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Who Owns Sepsis?

Michael Klompas, MD, MPH; Tiffany M. Osborn, MD, MPH; and Chanu Rhee, MD, MPH

To their great credit, critical care physicians founded the Surviving Sepsis Campaign, promulgated the Surviving Sepsis Campaign guidelines (for which 2 of us are committee members), popularized the principles of early recognition and bundled care, and spearheaded the latest overhaul of sepsis definitions. There is much to acknowledge and celebrate in critical care's leadership of sepsis. One underappreciated consequence, however, is that the critical care perspective, borne of their experiences treating the sickest subset of patients, dominates the popular conception of sepsis.

The common perception is that sepsis is always a dire emergency: Patients present in extremis, and failure to treat immediately and aggressively may lead to imminent death. Under this rubric, it is easy to understand the push for 1-hour treatment bundles, mandatory reporting legislation, and a philosophy of "treat first, ask questions later." This perspective makes sense for critically ill patients with septic shock. But only about 15% of patients with sepsis have septic shock, and fewer than half require admission to an intensive care unit (ICU) (1, 2). Indeed, up to 20% of patients diagnosed with sepsis in emergency departments are well enough to be sent home (2). Strategies that are appropriate for critically ill patients may not be appropriate for more stable patients.

Critical care's influence on how we view sepsis plays out in 3 realms: definitions, diagnosis, and management. The Sepsis-3 Task Force defined sepsis as a dysregulated host response to infection leading to life-threatening organ dysfunction, and suggested operationalizing the definition as suspected infection plus an increase in Sequential Organ Failure Assessment score of 2 or more points. The dominant critique has been that this definition is overly focused on the sickest subset of patients and misses those with "early sepsis" who have not yet developed organ dysfunction (3). Failure to rapidly identify these patients might diminish opportunities for early diagnostics and targeted interventions that could avert organ failure. Separately, sepsis encompasses a heterogeneous set of conditions that differ widely in anatomical location, likelihood of true infection, microbial cause, type of organ dysfunction, severity of illness, and prognosis. Applying a single term to all phenotypes that always connotes critical illness encourages providers to treat all patients in a homogeneous and aggressive fashion rather than customizing care to each patient's syndrome and severity of illness.

The second major area in which the critical care perspective may not be optimal for less sick patients is diagnosis. Sepsis is difficult to diagnose because many noninfectious syndromes mimic it. In contrast to myocardial infarction and stroke, there is no definitive test. Even when patients are clearly infected, it is often unclear whether the cause is viral or bacterial or whether infection is causing organ dysfunction. Organ dysfunction can also be caused by noninfectious exacerbations of chronic diseases, hypovolemia, fluid overload, drugs, medications, infarction, or cancer. Fewer than two thirds of patients initially diagnosed with sepsis are confirmed to have definite or even probable infections (4). Some intensivists may not fully appreciate the challenge frontline providers face trying to identify the sepsis needle in the haystack because their patients have already been selected for critical illness and they get the benefit of hearing frontline providers' initial impressions, seeing early test results, and observing how patients responded to pre-ICU interventions.

Diagnostic uncertainty has major implications for management. Many providers have internalized the message that any delay in antibiotics leads to poor outcomes. However, the literature on time to antibiotics is nuanced. Some studies found associations between delays in antibiotics and increased mortality, but others did not (5). Some report associations, but only for delays of days rather than hours (6). Most of the studies that found associations between hours-long delays in antibiotics and mortality were restricted to critically ill patients, most of whom had septic shock (typically defined as persistent or recurrent hypotension despite adequate fluid resuscitation) (7, 8). Studies large enough to stratify by sepsis with versus without shock found much stronger associations between time to antibiotics and death for sepsis with shock versus without shock (9, 10).

Rapidly treating all patients with broad-spectrum antibiotics makes sense for possible septic shock, where there is no room for error. The calculus is different, however, for normotensive, clinically stable patients outside the ICU given the high rate of sepsis misdiagnosis and the possible harms associated with antibiotics. In these patients, it makes more sense to increase diagnostic certainty before administering antibiotics, whether through directed testing; imaging; observation; or therapeutic trials for noninfectious conditions, such as pain control, heart rate control, fluids, diuretics, bronchodilators, or vasodilators. Of course, if there is convincing evidence of infection, there is no reason to delay antibiotics regardless of illness severity, and if patients are rapidly deteriorating, they should be treated immediately even if infection is uncertain.

Many of the controversies in sepsis diagnosis and management may stem from our inability to perfectly operationalize the conceptual definition of sepsis (we cannot always identify which patients are infected and when organ dysfunction is caused by a dysregulated host response to infection), but we cannot ignore the

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unintended consequences of our diagnostic limitations, namely the risk for overtreating patients who are not infected and those whose infections could be managed more parsimoniously.

We believe the time has come to bring more balance to sepsis. Other time-critical diagnoses have evolved triaging systems to inform the urgency and intensity of therapy. Not every patient with chest pain is automatically referred for cardiac catheterization, and not every trauma patient is rushed to surgery. We see sepsis evolving similarly, where potentially infected patients with worrisome signs or comorbidities, such as hypotension, altered mental status, or immunosuppression, are managed with one level of urgency and intensity and less severely ill patients are managed with another.

We further suggest broadening the breadth of providers responsible for sepsis definitions and guidelines. More than 50 of the 59 authors of the 2016 Surviving Sepsis Campaign guidelines were critical care practitioners. However, more than 85% of sepsis cases are first identified and managed outside ICUs. The Surviving Sepsis Campaign should include more emergency providers, hospitalists, primary care physicians, nurses, rehabilitation specialists, and infectious disease physicians. Clinicians who understand the unique challenges of practicing outside the ICU need to have a strong voice in guiding recommendations for these areas while critical care providers continue to lead recommendations for patients who require intensive care. A related suggestion is to encourage guidelines and treatment mandates to address antibiotic management of sepsis and septic shock separately in order to allow clinicians more room to tailor their approaches to patients' severity of illness. We should also encourage more research specifically on the epidemiology, diagnosis, and treatment of sepsis outside the ICU.

The critical care community has done exceptional work in improving sepsis care. We believe the next step is to better address the full spectrum of illness encompassed by sepsis. Expanding the circle of stakeholders will help bring more awareness and balance to the plurality of patients with sepsis who are diagnosed and treated outside the ICU.

From Harvard Medical School, Harvard Pilgrim Health Care Institute, and Brigham and Women's Hospital, Boston, Massachusetts (M.K., C.R.); and Washington University, St. Louis, Missouri (T.M.O.).

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Corresponding Author: Michael Klompas, MD, MPH, Department of Population Medicine, Harvard Medical School & Harvard Pilgrim Health Care Institute, 401 Park Drive, Suite 401 East, Boston, MA 02215; e-mail, mklompas@bwh.harvard.edu.

Current author addresses and author contributions are available at Annals.org.

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