Recombinant human activated protein C sentenced to the death of a thousand cuts?*

In this issue of *Critical Care Medicine*, Dr. Laterre and colleagues (1) present longer term follow-up data to the clinical trial of recombinant human activated protein C (rhAPC) in severe septic patients with lower severity of illness (ADDRESS) (2). There was no statistically significant difference in outcomes between subjects in the treatment and placebo groups. The report provides reassurance that there is no late effect of rhAPC. With data available for approximately 90% of subjects, the overall 1-yr mortality rate was 34.1%. Because most deaths occurred within 90 days, this is a reasonable mortality landmark for determining a benefit in clinical trials of severe sepsis. Although this study adds to a multitude of studies regarding rhAPC, we seem no closer to a consensus about the drug.

PROWESS included patients with severe sepsis and an *a priori* plan for a primary analysis stratified by a variety of clinical factors (3). Presumably, this would guide subsequent studies, should there be no overall effect. However, there was a mortality benefit for the whole cohort (absolute risk reduction, 6.1%; 95% confidence interval [CI], 1.9–10.3%). After analyzing subgroups, regulatory bodies concluded that the sickest patients benefited the most, and rhAPC was approved for those at a high risk for death. Statistically, an Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥25 provided the best discrimination of those likely to benefit (absolute risk reduction, 12.8%; 95% CI, 6.2–19.4%) (4).

ADDRESS was designed to answer the question about lower-risk patients for whom rhAPC was not already indicated (2). This study was stopped early because of a projected lack of effect. Among ADDRESS patients with an APACHE II score ≥25 (12% of those enrolled), those treated with rhAPC had numerically higher mortality than those assigned to placebo (absolute risk increase, 4.8%; 95% CI, 4.9% decrease to 14.2% increase). This raised questions about PROWESS' conclusions, despite the clear differences in studies, as shown by the dissimilarity in mortality among placebo patients (APACHE II ≥25: PROWESS = 43.7%, ADDRESS = 24.7%; APACHE II <25: PROWESS = 19.0%, ADDRESS = 16.0%).

The sequence in which we received data produced some of the uncertainty about rhAPC. PROWESS demonstrated a benefit, but only for half of the subjects. Then, ADDRESS showed no effect. We tend to simplify these results as contradictory: one was positive, and one was negative. If the sequence was changed, would the same conclusions have been reached? If PROWESS was without overall effect but the subgroup at highest risk showed a benefit, there would have been a second study examining only those at a higher risk. If that study demonstrated rhAPC was beneficial, we would have reached a consensus that rhAPC should be used for severe septic patients at a high risk for death. Instead, rhAPC has become contentious (5–8).

Given the heterogeneity of severe sepsis, it would be surprising if any single agent were uniformly effective. We certainly would not expect a single chemotherapeutic agent to be useful in all cancers. If a single drug were to be successful, it would have to address pathways common to the majority of patients. Alternatively, it may work only in a subgroup of patients with the targeted derangement. rhAPC may fit such a description. Considering the acceptance of other therapies without definitive mechanisms of action (e.g., lower tidal volume ventilation [9]), it is peculiar that similar uncertainty causes a reluctance to use rhAPC.

The increased risk of bleeding is important when considering rhAPC use. This is a complex issue because we cannot confidently predict who will benefit from treatment and who will bleed. We must determine the net effect for the entire study population and imperfectly extrapolate this as a probability of benefit for an individual patient. When rhAPC is given, there is no immediate feedback that a clinician made the *correct* decision. When thrombolytics are administered for acute myocardial infarction, chest pain resolves and the electrocardiogram normalizes. With rhAPC, the patient lives, dies, or bleeds. The clinician only credits rhAPC with bleeding. This favors an omission bias—omitting action with a net benefit to avoid the possibility of harm (10, 11).

Another rhAPC study is planned to "help clinicians better identify severe sepsis patients at high risk of death who are more likely to benefit (12)." Although it may not be intended as a "tie-breaking" study, some might view it as such. Dichotomizing studies as either positive or negative contributes to the confusion about rhAPC. PROWESS and ADDRESS did not demonstrate opposite results of equal magnitude. Among high-risk patients, PROWESS had very convincing results for a benefit and ADDRESS was too underpowered to show anything definitive. If we combine the high-risk patients from ADDRESS and PROWESS, the composite absolute risk reduction is 7.8% (95% CI, 2.3–13.3%; $p = .006$). However, because both studies were halted before target enrollment, it is difficult to determine the influence that early stopping had on the common estimate of effect.

The upcoming study should be designed with consideration of prior results. Early stopping should be discouraged. Suppose 500 subjects are randomized and the outcomes are identical to the high-risk group in ADDRESS. Enrollment in this study could be halted because of a trend toward harm with $p = .23$ and without definitive results. If we then combine data from all three studies, there is a composite 3.9% absolute risk reduction (95% CI, 0.6% risk increase to 8.4% risk reduction)

*See also p. 1457.

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and a number needed to treat of 26. Most would consider this clinically meaningful, but it is statistically "nonsignificant" owing to a combined power of 49%.

I suspect that without a statistically significant result in the pending trial, rhAPC will die—not because of clear ineffectiveness, but from our frustration with and confusion by the data. In the era of rofecoxib (13, 14), it is important to attend to toxicities of new therapies and be skeptical of reported benefits. However, we should also consider the consequences of discarding a potentially *curative* therapy. If we abandon rhAPC, we discard a drug that appears to have a benefit, treats a condition that kills every third patient, and is the only specific treatment available. We should weigh all of these issues before designing and interpreting the next study of rhAPC.

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Systemic inflammation and sexual dimorphism: More than meets the eye*

Several categories of critical illness are reported to affect men and women differently. Men are more likely than women to develop sepsis, but overall both have similar survival rates (1, 2). Women have a higher acute mortality after primary angioplasty for acute myocardial infarction and after coronary artery bypass surgery (3, 4). Autoimmune diseases, such as systemic lupus erythematosus, are much more common in women than men (5, 6). Some studies suggest that, following blunt trauma, men have a greater risk of death than women (7), although others have not found gender to be a risk factor for adverse outcomes (8). A better-defined contribution of gender on outcome from sepsis or trauma is found in animal models that suggest a survival advantage for females and beneficial effects of estrogens on outcome (8). Multiple *in vitro* models have begun to define novel physiologic and molecular mechanisms governing sexual dimorphism of kidney, cardiac, and vascular function (9). Clinical observations may not be as absolute as experimental models and likely reflect the interactions of gender with other biological factors, such as lifestyle activities, risk behaviors, and ethnicity, as well as healthcare access and delivery.

The biological basis of gender differences is more complex than simply the presence or absence of sex hormones and arises from a dynamic interplay of gene and protein expression. Gender is determined in normal males by X (maternally derived, Xm) and Y (paternally derived) chromosomes and normal females by the presence of two X chromosomes (Xm and one paternally derived, Xp). More than 1,000 functional genes reside on the X chromosome, including genes integral to the inflammatory response (e.g., interleukin [IL]-1 receptor associated kinase and nuclear factor-κ essential modulator) and to T and B lymphocyte function (e.g., gamma chain common cytokine receptor or Bruton tyrosine kinase), whereas <100 genes reside on the Y chromosome (6, 10). In females, one of the X chromosomes is randomly inactivated to equalize the gene expression of X-linked genes between males and females. This inactivation of one X chromosome also creates cellular mosaics in females with cells and tissues that differ in the parental origin of their active X chromosome (i.e., either Xm or Xp). Mosaicism may be advantageous for females, because some X-linked

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