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Getting sepsis therapy right:

Is decreasing inflammation or increasing the host immune response the better approach?

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Sepsis—a complication of infection—is a factor in at least a third of all hospital deaths—a sobering statistic. Patients with sepsis frequently present with fever, shock, and multiorgan failure. Because of this dramatic clinical scenario, investigators have generally assumed that sepsis mortality is due to unbridled inflammation (2). Research in animal models, in which administration of the cytokines tumor necrosis factor- α (TNF- α) and interleukin-1 (IL-1) reproduced many features of sepsis, supported that assertion. Yet, over 40 clinical trials of agents that block cytokines, pathogen recognition, or inflammation-signaling pathways have universally failed (3, 4). However, on page 1260 of this issue, Weber *et al.* (5) show that blocking a cytokine—specifically, IL-3—can indeed be protective against sepsis.

IL-3 is a pleiotropic cytokine that induces proliferation, differentiation, and enhanced function of a broad range of hemopoietic cells (blood cells derived from the bone marrow). Using a mouse abdominal sepsis model, Weber *et al.* identified IL-3 as a critical driving force of sepsis. The authors observed that the cytokine caused proliferation and mobilization of myeloid cells that generated excessive proinflammatory cytokines, thereby fueling systemic inflammation, organ injury, and death. Blocking IL-3 (by treating wild-type mice with an antibody that blocks the receptor for IL-3 or using IL-3-deficient mice) prevented sepsis-induced increases in the number of circulating neutrophils and inflammatory monocytes and decreased the amount of circulating inflammatory cytokines, thus ameliorating organ injury and improving survival. Additionally, the authors showed a correlation between mortality in septic patients and elevated blood IL-3 concentrations.

The findings of Weber *et al.* are mechanistically analogous to that of another study in which intravenous injection of mesenchymal stem cells (also known as bone marrow stromal cells) into a mouse model of sepsis led to reprogramming of immune cells toward a less inflammatory phenotype, thereby decreasing organ injury and mortality (6). In this scenario, mesenchymal stem cells released factors that reprogrammed monocytes and macrophages; the downstream effect was to prevent a damaging, unrestrained immune response. Thus, IL-3 blockade and mesenchymal stem cell-based therapy represent potential approaches for sepsis treatment because of their ability to broadly reshape early immune responses from a proinflammatory, damaging reaction to a more balanced and effective one.

However, a few cautionary caveats should be considered before adopting this approach. A phase II clinical trial of granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine that increases production, maturation, and function of monocytes, macrophages, and neutrophils, thereby mimicking selected properties of IL-3, was efficacious in treating sepsis and, indeed, a large multicenter trial of GM-CSF in sepsis is under way (7). This is contrary to the findings of Weber *et al.* that blocking IL-3 can ameliorate sepsis. Two other highly promising agents that are likely to enter clinical trials in sepsis are IL-7 (which promotes CD4⁺ and CD8⁺ T lymphocyte proliferation and maturation) and an antibody to programmed death–ligand 1 [(PD-L1), an immunosuppressive protein] (8, 9). Both IL-7 and anti-PD-L1 antibody are immunostimulatory agents that reverse key immunologic defects in lymphocytes and monocytes from septic patients *ex vivo* and are highly effective in multiple animal models of sepsis (9). Emerging evidence shows correlations between lymphopenia (decrease in lymphocytes) and impaired leukocyte functions with late mortality in patients with sepsis (8, 9). Thus, there is rationale for using approaches that selectively enhance antimicrobial immunity during sepsis.

“Which approach to sepsis... is correct? ...there are several clues...”

Which approach to sepsis—decreasing excessive inflammation versus boosting host immunity—is correct? The answer to this question is critical and there are several clues (see the figure). Immunologic status is highly dependent on the age and general health of the individual. Although young, previously healthy individuals acquire virulent infections, early inflammatory deaths are becoming less common in developed countries because of improved surveillance and advances in supportive care. In the United States, 75% of the deaths in sepsis occur in patients over the age of 65 (10). The immune system in the elderly is substantially impaired and renders them susceptible to infection. Patients with major comorbidities, including chronic renal and liver failure, also are immunosuppressed, rendering them more vulnerable to developing and dying from sepsis. Thus, the patient populations that represent the highest proportion of sepsis deaths are likely to require therapy that augments immunity. By contrast, the number of sepsis patients with overwhelming inflammation, who may benefit from therapies that reduce early hyper-release of proinflammatory cytokines (“cytokine storm”), is declining.

Another caveat affecting treatment selection is timing (11). Patients rapidly transition from the initial cytokine storm to a predominant immunosuppressed state as sepsis persists. This shift to an immunosuppressed state occurs for many reasons, including massive sepsis-induced death of immune cells, development of T cell exhaustion, and generation of T regulatory and myeloid-derived suppressor cells. A postmortem study of intensive care unit patients, in which spleens and lungs were harvested rapidly after death, showed that compared to patients dying of causes other than sepsis, immune effector cells from septic patients were massively depleted (12). Most of the sepsis deaths occurred after a prolonged course in the intensive care unit. This protracted septic course is difficult to reproduce in animal models. For example, animal sepsis mortality reported by Weber *et al.* generally occurred within 24 to 48 hours after sepsis onset (during the hyperinflammatory phase) and is therefore not reflective of most clinical deaths in sepsis.

Recent studies provide compelling evidence for this immunologic evolution. In patients admitted with sepsis, “late” positive blood and tissue cultures were detected in ~28% of patients, and over half of these infections were due to fungi or weakly virulent bacteria considered to be “opportunistic” pathogens (13). In addition, use of latent viral reactivation as a surrogate marker of loss of immunocompetence (14) showed that over 42% of septic patients had reactivation of two or more viruses. The amount of viral reactivation in septic patients was comparable to that occurring in organ transplant patients on immunosuppressive therapy, further evidence of the remarkable degree of impaired immunity in patients with sepsis.

So, how should sepsis be treated? The cornerstone of sepsis therapy remains drainage and/or removal of the infected site, fluid resuscitation, and rapid antibiotic administration. Although anti-inflammatory therapies, such as blocking IL-3, may be beneficial in selected patients, history has not been kind to such approaches. It may be that restorative immunotherapy, in which adjuvants that stimulate host immunity would be the centerpiece for response modification, offers the most promise. To guide sepsis immunotherapy, new methods to determine the health of the various components of a patient’s immune system are being developed and may direct the application of targeted immune-adjuvant therapies in the future (15).

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Inflammatory response to sepsis. Potential immune therapies can modulate immune responses that provoke excessive inflammation or enhance immunity if there is an impaired immune response to microbial infection. IFN- γ , interferon- γ .