Steroids and Drotrecogin Alfa (Activated) for Severe Sepsis

To The Editor:

Although steroids for severe sepsis have a long and controversial history, many practicing intensivists are considering steroids based on several studies, suggesting efficacy in a defined group of patients with severe sepsis. In the largest trial to date, although steroids were useful in a limited population with relative adrenal insufficiency and refractory septic shock, mortality increased 8% in those with normal adrenal function, and >50% of steroid recipients were dead at day 28. In a recent review by Marik et al (June 2002), a therapeutic approach to patients with presumed adrenal insufficiency, or for that matter lack of adrenal reserve, is recommended in patients with severe sepsis. However, the fundamental issues remain of how to define relative adrenal insufficiency in critically ill patients. More studies are needed to identify the prevalence of relative adrenal insufficiency, which will be dependent on the diagnostic criteria used to confirm this syndrome in critically ill patients. Additionally, we need to better define the precise dose and composition of steroids and the potential interaction of steroids and other proven interventions that have been shown to enhance severe sepsis outcome. Though many intensivists are “jumping on the steroid bandwagon,” we must remain cautious in our haste to accept the benefits of steroids without careful considerations of its effects, especially in patients who do not have adrenal insufficiency.

There has been growing optimism in the field of critical care medicine owing to our better understanding of the pathophysiology underlying severe sepsis. We now recognize that hemodynamic abnormalities appear to be almost universal in patients with severe sepsis, with the coagulation and fibrinolytic systems being profoundly deregulated during sepsis. Drotrecogin alfa (activated) has clearly demonstrated outcome benefit in patients with severe sepsis, perhaps attributed to its multiple mechanisms of action, including modulation of the inflammatory responses, and displaying both antithrombotic and profibrinolytic properties. Threatening bleeds and intracranial hemorrhage appear to be uncommon in approximately 2,786 treated patients in controlled and open-label trials (0.4% and 0.5%, respectively). The reduction in mortality with this drug is far greater than the risk of a serious bleed, especially in the high-risk, severe septic population. Although some would have expected overwhelming adoption of this novel therapy in both academic and community hospital settings, it appears that clinicians have been slow to adopt this highly beneficial, although cost-effective therapy. This is surprising since the study results were very positive, particularly in high-risk patients, and presented widely in the medical domain. Interinstitutional and interregional practice variations in employing this therapy may likely have several causes, including local practice style or habit, inertia, and economic pressures from hospital administrators and pharmacists. Given the magnitude of the problem of severe sepsis, a rigorous evaluation should be undertaken to further understand the nonscientific circumstances that have potentially influenced the implementation of drotrecogin alfa (activated) therapy for severe sepsis in ICUs. For now, it should be our desire as physicians to embrace new life-saving technology.

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To the Editor:

The last 2 decades have seen a remarkable growth in our understanding of sepsis and the complex interconnection of multiple biological pathways involved in the septic process. This increased knowledge has opened the door to new therapeutic approaches, and the reincarnation of others that had been laid to rest. Foremost among these is the use of stress doses of hydrocortisone in patients with septic shock, the use of drotrecogin alfa (activated) in patients with severe sepsis, and tight glucose control with insulin in patients with stress-induced hyperglycemia. The use of these “biological agents” in patients with sepsis is based on a wealth of experimental and clinical studies performed in recent years. All three agents have proven benefit in randomized controlled trials. Furthermore, based on our current knowledge, the use of these agents is both logical and their benefit is biologically plausible.

It is now well established that severe sepsis is associated with reversible failure of the hypothalamic-pituitary-adrenal axis. Cortisol plays an essential role in maintaining hemodynamic stability and preventing an excessive proinflammatory response in patients with sepsis. Impaired cellular glucocorticoid activity is

References

associated with refractory hypotension and excessive activation of nuclear factor (NF)-κB; these features are rapidly reversed with stress doses of hydrocortisone.\textsuperscript{5,7,8} Sepsis is frequently associated with stress-induced hyperglycemia. A combination of several factors including insulin resistance, the presence of excessive counter regulatory hormones such as glucagon, growth hormone, catecholamines, glucocorticoids (sometimes), and cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α combined with exogenous administration of catecholamines, dextrose, and nutritional support are responsible for this metabolic syndrome.\textsuperscript{9} Hyperglycemia has been demonstrated to have potent proinflammatory effects.\textsuperscript{10} Glucose induces an increase in NF-κB, a fall in cytosolic IkB, and an increase in 1κB kinase.\textsuperscript{11,12} Glucose also has been shown to exert prothrombotic effects and to increase oxidative stress by causing lipid peroxidation.\textsuperscript{13,14} Besides controlling hyperglycemia, insulin has immune-modulatory and anti-inflammatory properties similar to glucocorticoids. Insulin has been shown to suppress NF-κB, the expression of intercellular adhesion molecule-1, the chemokine, monocyte chemotactic protein-1, tissue factor, and plasminogen activator inhibitor-1.\textsuperscript{15–17} Tight blood glucose control with insulin is therefore likely to have important immunomodulating effects in patients with severe sepsis.

An overwhelming body of evidence has demonstrated that sepsis is characterized by a systemic microvascular injury.\textsuperscript{1} Activation of the coagulation cascade with impaired fibrinolysis results in widespread microvascular thrombosis.\textsuperscript{2} This microvascular injury has been pathogenetically implicated in the progressive organ failure that occurs in patients with severe sepsis. Decreased levels of activated protein C are believed to play an important role in propagating the microvascular injury in sepsis. This concept is supported by data from the PROWESS study (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis Study Group),\textsuperscript{3} which demonstrated that drotrecogin alfa (activated) significantly deceased the 28-day mortality and resulted in a more rapid recovery of organ failure in patients with severe sepsis when compared to placebo.

The therapeutic value of these biological agents in sepsis is complementary; the use of one does not preclude the use of the others. Stress doses of hydrocortisone are indicated in all vasopressor-dependant patients with septic shock who have a stress (random) cortisol level of < 25 μg/dL. An insulin infusion is indicated in all critically ill septic patients with stress hyperglycemia. Similarly, drotrecogin alfa (activated) should be administered to all patients with severe sepsis in whom a contraindication to the drug does not exist. Timing, however, is critical. It likely that these agents will have minimal impact on the outcome of patients with severe sepsis if administered late in the course of their disease.

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Reporting of Predictive Logistic Models Should Be Based on Evidence-Based Guidelines

To the Editor:

Moss et al (March 2003)\textsuperscript{3} reviewed the deficiencies in reporting multivariable logistic regression analysis in the pulmonary and critical care medicine literature. They also suggested some potential guidelines to improve this reporting in both descriptive and predictive modeling. We would like to make some further suggestions, with emphasis on predictive models.

Recently, guidelines have been developed to adequately report randomized controlled trials (Consolidated Standards of Report-