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The Lingering Consequences of Sepsis
A Hidden Public Health Disaster?

Derek C. Angus, MD, MPH

Sepsis, the syndrome of infection complicated by vital organ dysfunction, is a medical emergency that affects more than 750,000 patients in the United States each year and remains one of the world’s leading causes of death. Without prompt resuscitation, antibiotics, and institution of life support, patients can quickly develop shock, multisystem organ failure, and death. It is not surprising, therefore, that the main goal of care and of research has been to reduce short-term mortality. Assuming a patient survives the initial insult, traditional medical wisdom holds that the crisis has been averted and the patient should do well. However, this conventional thinking is being seriously challenged.

In 1997, Quartin et al reported that sepsis survivors had double the risk of death in the following 5 years compared with hospitalized controls. Elderly patients and those with underlying disease have a higher risk of sepsis, and thus it seemed possible that this late increased mortality was unrelated to the sepsis episode but rather due to poor preexisting health condition. However, later studies that attempted more rigorous adjustment for preexisting conditions similarly found that survivors of sepsis had a long-term increased risk of death. Other studies reported that sepsis survivors, and survivors of other related conditions, such as the acute respiratory distress syndrome, often developed physical, cognitive, and affective problems in the months and years after discharge. There was no clear mechanism to explain these findings, which were broad and often nonspecific, and all these studies only initiated follow-up after the onset of the critical illness. Prospectively measured, detailed knowledge of function and health before the acute sepsis event was lacking, and thus the argument that underlying health status was the cause of subsequent decline could not be ruled out.

In this issue of JAMA, Iwashyna and colleagues report the results of their study examining whether sepsis is associated with an increased risk of physical and cognitive impairment. To circumvent problems of prior studies, the investigators studied individuals in the Health and Retirement Study, a long-running cohort study of more than 27,000 older Americans, for whom they had detailed information on physical and neurocognitive function both before and after an episode of sepsis. The authors identified sepsis by screening all hospitalizations between 1998 and 2005 in the subset of participants for whom Medicare claims data were available. The diagnosis of sepsis is not easy to establish, especially using claims data. The authors used an existing diagnostic scheme that others have applied; this approach is by no means perfect, but it identifies patients similar to those detected by prospectively trained clinical study coordinators.

Once the patients were identified, Iwashyna et al constructed models to predict how an individual patient’s physical and cognitive function was affected by sepsis. This question is not trivial, and the answer could depend on the domain of physical or cognitive function measured, as well as whether the primary interest was in the magnitude or duration of any effect, in the absolute effect of sepsis, or simply in the marginal effect compared with the effect of hospitalizations in general. The authors approached the problem in several different ways and found consistent results: following sepsis, there was a significant increase in the odds of both physical and cognitive dysfunction that persisted throughout the 8-year follow-up. The new deficits were relatively more severe among patients who were in better health beforehand, possibly because there was less room for further deterioration among patients who already had poor physical or cognitive function prior to the sepsis episode. The magnitude of these findings was striking. For example, moderate to severe cognitive impairment increased 3-fold, from 6.1% before sepsis to 16.7% afterward. Extrapolating from national data, the authors estimated that sepsis may contribute to 20,000 new cases of moderate or severe cognitive impairment in the United States each year.

There are, however, important caveats. As with previous studies, the study design was observational—patients cannot be randomized to a bout of sepsis, and thus the inference is one of association, not causality. Furthermore, the exposure was a hospitalization during which sepsis occurred. Although patients who developed sepsis fared far
worse than patients hospitalized generally, the authors cannot determine whether sepsis was the primary reason for subsequent deterioration, or whether the outcomes were due to other aspects of the patient’s health or care precipitating or during the hospitalization in which sepsis occurred. In addition, the sample was relatively large but not large enough to explore, for example, whether the magnitude of the findings varied according to site and etiology of infection, magnitude of acute organ dysfunction, duration of intensive care unit (ICU) care, or use of different interventions. Moreover, patients who died before their postsepsis interview did not contribute to the analysis. These patients were probably more likely than those who survived to have dysfunction. Thus, their exclusion probably leads to an underestimate of the effects of sepsis on postdischarge outcomes. Finally, the study does not permit any interrogation of potential mechanisms to explain why sepsis would impair physical and cognitive function.

As the authors point out, there are a number of plausible explanations for their findings. Intensive care unit–acquired weakness, a constellation of myopathic and neuromyopathic syndromes, is well-described in sepsis and is thought to be due in part to muscle and nerve injury from inflammation, ischemia, and ischemia-reperfusion, pathways all implicated in the pathogenesis of sepsis. Myopathy is further exacerbated by prolonged immobilization and use of certain drugs common in sepsis, such as corticosteroids and neuromuscular blockers. The brain is also susceptible to direct damage from inflammation, ischemia, and ischemia-reperfusion. Encephalopathy and delirium are both commonly described during the ICU care of patients with sepsis and are risk factors for dementia. Inflammation may also be a direct cause of dementia. In addition, many drugs used in the care of patients with sepsis and organ dysfunction potentially interfere with neurotransmitter and receptor pathways implicated in the development of neurocognitive impairment in other conditions such as schizophrenia and dementia.

So, what are the important implications of the study by Iwashyna et al? First, the information in this study can help physicians when assessing care options and discussing outcomes with patients and families. Even if clinicians do not know why patients who develop sepsis experience a decline in function, it is clear that many patients do. Second, the development of preclinical models could help establish a better understanding of causality, potential mechanisms, and therapeutic targets. Current models of sepsis only crudely mimic sepsis in the modern ICU and rarely afford an assessment of long-term outcomes among survivors. Third, a number of relatively simple strategies used in other areas of medicine to promote physical rehabilitation and minimize the effects of neurocognitive dysfunction might be adaptable to the ICU and post-ICU setting and ought to be evaluated in clinical trials. Fourth, the traditional end point of day 28 all-cause mortality used in the evaluation of any therapy for sepsis should be replaced by longer-term survival data and functional outcomes. Assessing detailed physical and cognitive function is challenging and costly in the multicenter trial environment. However, the larger cost may be from failure to measure these outcomes and miss important benefits or harms of therapies on the lingering consequences of sepsis.

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