GUEST EDITORIAL

MEETING UNMET NEEDS IN PATIENTS WITH SEPSIS: THE ROLE OF DROTRECOGIN ALFA (ACTIVATED)

By Peter E. Morris, MD. From Pulmonary Medicine, Wake Forest University School of Medicine, Winston-Salem, NC.

Sepsis has been with us through the ages. Almost 5000 years ago, the Chinese were investigating therapies for patients with fever.[1] Significant advances in the therapy of sepsis occurred at the beginning of the 20th century when Paul Ehrlich ushered in the era of antimicrobial therapy with the use of organic arsenical for syphilis.[2] Since then, interventions for patients with severe sepsis have produced gradual improvements in outcomes. Improvements in care include development of new pharmaceutical agents for hemodynamic support and antibiosis, certification in the specialties of critical care medicine and nursing, and implementation of critical care units staffed by physicians and nurses who are board certified or eligible for certification in critical care who can respond rapidly to changes in patients' medical conditions.[3-5] Other improvements are the results of advances in diagnostic procedures, monitoring methods, supportive care, and implementation of critical care guidelines and pathways. For example, the Acute Respiratory Distress Syndrome Clinical Network investigators[6] found that compared with ventilation with traditional tidal volumes, ventilation with lower tidal volumes significantly reduced mortality in patients with acute lung injury and acute respiratory distress syndrome, a major cause of organ failure and death in patients with sepsis and acute organ dysfunction (severe sepsis).

As we enter the 21st century, however, sepsis remains a major clinical problem affecting thousands of patients in the United States each year.[7] With a death rate that hovers in the range of 28% to 50%, severe sepsis accounts for at least 215 000 deaths annually and is the leading cause of death in noncoronary intensive care units.[7-11] Severe sepsis affects patients of all ages, with increased prevalence in the very young and the elderly. Patients in all medical settings and populations experience this disease. It occurs not only in patients who are neutropenic after chemotherapy but also in otherwise healthy persons after elective surgery, automobile accidents, and other traumatic situations. It can also complicate pregnancy and infections that appear to be resolving.

Furthermore, the incidence of severe sepsis has been projected to increase at a rate of 1.5% per year well into the middle of this century, a rate that outstrips the growth in the general population.[7] The increase in the number of patients with severe sepsis most likely is due to a number of factors, including the aging of the population, an increase in the number of immunosuppressed patients, and the increased use of invasive procedures.

One problem in fully understanding the implications of severe sepsis for modern society is our failure to fully identify and characterize patients with this condition. Because a large proportion of patients with severe sepsis will have progressed from earlier stages of sepsis to multiple organ dysfunction syndrome, septic shock, and death, early recognition and treatment can decrease mortality associated with severe sepsis.[11]

Great steps were made in this direction when the American College of Chest Physicians and the Society of Critical Care Medicine developed consensus guidelines for identification and characterization of patients with sepsis.[12] However, these guidelines were based on expert opinion and have limitations. For example, the guidelines did not address the basic pathophysiology of the condition, and the criteria for systemic inflammatory response syndrome (SIRS) were considered too sensitive and not reflective of the severity of the underlying disease process.[13] Consequently, a committee composed of representatives from the American College of Chest Physicians, the Society of Critical Care Medicine, the American Thoracic

Society, and the European Society of Intensive Care Medicine met in late 2001 to consider the guidelines, and a report was expected to be issued in late 2002.

Notwithstanding significant advances in our knowledge of the molecular and pathophysiological components of severe sepsis, experimental interventions specifically directed at preventing the complex biological events that lead to organ failure have a dismal track record. Despite this unmet need in the therapy of severe sepsis, the results of more than 23 clinical trials with more than 13 000 patients have not indicated an approach that could significantly reduce mortality due to severe sepsis.[14] The reasons for the lack of mortality reduction in these trials include timing of entry criteria, study design, ineffective drugs or concepts, inappropriate dosing, and the heterogeneous nature of the population with severe sepsis.

Perhaps previously studied investigational agents could not modify the combined pathophysiological alterations of the disease that contribute to organ dysfunction and death. For example, although it is widely acknowledged that severe sepsis has a marked inflammatory component, it was only recently that investigators recognized the role of integrated endothelial, inflammatory, and hemostatic abnormalities in patients with this disease. The endothelium is suspected of playing a central role in the inflammatory, prothrombotic, and impaired fibrinolytic elements of severe sepsis. At the junction of the flowing blood and extracellular space, the endothelium is a dynamic organ that modulates local hemostasis, cell trafficking, and microcirculatory blood flow.[15]

Endothelial dysfunction is a common element in patients with sepsis and can be recognized by the appearance of elevated levels of circulating endothelial cell-surface molecules such as thrombomodulin, intercellular adhesion molecule-1 and E-selectin.[16,17] In severe sepsis, the endothelium cannot convert protein C to its activated form.[18] Although the clinicopathological changes of overt disseminated intravascular coagulation are uncommon, a sepsis-associated coagulopathy indicated by the presence of elevated levels of D-dimer and depressed concentrations of naturally occurring anticoagulants is universal in patients with severe sepsis.[19]

