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Severity and Timing of Onset Drives Economic Costs and Clinical Outcomes with Sepsis

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This newest paper by Paoli, et al., (1) “Epidemiology and Costs of Sepsis in the US: An Analysis Based on Timing of Diagnosis and Severity Level” adds to the body of literature on sepsis epidemiology using the increasingly available pool of large clinical and administrative databases to characterize the financial burden of sepsis in the United States. This particular study uses data from Premier, a US healthcare improvement company that provides analytics and other services to its hospital alliance members (2). The 2010–2016 data in this study represent an approximately 20% non-random sample of US hospitalizations, capturing >2.5 million sepsis hospitalizations using a combination of ICD-9-CM, ICD-10, and Diagnosis-Related Group (DRG) case-finding definitions. These recent data demonstrate important, recurrent themes in sepsis epidemiology: sepsis disproportionately affects older adults (mean age 65 years); sepsis is predominantly community-acquired (87%), sepsis is expensive (mean hospital costs \$21,500), and sepsis is associated with high hospital mortality (1 in 8 patients) and high rates of 30-day readmission for survivors (1 in 8 patients). Importantly, there are two axes along which the investigators add novel information to the field of sepsis epidemiology: comparisons of *aggregate* costs by sepsis severity and comparisons of sepsis outcomes and resource utilization by *present on admission* (POA) status.

The investigators analyze their data by sepsis severity, utilizing administrative coding that is consistent with the sepsis, severe sepsis, and septic shock classifications in existence before sepsis-3 (3). The finding that increasing sepsis severity is associated with increasingly worse outcomes and higher costs is intuitively correct and a check on internal validity, and is expanded with provocative assertions regarding the societal burden of sepsis under its earlier clinical definitions. While sepsis without organ dysfunction was associated with shorter length of stay, lower costs, and lower hospital mortality than more severe forms of sepsis,

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given that it accounted for 55% of the sepsis cases, it accounted for the highest aggregated cost and hospital bed utilization. This highlights an important aspect of the evolution to the sepsis-3 definition where sepsis requires organ dysfunction and less ill patients are simply 'infected,' and in the process altering the epidemiologic estimates of "sepsis" and challenging epidemiologists, providers and policy-makers to translate across the definitional, clinical and administrative categorizations.

Before delving into the analyses of sepsis by POA status, background on the creation of POA indicators is important. These indicators arose from the 2005 Deficit Reduction Act, which called for the ongoing identification of conditions that are "high cost or high volume or both, result in the assignment of a case to a Diagnosis-Related Group that has a higher payment when present as a secondary diagnosis, and could reasonably have been prevented through the application of evidence-based guidelines" (4). The intent of the regulation was to encourage hospitals to avoid these conditions by not reimbursing for hospital-acquired (i.e. not POA) conditions that may have been preventable. Since its operationalization in 2008, the Centers for Medicare & Medicaid Services (CMS) has not paid hospitals for the costs associated with these conditions when they are included among the secondary diagnoses of the discharge record without a POA designation. CMS requires hospitals to record POA indicators on all hospital discharge diagnoses, and while sepsis is not explicitly on this list, six of the fourteen categories of hospital-acquired conditions are related to sepsis, such as catheter-associated urinary tract infections, vascular catheter-associated infections, and surgical site infections (5). An important caveat to the POA system acknowledged by the authors is that POA sepsis may include community-acquired and healthcare-associated sepsis identified at admission, whereas not POA sepsis may include hospital-acquired sepsis as well as any other sepsis case that was not recognized at the time of admission. In 2015, an article in this journal laid the foundation for deconstructing the POA groups with respect to sepsis. That study utilized the 2012 University HealthSystem Consortium data of >3.3 million discharges, demonstrating that sepsis cases were 63% community-acquired, 26% healthcare-associated (combined 89% POA), and 11% hospital-acquired, with the last group being defined by infection not POA (6). These results are consistent with Paoli's findings of 87% of sepsis being POA, which likely reflects a mixture of community-acquired and healthcare-associated sepsis. Additionally, Paoli's supposition that the not POA status represents a delayed sepsis diagnosis remains speculative as this analysis cannot distinguish later onset hospital-acquired sepsis from sepsis that was POA but for which the diagnosis was not evident at admission.

Moving beyond the nuances of the terminology, the investigators report provocative differences between sepsis POA and sepsis not POA. Sepsis not POA was associated with: a 2-fold higher hospital mortality (26% vs. 11%), a lower rate of discharge to home among survivors (47% vs. 63%), longer stays in the ICU (10.1 days vs. 5.2 days), and higher average hospital costs (\$51,000 vs. \$18,000). In interpreting these comparisons, bear in mind the issues of severity of illness adjustment and reverse causality. In regard to the first issue, these estimates are not adjusted for the underlying severity of illness of the patients and the data demonstrate that sepsis not POA patient had higher prevalence of comorbidities, notably congestive heart failure, chronic kidney disease, atrial fibrillation, and active cancer. Therefore it may be possible that the worse outcomes and higher resource utilization of the

sepsis not POA group are in part due to residual confounding of the increase severity of underlying illness of these patients. Reverse causality refers to the interpreted direction of causal connections, in this case between POA status and increased resource utilization. One possible interpretation of the association is that in comparison to sepsis POA, sepsis not POA leads to increases in ICU and hospital lengths of stay and resultant costs. Conversely, an alternative explanation of the observed associations is that increased stays in the hospital and/or ICU lead to hospital-acquired sepsis. From one point of view, to be concerned with which interpretation is correct may be purely academic. The large magnitude of the differences between sepsis POA and sepsis not POA are sufficient to consider sepsis not POA as a distinct and major problem. Furthermore, when contemplating potential sepsis prevention strategies, even though sepsis not POA represents a minority of sepsis cases, it potentially represents those cases that are most amenable to developing such strategies given the accessibility of this at-risk population during the risk period (7).

In conclusion, this manuscript makes two important points utilizing opposite constructs to make arguments for the public health importance of sepsis. On one hand the authors conclude that severe infections (*sepsis* by the original definition, called “*sepsis without organ dysfunction*” in this publication) represents a dominant burden to society despite its lower risk and burden to the individual due to its high prevalence in relation to other more severe forms of sepsis. Conversely, the authors point out that sepsis POA presents a large burden despite its lower prevalence when compared to sepsis not POA, due to its markedly worse outcomes and higher resource utilization. These considerations are most relevant to those making policy and hospital-administration decisions. In this regard the Centers for Disease Control and Prevention (CDC), the National Hospital Safety Network, and CMS continue to effect policies directed to the prevention of community- and hospital-acquired infections that precede all forms of sepsis (8). Emerging research questions remain as to what community- and systems-based interventions may further disrupt the continuum from infection to sepsis.

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