The Search for Effective Therapy for Sepsis
Back to the Drawing Board?

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NEW THERAPEUTIC APPROACHES FOR SEPSIS HAVE NOT fared well recently. In January, Eisai announced that its worldwide phase 3 randomized trial of a novel anti–Toll-like receptor (TLR)-4 compound, eritoran tetrasodium, had failed to demonstrate an improvement in the primary end point of 28-day all-cause mortality in a cohort of 2000 patients with severe sepsis.[1] This news was disappointing, especially because the manipulation of TLR4 signaling would represent a new avenue of research and drug development. Perhaps ironically, only a few months later, the importance of TLR4 signaling was recognized with the award of the Nobel Prize in Physiology or Medicine to Jules Hoffmann and Bruce Beutler for their work in this area.[2]

In October, Eli Lilly announced it was withdrawing Xigris (drotrecogin alfa, a recombinant activated protein C) from the market following the failure of its worldwide trial, PROWESS Shock, to demonstrate improved outcome.[3] Drotrecogin alfa, the only approved drug specifically indicated for the treatment of severe sepsis, had been approved on the basis of an earlier trial, PROWESS, which had demonstrated a large improvement in survival.[4] That the findings were not confirmed by the subsequent trial was another major disappointment.

So what now? At a minimum, researchers and clinicians need to rethink the therapeutic approach to sepsis. Some obvious questions come to mind. First, is the current understanding of the pathophysiology of sepsis flawed in some important way? Second, is the current approach to the discovery and evaluation of potential therapies in need of overhaul? Third, assuming the answer is yes to either of these questions, where should researchers go next?

Sepsis is a broad term, with its roots in the writings of Hippocrates. At its heart is the concept of a patient fighting to survive a life-threatening infection. And it is the fight that is thought to be injurious. The invading pathogen can be directly toxic and destructive to tissue, but much of the pathology associated with sepsis is attributed to the host response. Host immune cells exposed to pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), rapidly produce a broad array of cytokines, chemokines, and other proteins to sequester and eradicate invading pathogens. However, these same proteins can profoundly disturb and harm host tissue function and anatomy, a form of "friendly fire."

These findings led to 2 central tenets of current sepsis research. First, the host response in sepsis is unhelpfully exuberant, and thus agents that block or suppress the host response should improve outcome. Second, the host response represents a "final common pathway," and thus agents that manipulate this pathway should work regardless of the source of infection. Neither tenet may be true. The host response does not appear to be ubiquitously overexuberant. Indeed, patients with similar signs and symptoms can have widely different cytokine profiles.[5] As noted in the report by Boomer et al in this issue of *JAMA*, the host response can be dramatically suppressed rather than overly exuberant.[6] Second, the discovery of PAMP-induced host response has helped highlight that host-pathogen interactions are much more sophisticated and nuanced than previously recognized.[7] In short, there may not be a "final common pathway."

Current preclinical experiments and clinical trials of potential therapies account only partially for these observations. Preclinical animal experiments may be too simplistic. The animals are usually young and have no comorbidity. In contrast, patients with sepsis are often older and have underlying comorbidity, both of which are strong predictors of sepsis susceptibility and outcome. The insult in animal models is typically LPS, cecal ligation and puncture, or instillation of live bacteria into the lung to induce pneumonia, but formal evaluation of differences in response across these different infectious challenges is not usually done. Antibiotics are often not given in animal models, and there is little or no supportive care for the ensuing organ dysfunction. The ideal host response to fight infection in the absence of antibiotics and life support may be very different from that required in a modern intensive care unit setting. It would also be helpful to evaluate how a drug works in an animal model in terms of the effect on the immune system

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and organ function, ideally using biomarkers and imaging studies that could be duplicated in later human studies.

The clinical research portfolio also has a number of serious limitations. Patient selection for enrollment in all phases of clinical trials is based on meeting criteria for severe sepsis, the syndrome of acute infection complicated by acute organ dysfunction.[8] Determining the presence of infection and infection-related organ dysfunction in a time-pressured setting, typically before the results of microbiologic cultures are available, involves arbitrary and necessarily subjective rules. Furthermore, the number of patients who meet these criteria is extremely large, and the underlying biology and clinical trajectory can vary considerably from patient to patient. The lack of explicit, reproducible criteria to enroll patients based on specific mechanisms of disease limits generalizability across trials and limits the ability to identify patients most likely to benefit from a specific therapy.

Ideally, phase 1 and phase 2 studies should help researchers validate preclinical findings, select optimal drug doses, and make smart decisions about when to proceed to the much larger phase 3 trials. There are several threats to these objectives in sepsis research. There is no common set of biomarkers to trace the effect of a drug on the purported mechanism of action in both preclinical and clinical studies. Pharmacokinetic studies focus on traditional biochemical metrics. Yet when the goal is to manipulate the host response, more sophisticated understanding of the immunomodulating effects of the drug, ideally in different tissue beds, would be much more insightful. In addition, phase 2 studies are usually underpowered to detect reasonable differences in mortality (or other patient-centered outcomes), and there are no well-accepted proxies. Consequently, investigators often fall into the trap of either overinterpreting nonsignificant differences in mortality or overrelying on a significant difference in an outcome of unknown significance. Reliable well-performing proxies for patient-centered outcomes are a "must-have" for sepsis.

Perhaps the most hand-wringing in sepsis has been over failed phase 3 trials. With more specific entry criteria and a more robust design, execution, and evaluation of the preclinical and early clinical research portfolio, future phase 3 trials may well enjoy greater success without any change to their intrinsic design. However, it may still be useful to consider some modifications. Researchers have often powered studies for absolute reductions in mortality of 6% or higher. With advances in care, sepsis mortality has declined to 20% to 25% in recent years.[9] Thus, especially when testing a highly specific agent that targets only one part of a complex host response, it would seem prudent to consider sample sizes capable of detecting smaller treatment effects. Of course, the need to enroll more patients will force researchers to recruit from more sites, increasing heterogeneity in care provided across sites. This heterogeneity is an advantage for generalizability, but it may be a threat to the goal of reproducing the phase 2 setting. Prospective involvement of a clinical coordinating center may help, but the role of such a center must be explicit and reproducible. Alternatively, greater recruitment rates from a smaller set of sites may be preferable.

Moreover, 28-day all-cause mortality, the typical primary end point of phase 3 sepsis trials, may not be the best measure of success. Many patients with sepsis are still hospitalized at day 28, and mounting evidence suggests that many late sequelae from sepsis are not captured by this end point.[10] Consideration of later end points that capture both mortality and physical, affective, and cognitive sequelae may be more patient-centered and perhaps even change the focus for drug development in sepsis. Indeed, an important shift for novel drug development in sepsis could be to abandon efforts to manipulate the early course of the host response. Modern emergency care and intensive care are excellent at keeping patients alive and controlling the initial infection, and many of the problems of sepsis research can be traced to making important time-pressured decisions in the knowledge vacuum that accompanies the early hours of sepsis. Perhaps researchers should turn to manipulation of the later response and recovery phases, starting therapy for patients with established acute organ dysfunction, based on specific immune and organ function characteristics, to promote earlier recovery with the goal of mitigating late morbidity and mortality.

Care of patients with sepsis has improved over the last decade. However, the recent failure of 2 promising drugs to further reduce mortality suggests that new approaches are needed. Perhaps it is time to go back to the drawing board.

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