Severe Sepsis and Therapy with Activated Protein C

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Sepsis, severe sepsis, and septic shock represent a spectrum of increasingly severe diseases that result from serious infection and the body's response to microbiologic invasion. Population data suggest that 750,000 cases of severe sepsis occur in the United States annually; this illness is responsible for as many deaths as acute myocardial infarction (215,000, or 9.3 percent of deaths from all causes).[1-3] Almost every discipline in medicine must deal with this disease, from neonatology to orthopedic surgery to emergency medicine, though much of the management is performed by critical care physicians in intensive care units.

The pathogenic mechanisms underlying severe sepsis and septic shock are remarkably complex.[2,3] Microorganisms proliferate at a nidus of infection, and they or their toxins may enter the bloodstream. In response, a large number of host-derived mediators are released from plasma proteins (the coagulation, fibrinolytic, and complement systems) or cells (endothelial cells, monocyte macrophages, and neutrophils). These endogenous mediators have a profound physiologic effect on vasculature and multiorgan systems. Septic shock can produce dysfunction in the cardiovascular, respiratory, renal, hematologic, metabolic, hepatic, and neurologic systems. Death results from progressive hypotension or the failure of at least one organ. Severe sepsis (i.e., sepsis plus the dysfunction of at least one organ) is associated with in-hospital mortality of approximately 30 percent, and septic shock (i.e., sepsis with hypotension despite adequate fluid replacement) with in-hospital mortality of approximately 50 percent.

Current management of severe sepsis and septic shock consists of eradication of the infection (by means of surgical drainage and early administration of antimicrobial agents); cardiovascular support (early monitoring, aggressive fluid administration, the use of vasopressor agents, inotropic agents, or both, and possibly blood transfusions); pulmonary therapy (supplemental oxygen, mechanical ventilation with low tidal volumes, positive end-expiratory pressure to treat acute lung injury or acute respiratory distress syndrome); and renal replacement therapy, if indicated. Other general recommendations for the management of these conditions in the intensive care unit include maintenance of blood glucose levels at less than 150 mg per deciliter (8.3 mmol per liter), prophylaxis against deep-vein thrombosis and stress ulcer, maintenance of the patient in a semirecumbent position in bed, and protocols for weaning patients from mechanical ventilation and for sedation and analgesia. Many experts would recommend stress doses of corticosteroids (hydrocortisone, at a dose of 200 to 300 mg per day) to treat persistent septic shock or severe sepsis with evidence of relative adrenal insufficiency.[4]

An important mediator-inhibition therapy for severe sepsis is activated protein C (drotrecogin alfa [activated]). Activated protein C inhibits factor Va and factor VIIIa and has effects on in vitro coagulation, fibrinolysis, and the immune system. A phase 3, randomized, controlled trial (the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis [PROWESS]) involving 1690 patients showed an absolute reduction in the relative risk of death from all causes at 28 days of 6.1 percent (from 30.8 percent to 24.7 percent, $P=0.005$) with an increase in serious bleeding (from 2.0 percent among those receiving placebo to 3.5 percent among those receiving activated protein C; $P=0.006$).[5] A subgroup analysis performed with the use of Acute Physiology and Chronic Health Evaluation (APACHE II) quartiles showed that most of the reduction in mortality occurred among patients receiving activated protein C with APACHE II scores in the third and fourth quartiles, representing those with the most severe disease.[6] On the basis of this subgroup analysis, in 2001 the regulatory agencies in the United States and Europe approved activated protein C for the treatment of adult patients with severe sepsis who have a high risk of death (as defined by an APACHE II score ≥25 in the United States and by the failure of at least two organs in most European countries).

There was considerable disagreement during the deliberations of the advisory panel convened by the U.S. Food and Drug Administration (FDA) with regard to approval of activated protein C for severe sepsis. Experts testifying against approval before the panel expressed concern about revisions of the protocol of the trial, the difficulty of determining APACHE II scores clinically, and a substantial risk of bleeding associated with activated protein C.[7]

The FDA argued that the protocol revisions could not account for the reduction in 28-day mortality, that APACHE II scores could be easily and rapidly determined clinically, and that the FDA-required labeling would minimize the risk of bleeding. It noted an absolute reduction in mortality in the PROWESS trial of 13 percent in the subgroup of patients with APACHE II scores of 25 or higher, and the agency argued that the magnitude of this benefit greatly outweighed the risk of bleeding.[8]

As a part of the FDA's approval process, the agency required the sponsor of the study (Lilly) to complete a number of phase 4 trials. A report from one of these trials (the Administration of Drotrecogin Alfa [Activated] in Early Stage Severe Sepsis [ADDRESS]) appears in this issue of the *Journal*.[9] ADDRESS was a randomized, placebo-controlled, blinded trial of activated protein C involving adult patients with severe sepsis who were at low risk of death (as defined by APACHE II scores <25 or single-organ failure). Enrollment was discontinued early on grounds of futility: with 2640 patients enrolled in the study, there was considered to be a low likelihood of its demonstrating reduced mortality with the use of activated protein C. Twenty-eight day mortality and in-hospital mortality were statistically the same in the group receiving activated protein C and the control group, and the rate of serious bleeding was similar to that in the PROWESS trial.

