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The Medical Perspective on a Disease Life Cycle Sepsis in the Realm of Implementation Science

In *The Prince*, Niccolo Machiavelli presciently described two important aspects of sepsis. In the first of these, Machiavelli wrote: “Hectic fever, at its inception, is difficult to recognize but easy to treat; left unattended it becomes easy to recognize and difficult to treat” (1). This eloquently captures several key aspects of how we consider sepsis today: early recognition is difficult, early treatment is most effective, untreated sepsis progresses over time, and late sepsis is exceptionally difficult to treat. In the modern sepsis era, the earliest (2) and current sepsis definitions (3) facilitated discoveries in pathogenesis (4) and epidemiology (5). Altogether, these efforts have characterized sepsis as occurring more than

1,700,000 times and causing 270,000 deaths each year in the United States (6), being present in 6% of adult hospitalizations and contributing to 33–50% of all hospital deaths (7), counting as the third leading cause of death in the United States, and globally causing more than 30 million cases and 6 million deaths, potentially making it possibly the leading cause of death in the developing world (8).

From a medical perspective, the life cycle of biological diseases begins with clinical discovery; discovery of a new condition leads to efforts to diagnose clinical cases and ascertain the causal and associative characteristics of the disease, describe its occurrence, and identify treatments. For HIV, the earliest clinical cases were soon followed by a basic understanding of disease pathogenesis (retrovirus infection) and a biomarker (CD4 T cells) (9). There are parallels with sepsis: making a diagnosis, pursuing biomarkers, understanding disease pathogenesis, characterizing epidemiology and public health, identifying therapies, and ultimately focusing on

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prevention. To optimize clinical care, the medical life cycle relies on implementation science: the study of methods that influence integration and adoption of research findings and evidence into sustained healthcare practice and policy.

In this issue of the *Journal*, Levy and colleagues (pp. 1406–1412) (10) showcase implementation science for facilitating high-quality healthcare through the New York State Department of Health sepsis initiative by presenting the process and outcome public reporting from the first 2 years of the New York State Department of Health sepsis initiative (11). In 183 hospitals from 2014 to 2016, there were 91,357 sepsis hospitalizations, of which 48% were septic shock. Protocol initiation was most common in the emergency department (80%) and increased over the course of 2 years from 74% to 86%, with similar increases in protocol compliance. Among patients for which the protocol was initiated, the risk of dying declined over time, and hospital performance with the quality initiative was associated with reduced hospital length of stay.

Although these results are robust across multiple indicators, the primary limitation is that the findings are strictly association, and may not indicate causation of the observed patient benefits. It is impossible to know whether the effect is a “wave” of protocol efficacy or a “rising tide” of general quality improvement effectively lifting all boats. Alternatively, this could represent the Will Rogers phenomenon (12), with less ill patients progressively identified over time to improve outcomes. The results are additionally confounded by the national early sepsis management bundle (SEP-1) from CMS in mid-2015, and by the heterogeneity in sepsis protocols, screening, activation, and compliance.

The implications of this work are myriad. For patients, public reporting of hospital quality permits informed healthcare consumers. For providers, this report identifies processes for effective sepsis care. For hospitals and health systems, it demonstrates effectiveness and expectations for net benefits and discounts concerns that mandatory sepsis protocols may foster mediocrity at the expense of excellence. And for public health and policy makers, it glimpses the effects of public reporting on sepsis care (13). However, implementation science is particularly challenging for sepsis, where reliability requires workflow coordination and addressing operational failures and interruptions that obstruct task completion amid fluctuating patient trajectories (14).

The second sepsis description from Machiavelli foretells the effects of promulgating protocols and public reporting in sepsis care: “For he who innovates will have for his enemies all those who are well off under the existing order of things, and only lukewarm supporters in those who might be better off under the new” (1). Despite this warning, these results use implementation science to advance the medical life cycle for sepsis and set the stage for targeting sepsis prevention (15). ■

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