consequence. Further challenges include both limited funding for this type of research and reporting biases, as these types of observations are less novel and exciting than the results of the initial prophylactic study. The challenge in natural experiments involving actual clinical practice is to quantify precisely the effect of increased antimicrobial use on the emergence of resistance in the setting of complex medical care. I encourage Dr. Ito and colleagues to study in detail what has occurred at their institution, for an improved understanding of the risk-to-benefit ratio.

Lindsey R. Baden, M.D.

Drotrecogin Alfa (Activated) in Severe Sepsis

TO THE EDITOR: In the article by Abraham et al. (Sept. 29 issue),[1] the ADDRESS (Administration of Drotrecogin Alfa [Activated] in Early Stage Severe Sepsis) trial showed no benefit of drotrecogin alfa (activated) (DrotAA) in patients with severe sepsis and a low risk of death (defined by single-organ failure or an Acute Physiology and Chronic Health Evaluation [APACHE II] score <25).[2] In contrast to the prematurely terminated PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial,[3] the ADDRESS study showed higher mortality in its subgroup of patients treated with DrotAA who had an APACHE II score of 25 or more. When the subgroups of the two trials that had an APACHE II score of 25 or more were combined with the use of standard meta-analysis software (Review Manager, version 4.2) and a random-effects model, there was substantial heterogeneity between the two results ($P=0.01$; $I^2=84$ percent, where I denotes quantification of the degree of heterogeneity), and no significant benefit in 28-day mortality was shown (relative risk, 0.90; 95 percent confidence interval, 0.54 to 1.49) (Fig. 1). Likewise, combining subgroups that had multiple-organ failure did not show a major benefit. The previous discrepant results in trials of treatment for sepsis that used early-stopping rules[4] or retro-

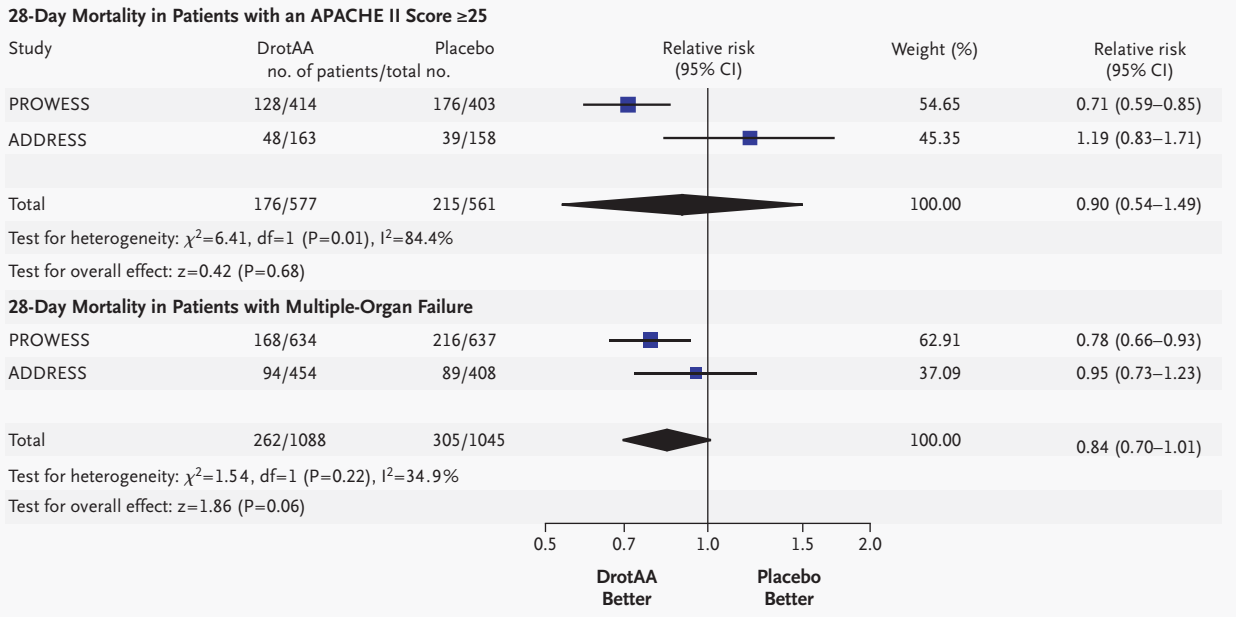

Figure 1. Effects of DrotAA on Combined 28-Day Mortality among Patients with Severe Sepsis in the PROWESS and ADDRESS Trials.

CI denotes confidence interval. A random-effects model was used to pool the relative risks. The size of each square is proportional to the relative weighting of the study's relative risk in the calculation of the overall pooled relative risk. The center of each diamond indicates the pooled relative risk, and the width of the diamonds reflects the size of the 95 percent confidence interval.

spective subgroups[5] and had apparently even higher risks of bleeding events, including intracranial hemorrhage (e.g., in the open-label DrotAA study Extended Evaluation of Recombinant Human Activated Protein C [ENHANCE][6]), suggest that another study in which a high risk of death is prospectively defined is urgently needed to determine whether DrotAA is beneficial even in this subgroup.

