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Trends in Mortality and Early Central Line Placement in Septic Shock: True, True, and Related?

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Each year, millions of people around the world are diagnosed with severe sepsis and septic shock^{1,2}. Approximately one-third of individuals hospitalized with severe sepsis will die during their hospital stay¹, while those who survive acquire new disabilities and experience increased mortality for many years following the resolution of their acute illness^{3,4}. Until recently, decades of research efforts failed to identify new therapies that significantly improved mortality from this disease. However, the early 2000s witnessed important expansions in the evidence for sepsis treatment. In 2001, Rivers et al. demonstrated that early (within 6 hours) resuscitation targeted to physiologic end-points measured with a central venous catheter (CVC) provided a mortality benefit over usual care⁵. This approach, termed early goal-directed therapy, was subsequently incorporated into the clinical practice guidelines developed by the Surviving Sepsis Campaign (SSC)—a multi-society educational and quality-improvement initiative to reduce mortality from sepsis⁶. Although these guidelines have undergone several revisions since 2004, early goal-directed therapy remains a central feature of the bundle of interventions recommended during the first 6-hours of sepsis resuscitation^{6,7}.

Around the world, hospitals that adhere to SSC guidelines achieve lower case fatality rates for sepsis^{8,9}. For example, upon implementing the SSC guidelines in 21% of ICUs in Spain, investigators observed a 4% absolute reduction in mortality from severe sepsis, despite fairly low attainment of bundle targets that waned with time⁸. A more recent study of hospitals across three continents that voluntarily participated in the SSC reported a similar reduction in mortality⁹. While SSC's impact on sepsis mortality among participating hospitals is

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evident, it is unclear how well these guidelines have penetrated the standard practice patterns of US physicians within non-SSC hospitals.

In this issue of *Critical Care Medicine*, Walkey and colleagues seek to define the relationship between trends in mortality from septic shock and implementation of SSC guidelines¹⁰. The authors examine the Nationwide Inpatient Sample (NIS) in the years surrounding publication of the Rivers trial and the SSC guidelines to determine temporal trends in septic shock mortality in the US. Because NIS does not include data on early goal-directed therapy or SSC guideline adherence, the authors instead use an indirect measure of adherence: placement of a CVC early in the course of septic shock. They then compare in-hospital mortality associated with early (day 0) CVC placement versus no or late (after day 0) CVC placement. They determined that, from 1998 to 2009, early CVC placement in septic shock tripled, albeit only to 19%. Over the same time frame, in-hospital mortality decreased from 40% to 31%, with greater rates of decline observed in patients who received an early CVC. Joinpoint regression, an empirical method for analyzing changes in trends over time, identified 2004 — the year the SSC endorsed early goal-directed therapy — as the time point where mortality began to decrease more rapidly. Taken together, these results suggest US physicians have increasingly observed evidence-based guidelines that recommend early CVC placement for physiologic monitoring in septic shock, and this adherence to guidelines has been associated with a decrease in mortality.

While the results of Walkey and colleagues are intriguing, it is difficult to invoke causal relationships between the publication of the Rivers trial and SSC guidelines, early CVC placement, and decreased mortality from septic shock. Due to the resolution of procedural data available in the NIS, it is impossible to determine whether CVC placement occurred within 6 hours of the onset of septic shock. In fact, many patients may have developed sepsis long after a CVC was placed for another reason. Although present on admission codes in an alternative database from California suggested that sepsis is the true admitting diagnosis for patients similar to those identified in the current study, the validity of these codes in the NIS and in sepsis more broadly, and the exact timing of shock remain unknown. Finally, early goal-directed therapy is only one of several interventions included in the SSC guidelines, such as early appropriate antibiotic administration and lung-protective ventilation, which were recognized to be important around the same time period, and may confer a similar mortality benefit. As investigators have noted previously, it is difficult to isolate the impact of any single intervention within the SSC 6-hours bundle on overall outcome⁹.

Even though the associations observed in the study by Walkey and colleagues are not causal, the study still provides important insights into the care of patients with septic shock. First, mortality associated with septic shock is declining. While shifts in coding practice undoubtedly contribute to such reductions in mortality, an equally plausible contributor includes better translation of evidence into practice¹¹. Second, the 19% rate of early CVC placement observed in this study is disappointingly low. Potential explanations for this include the modest sensitivity of ICD-9-CM coding for CVC placement, ambiguity in the timing of CVC placement relative to shock onset, presence of contraindications to CVC placement in certain patients, and the possibility that some patients improved with initial

fluid administration making CVC placement less crucial. Despite these possibilities, however, the rate of early CVC placement is likely far less than what would be considered ideal for goal-directed treatment of septic shock.

When looking to the future, the present study serves as an important reminder that, despite improvements over the past decade, there is still substantial morbidity associated with septic shock and a need to further improve early resuscitation practices. Optimistically, if we assume the relationship between early CVC placement and mortality is causal, it is promising that such a modest absolute increase in early CVC placement altered mortality. This suggests that educational initiatives to further enhance adherence to SSC guidelines will likely translate into additional improvements in survival.

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