In a subgroup of patients who had recently had surgery (within the previous 30 days) and had single-organ dysfunction, the patients receiving activated protein C had higher 28-day mortality than those receiving placebo (21 percent vs. 14 percent), an outcome that argued against the use of activated protein C in this subgroup. It was also disconcerting that the results of the ADDRESS trial failed to confirm the observation made in the PROWESS trial of a large reduction in mortality among patients with APACHE II scores of 25 or higher, although the number of patients (324) in this group was too small for a meaningful statistical comparison and these patients had been categorized as at low risk by the investigator entering them into the study.

Several other recently completed trials of activated protein C have provided additional important insights. An economic evaluation of activated protein C in the treatment of patients who had severe sepsis and had APACHE II scores of 25 or higher found activated protein C therapy to be relatively cost-effective (approximately $28,000 per quality-adjusted life-year saved).[10] Subsequent long-term follow-up of the PROWESS population found that the groups with APACHE II scores of 25 or higher did have significant improvements in survival up to 2.5 years.[11] A single-group, open-label trial (ENHANCE) of activated protein C in severe sepsis found a higher rate of serious bleeding associated with the therapy (6.5 percent, as compared with 3.5 percent in PROWESS) and a higher rate of intracranial hemorrhage (1.5 percent, as compared with 0.2 percent in PROWESS).[12] A trial involving pediatric patients who had severe sepsis was stopped after approximately 400 patients had been enrolled, again because of futility.

Where do all these clinical trials leave the clinician faced with patients who have severe sepsis — patients in shock requiring vasopressor support and those with acute lung injury and respiratory failure requiring mechanical ventilation who are likely to benefit from activated protein C? In my judgment, the FDA decision in 2001 was correct. On the basis of a well-conducted phase 3, randomized, blinded, controlled trial (PROWESS), activated protein C was found to have efficacy in reducing mortality in severe sepsis. Since all the benefit of reduced mortality was confined to patients with an APACHE II score of 25 or higher, the drug was approved for such patients, and studies in other groups were mandated to define appropriate populations. The ADDRESS trial confirms the lack of efficacy in patients with APACHE II scores of less than 25. The ENHANCE trial and the pediatric study confirm that bleeding is a significant risk with activated protein C, and clinicians must carefully exclude patients who have a high likelihood of bleeding. With approval of activated protein C in 2001, the FDA's Jay Siegel wrote that the agency hoped to save lives with this therapy and to "gather the information necessary to refine its use further."[8] This refinement is under way.

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Vasodilators in Aortic Regurgitation — Where Is the Evidence of Their Effectiveness?

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Although aortic regurgitation imposes a volume load on the left ventricle, it became clear more than two decades ago that the resulting large stroke volume and wide pulse pressure also lead to systolic hypertension and concomitant left ventricular pressure overload.[1,2] In fact, afterload is much higher in aortic regurgitation than in mitral regurgitation and may be as high as that in the more typically recognized pressure overload of aortic stenosis.[3] The excess afterload in aortic regurgitation, in turn, forms the basis for the idea that afterload-reducing agents, such as vasodilators, might be beneficial in the medical treatment of this disease.

After several smaller reports showing beneficial hemodynamic and positive remodeling effects of various vasodilators in patients with aortic regurgitation,[4-7] Scognamiglio et al. reported more than a decade ago in the *Journal* that the vasodilator nifedipine forestalled the need for aortic-valve replacement as indicated by the development of either symptoms or left ventricular dysfunction.[8] In that randomized trial, nifedipine was compared with digoxin rather than placebo. The same group subsequently reported that the benefit from preoperative administration of nifedipine persisted years after aortic-valve replacement.[9]

In striking contrast, in this issue of the *Journal*, Evangelista et al. report that neither enalapril nor the same dose of nifedipine as that used by Scognamiglio et al. delayed or reduced the need for aortic-valve replacement, as compared with placebo.[10] In other words, the two studies came to virtually opposite conclusions with regard to the usefulness of vasodilators in the treatment of patients with asymptomatic aortic regurgitation.

How can this discrepancy be reconciled? Looking first at the digoxin group in the study by Scognamiglio et al. and the placebo group in the study by Evangelista et al., it is clear that the need for aortic-valve replacement was similar in the two groups. Obviously, many arguments could be and have been leveled against the use of an active cardiovascular drug such as digoxin in the control group of a trial, as was done by Scognamiglio et al. Even so, the main differences appear to be in the nifedipine groups. In the study by Evangelista et al., the need for aortic-valve replacement at six years in the nifedipine group was about 22 percent, a rate similar to that in the placebo group, whereas in the study by Scognamiglio et al., the corresponding rate was only 10 percent. Evangelista et al. note that the other researchers may have waited a longer time before performing aortic-valve replacement, since the patients in that study had more advanced left ventricular dysfunction. Waiting a longer time would decrease the rate of aortic-valve replacement, but a delay in surgery should have affected both groups in the trial equally.

In the study by Evangelista et al., it is not surprising that nifedipine failed to improve the outcome, because the drug appeared to have almost no effect on any measured variable. The drug did not significantly alter blood pressure, heart rate, or ventricular geometry over the course of the study. In fact, given these data, it would have been surprising if nifedipine had had a positive effect. This

CORRECTION

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Severe Sepsis and Therapy with Activated Protein C . On page 1398, in the right-hand column, the P value in line 15 of the first full paragraph should have read ``P=0.06,´´ rather than ``P=0.006,´´ as printed.

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