Because coagulation augments inflammation, antithrombotics might be expected to downregulate inflammation in patients with severe sepsis.[20] Three natural antithrombotic pathways exist: antithrombin, tissue factor pathway inhibitor, and protein C. In some in vivo models, these natural antithrombotics inhibit endotoxin-mediated leukocyte activation and diminish elaboration of cytokines such as tumor necrosis factor, interleukin-6, and interleukin-8. Unfortunately, in phase 3 clinical trials, neither antithrombin nor tissue factor pathway inhibitor caused a significant reduction in 28-day mortality due to all causes in patients with severe sepsis.[21,22]

Because patients with severe sepsis may be unable to convert protein C to activated protein C, they also may be unable to generate sufficient levels of endogenous activated protein C to benefit from its antithrombotic, profibrinolytic, and anti-inflammatory properties.[18,23] Results of the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial indicate that therapy with recombinant human activated protein C, drotrecogin alfa (activated), can significantly reduce the mortality of patients with severe sepsis. Further details of the PROWESS trial are presented in the article by Ely et al[24] in this issue of *AJCC*. These authors provide an extensive history of drotrecogin alfa (activated), from its conception to use at the bedside, allowing a better understanding of treatment with this compound.

An ongoing concern of practicing clinicians and nurses is the cost of treatment. As the science of medicine expands and more high-tech treatments become available, so too does the cost of treatment. Treatment of sepsis is expensive. With the development of new and innovative therapies such as drotrecogin alfa (activated), which can lead to high treatment costs, what should we do? Opinions differ, but the most important thing to keep in mind is the care of the patient.[25] If a therapeutic agent is available that can significantly reduce mortality, and a patient meets the guidelines mandated by the Food and Drug Administration for treatment, then rationing that treatment could be considered unethical. However, it is critical to maintain a treatment structure that ensures that patients are not unnecessarily treated, leading to an unjustified, marked financial burden.

Although treatment of patients with severe sepsis costs more than $16 billion annually, the health-economic aspects of treatment with drotrecogin alfa (activated) must be considered.[7] It is estimated that therapy with this novel compound costs approximately $6800 per 96-hour infusion, an amount that may require adjustments in intensive care unit budgets to account for this treatment. To determine the impact of drotrecogin alfa (activated) on patients' expenses, 2 groups of investigators[26,27] examined the cost-effectiveness of treatment with the drug. Manns et al[26] retrospectively determined cost per life-year gained in patients treated with drotrecogin alfa (activated) and patients given conventional treatment in an intensive care unit in Canada. The cost per life-year gained by using drotrecogin alfa (activated) was US$27 936, and

the treatment was more cost-effective in patients with a score of 25 or greater on the Acute Physiology and Chronic Health Evaluation II. Angus et al[27] used billing data on patients involved in the PROWESS trial who were enrolled from US sites. Their analysis indicated that costs per life-year and per quality-adjusted life-year (QALY) were US$31 900 and US$46 700, respectively.

Both of these studies were unique in their specific assumptions; however, despite the differences in structure between the 2 analyses, both groups of authors concluded that a favorable QALY figure exists for the use of drotrecogin alfa (activated) in patients with a score greater than 25 on the Acute Physiology and Chronic Health Evaluation II. These figures are also similar to estimates of QALYs from other interventions such as lytic therapy for myocardial infarction[28] and use of implantable cardiac defibrillators for the prevention of sudden cardiac death.[29]

Selection of patients is key in maintaining the highest benefit while reducing the amount of unnecessary treatment. Specifically, the inclusion criteria from the PROWESS trial should be used when patients are considered for treatment with drotrecogin alfa (activated).[30] These criteria are straightforward and include (1) presence of a known or suspected infection, (2) presence of at least 3 signs of systemic inflammation, and (3) dysfunction of at least 1 organ or system that has persisted no longer than 24 hours. By using these criteria and good clinical judgment as a guide, physicians and nurses can determine the most efficient path for the treatment of sepsis with this drug.

Future issues related to drotrecogin alfa (activated) therapy are numerous. They include the ideal duration of therapy with the drug, its use in immunosuppressed patients, and health-economic considerations. Because drotrecogin alfa (activated) has anti-inflammatory properties, treatment with it could have been associated with an increase in secondary infections; however, no increase in nosocomial infections was noted. The role of treatment with drotrecogin alfa (activated) in severely immunocompromised patients who have sepsis (eg, bone marrow transplant recipients) is yet to be determined. Although the current economic data is encouraging, further studies are needed to determine the exact impact of the drug on the medical community. Perhaps a federally funded network to study treatment issues related to severe sepsis, comparable to the Acute Respiratory Distress Syndrome Clinical Network funded by the National Institutes of Health, could further define the role of different therapies for sepsis and lower mortality due to severe sepsis by clarifying the most efficacious management practices currently used in treatment of patients with severe sepsis.

The PROWESS trial built on the work of numerous investigators in sepsis research and provides evidence that interventions that attack multiple components of the septic process can significantly decrease morbidity and mortality associated with severe sepsis. The results of the PROWESS trial and other studies of natural antithrombotics provide clinicians and nurses with the first opportunity to modify the complex interactions of the inflammatory cascade and the hemostatic system in patients with severe sepsis. With evidence from interventions with sepsis modifiers such as drotrecogin alfa (activated) and lessons learned about trial design in this field, we have taken our first steps in meeting the unmet needs in this common, frequently fatal and expensive disorder.

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