Letter
Activated protein C in sepsis: down but not out, yet
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We read with interest the recent commentary by Friedrich and coworkers [1], in which they consider whether the current evidence supports treatment for severe sepsis with drotrecogin alfa (activated). They conclude that the survival benefit is weak in patients with severe sepsis treated with activated protein C (APC) [1]. However, this conclusion has a number of limitations.

First, the authors have summated the individual studies by using a random effects model. Although the random effects model is generally used in the presence of significant hetero-geneity, statistical tests erroneously detect heterogeneity when there are few studies [2]. Another problem with this model is that by adding a constant number to the weight of each study, the relative contributions of each trial become more equal. This can have a marked effect on the results, and only seldom does it afford an appropriate representation of the efficacy expected [3,4]. In fact, if we use a fixed effects model then there is significant benefit with the use of APC in both of the classic indications, namely Acute Physiology and Chronic Health Evaluation II score above 25 (odds ratio 0.71, 95% confidence interval [CI] 0.56-0.91) and two or more organ dysfunctions (odds ratio 0.78, 95% CI 0.64-0.94), with the numbers needed to treat being 14 (95% CI 8-46) and 20 (95% CI 12-72), respectively.

The problem thus lies with the recognition of heterogeneity in a trial, which includes clinical heterogeneity (variability in the participants, interventions and outcomes), methodological heterogeneity (variability in trial design and quality) and statistical heterogeneity (variability in the treatment effects evaluated in different trials). Ideally, a meta-analysis should only be considered when a group of trials is sufficiently homogeneous. Such a situation is Utopian. Indeed, one could argue that because clinical and methodological diversity always occur in a meta-analysis, statistical heterogeneity is inevitable. Thus, the test for heterogeneity is irrelevant to the choice of analysis; heterogeneity will always exist, whether we are able to detect it using a statistical test or not [5].

Finally, the authors base their conclusions on an abstract patient data meta-analysis rather than individual patient data meta-analysis. Abstract patient data meta-analyses reflect the first step toward generating hypotheses, which need to be retested in a fully fledged individual patient data meta-analysis. Although methodologically difficult, the latter can evaluate ran-domization methods and correctness of data, re-analyze the original data, perform additional analyses and update patient outcomes that become 'frozen' in time, and can thus overcome the limitations of abstract patient data meta-analysis [6].

Is there a role for APC in severe sepsis? The PROWESS (Recombinant Human Activated Protein C Worldwide Evalua-tion of Severe Sepsis) trial [7] demonstrated a 6.1% absolute reduction in mortality rate ($P = 0.005$). Therefore, the use of this drug should be continued in high-risk situations, as defined by the Surviving Sepsis Campaign guidelines, unless this recommendation is refuted in further trials.

Competing interests
The authors declare that they have no competing interests.

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