

Letter

Drotrecogin alfa (activated) in patients with severe sepsis and a high risk of deathJan O Friedrich¹, Neill KJ Adhikari² and Maureen O Meade³¹Critical Care and Medicine Departments, St. Michael's Hospital, Interdepartmental Division of Critical Care, University of Toronto, Bond Street, Toronto, Ontario, Canada M5B 1W8²Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, Interdepartmental Division of Critical Care, University of Toronto, Bayview Avenue, Toronto, Ontario, Canada M4N 3M5³Departments of Medicine and Clinical Epidemiology & Biostatistics, McMaster University, Department of Critical Care, Hamilton Health Sciences, Main Street West, Hamilton, Ontario, Canada L8N 3Z5Correspondence: Jan O Friedrich, j.friedrich@utoronto.ca

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Critical Care 2006, **10**:427 (doi:10.1186/cc5117)See related letter by Williams *et al.*, <http://ccforum.com/content/10/5/424>, letter by Friedrich *et al.*, <http://ccforum.com/content/10/5/420>, letter by Agarwal and Nath, <http://ccforum.com/content/10/4/416>, and commentary by Friedrich *et al.*, <http://ccforum.com/content/10/3/145>

We are pleased that Williams and coworkers [1] confirmed our random effects analysis [2], which relied on publicly available data. This analysis pooled the results from patients with Acute Physiology and Chronic Health Evaluation (APACHE) II scores of 25 or greater from the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation of Severe Sepsis) [3] and ADDRESS (Administration of Drotrecogin Alfa [Activated] in Early Stage Severe Sepsis) [4] trials. As we discussed previously [5], this analysis demonstrates a surprising degree of statistical heterogeneity, which remains despite minimal methodologic differences between the two trials and further minimization of clinical heterogeneity by selecting a more uniform subgroup of patients with severe sepsis and a high risk for death. This heterogeneity is illustrated in Figure 1 presented by Williams and coworkers [1], in which I^2 (the percentage of total variation in results across studies that is due to heterogeneity rather than chance [6]), is more than 80% for each of the methods presented. Given this degree of unexplained heterogeneity, the use of a fixed effects model, as suggested by Williams and coworkers [1], would be highly unconventional [7].

We also support the pooling of individual patient data from these trials to generate hypotheses regarding appropriate patient selection for drotrecogin alfa (activated) that could be tested in subsequent trials [5]. Furthermore, we encourage public release of these data for the purposes of a meta-analysis of individual patient data to be undertaken by an independent group, using appropriate statistical methods that incorporate random effects, and that is subject to peer review.

Competing interests

The authors declare that they have no competing interests.

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