Commentary

Understanding the sepsis mortality belt: time to buckle down!

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Despite a documented decrease in sepsis-associated mortality in the developed world over the past decade, sepsis remains a major public health problem that claims more than 200,000 deaths each year in the United States (US) alone (1,2). The ongoing challenge to understand the complex biological mechanisms underlying susceptibility to infection and organ dysfunction and its associated mortality is complemented by the persistent need for high-quality clinical epidemiology studies that provide investigators and health-policy makers with updated data about disease patterns.

In their recent study (3) published in *Critical Care Medicine*, Moore *et al.* attempted to understand regional disparities in sepsis by identifying US counties with high sepsis mortality and characterizing associated community-level factors. They analyzed county-level sepsis mortality data from 2003 until 2012 obtained from the National Center for Health Statistics and linked these data to community characteristics and demographic data from the American Community Survey (ACS) for the years 2006–2010. They then combined three separate analytic spatial clustering methods and identified 161 (of 3,108; 5.2%) strongly clustered counties that had disproportionally high age-adjusted sepsis mortality rates. These counties were clustered in the southeastern US within three main regions: Central Appalachia, Middle Georgia, and Mississippi Valley. Strongly clustered counties had the largest proportions of older adults and black people, whereas non-clustered counties had the largest Hispanic population. In addition, on average, people living in strongly clustered counties were socioeconomically disadvantaged based on median numbers of household income, housing value, level of education, unemployment and medical insurance.

Regional variation in sepsis mortality has been previously reported. In 2010, Wang *et al.* reported widely varying sepsis mortality at the state level, analyzing mortality data from the US National Center of Health Statistics (NCHS) (4). He identified a sepsis mortality "belt" of 11 adjacent states in the Southeastern and mid-Atlantic US with a 30% higher sepsis mortality incident rate ratio compared with non-belt regions. The current study represents a significant advancement compared to this earlier study by (I) disaggregating the analysis unit to the county level, (II) associating sepsis mortality rates with demographic and community-level data and (III) utilizing geospatial autocorrelation methods to define highly clustered sepsis mortality counties, thereby making results more tangible for health policy decision makers.

One of the most famous examples for regional disease variation is the so-called "stroke belt", a region in the Southeastern US with excess stroke mortality first described more than 50 years ago (5,6). Recent research suggests that the increased stroke mortality in this region is due to higher stroke prevalence (not case fatality), and that currently well-established risk factors such as hypertension, diabetes, coronary artery disease as well as lower socioeconomic status explain 75% of the excess stroke incidence (7). We and others have previously reported higher infection and organ dysfunction rates in black patients after adjusting for differences in co-morbid conditions (e.g., chronic kidney disease and diabetes) and socioeconomic status (ZIP code level income) (8). It is therefore not too surprising that some of these factors were associated with higher sepsis mortality in the current study. While available administrative datasets capture many of these variables and may be sufficient to identify areas with unusual disease patterns, more granular data will be necessary to understand the underlying mechanisms. For instance, sepsis mortality

is a product of both sepsis incidence and case fatality. We can only speculate whether the excess sepsis mortality in clustered counties was due to higher incidence of sepsis, higher case-fatality rate, or a combination of both. Second, patient-level microbiologic data and local antibiotic resistance patterns could help to understand whether certain types of particularly virulent infections are contributing to excess sepsis mortality in certain communities. Third and more likely, however, some of the excess mortality in certain regions may be due to residual confounding, which could be partly resolved with more granular patient-level data. For instance, a sharp increase in hepatitis C infections in central Appalachia during the past decade has been linked to the region's epidemic of prescription opioid abuse and injection drug use (9). Drug users have a higher prevalence of blood-borne pathogens, sexually transmitted diseases, tuberculosis, soft tissue infections and endocarditis, all of which may predispose to higher sepsis incidence and mortality. Thus additional person-level data about health behaviors may be necessary to reduce residual confounding, particularly when trying to understand infection susceptibility in certain communities. Last, the number of physicians or hospital beds per capita likely does not adequately capture the actual care provided. Particularly socioeconomically disadvantaged patients may not have sufficient access to high quality health care in their community and only present to the hospital late in the course with higher severity of illness. In addition, over the past decade many small hospitals in rural regions have downsized their number of critical care beds (10), which may be an additional barrier to high quality care access.

In summary, Moore *et al.* extend their group's previous work on regional variation in sepsis mortality by identifying counties in three distinct areas with highly clustered mortality. Only by generating more granular data at the patient-level will we be able to identify modifiable risk factors and design interventions to further reduce the incidence and mortality of sepsis.

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Footnote

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