifications that could lead to reduced sepsis incidence. Third, the sepsis risk prediction score could be used to identify a significant number of outpatients at highest risk for sepsis hospitalization for enrollment in future clinical trials or for mechanistic studies of how chronic risk factors alter sepsis risk. For example, observational studies have demonstrated an association of long-term statin use and reduced sepsis mortality, possibly secondary to the immunomodulatory effects of statins (13, 14). The sepsis risk prediction score may identify an ideal population to enroll in a clinical

trial of statins for the primary prevention of sepsis. Future research should first focus on validating the sepsis risk prediction tool in independent population cohorts as well as refining the tool with the addition of other clinical risk factors and potentially additional biomarkers or genetic factors. The ultimate goal will be to develop targeted therapies aimed at patients identified by a prediction tool to be at highest risk. In other words, changing from predicting to preventing the future.

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