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TO THE EDITOR: The lack of an observed treatment benefit with DrotAA in the subgroup of patients with APACHE II scores of 25 or more in the ADDRESS trial is worrisome, given that the agent is approved in the United States for this population. The authors attempted to explain this finding on the basis of statistical considerations, but questions remain. For this subgroup, baseline characteristics including each component of the APACHE II score, the site and type of infection, and types of organ dysfunction should be described according to treatment group to see if an imbalance existed. Similarly, the percentage of patients in each treatment group who received inadequate antibiotic therapy, had severe coexisting disorders, or were moribund should be presented.

Finally, a breakdown of the causes of death and types of adverse events, including bleeding events, in each treatment group may shed light on this result. If these investigations do not reveal additional potential explanations for the lack of observed efficacy in the subgroup of patients with high APACHE II scores, then a renewed call for a confirmatory, placebo-controlled trial of DrotAA is warranted.[1]

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1. Warren HS, Suffredini AF, Eichacker PQ, Munford RS. Risks and benefits of activated protein C treatment for severe sepsis. N Engl J Med 2002;347:1027-30.

TO THE EDITOR: The results of the ADDRESS trial of DrotAA in patients with severe sepsis are in startling contrast with those of the PROWESS trial of the same drug. Of particular interest is the high-risk group for whom the indication for DrotAA is currently widely accepted (APACHE II score ≥25). Within this group, there is an important discrepancy between the trials. The relative risk of death in the treatment group was 1.19 for the ADDRESS trial (95 percent confidence interval, 0.83 to 1.71) and 0.71 in the PROWESS trial (95 percent confidence interval, 0.59 to 0.84). The authors point out that the confidence intervals for the two studies overlap, and they imply that the results are therefore consistent with each other.

Our analysis of the data reveals that an alternative hypothesis is more likely. A z-test comparing the two relative risks shows that $P=0.01$, indicating a statistically significant difference between the relative risk observed in the high-risk subgroup in the ADDRESS trial and that observed in the high-risk subgroup in the PROWESS trial. We believe that these new data cast doubt on the evidence on which worldwide practice is currently based.

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THE AUTHORS REPLY: Drs. Baillie and Murray are correct that the relative risk (DrotAA vs. placebo) observed for patients with APACHE II scores of 25 or more in the ADDRESS trial is statistically different from that observed in the PROWESS trial. They are concerned that the outcomes observed are inconsistent between the trials. How-

ever, in neither trial was the APACHE II score used to stratify randomization. Therefore, subpopulations defined according to APACHE II scores cannot be assumed to be comparable. On the basis of PROWESS, DrotAA was approved for use in patients at high risk for death, but only after extensive analyses of important characteristics of the subgroups. In the ADDRESS trial, the subgroups defined by an APACHE II score of 25 or more differed statistically, in that more patients receiving DrotAA had multiple-organ dysfunction (46.7 percent vs. 31.4 percent, P=0.02) and respiratory dysfunction (64.2 percent vs. 50.3 percent, P=0.01) and more were 65 years of age or older (62.4 percent vs. 56.6 percent, P=0.02). Such imbalances in baseline characteristics limit the assessment of outcomes in this subpopulation.

Dr. Friedrich has similar concerns but also notes that combining the subgroups of patients with multiple-organ dysfunction in the ADDRESS and PROWESS trials does not indicate a major benefit of DrotAA (relative risk of death, 0.84; 95 percent confidence interval, 0.70 to 1.01). However, there seems to be an error in his estimate of the number of patients with multiple-organ dysfunction in the ADDRESS study. The number of patients with multiple-organ dysfunction included 455 who received DrotAA and 407 who received placebo, reflecting the higher number of patients with multiple-organ dysfunction who were randomly assigned to the active-treatment group. With the use of the correct data and a chi-square test, a combined analysis of all 2133 patients with multiple-organ dysfunction from both the PROWESS and ADDRESS trials yields a relative risk of 0.82 (P=0.007; 95 percent confidence interval, 0.71 to 0.95). Furthermore, sensitivity analysis with the use of logistic models to investigate a potential study effect reveals no significant interaction between the study and the assigned treatment, and the treatment-effect estimate (P=0.01) was unaltered.

Dr. LaRosa is correct to inquire about the baseline characteristics of the subgroups of patients in the ADDRESS trial with an APACHE II score of 25 or more. Imbalances in baseline characteristics coupled with the small sample size limit the interpretation of outcomes in this subgroup of patients.

The ADDRESS trial was designed to enroll patients who had severe sepsis and a low risk of death and for whom DrotAA was not indicated under the approved label applicable to the investigative site. The study was discontinued for reasons of futility, limiting any comparison between subpopulations in the ADDRESS trial and the high-risk populations in the PROWESS trial.

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γ-Hydroxybutyric Acid in Hair

TO THE EDITOR: The review (June 30 issue)[1] on γ-hydroxybutyric acid (GHB) generated correspondence (Oct. 13 issue),[2] which revealed that biochemical genetics laboratories can detect GHB.[2] There is an additional detection method worth noting.

When a medicolegal issue is present (e.g., a drug-facilitated crime), finding a hard-to-detect drug can be important.[3] GHB has amnesic properties[3] and is fully and rapidly metabolized to carbon dioxide and water. Even succinic acid, a product of GHB metabolism, becomes undetectable in urine within hours of ingestion.

However, the GHB in the body of a crime victim is still present, even after it has been totally removed from the circulation: GHB, like other substances, accumulates in hair, after a single exposure.[4] If the hair shaft is negative for GHB, the drug may still be detected in the root bulb, at hair concentrations measured in nanograms per milligram.[5]

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