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Can we RESOLVE the treatment of sepsis?

See **Articles** page 836

In today's *Lancet*, Simon Nadel and colleagues[1] report the much anticipated results of the RESOLVE (REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspectiVE) trial, in which they assessed activated drotrecogin alfa (recombinant human activated protein C) in children with sepsis. In this double-blind placebo-controlled international trial, the investigators randomly assigned children with severe sepsis to a 4-day course of drotrecogin alfa or placebo (intravenous saline). The primary endpoint was a composite score for resolution of organ failure; secondary endpoints were all-cause mortality up to 28 days after treatment and safety. The overall results are unexpected and profoundly disappointing: no efficacy signal was detectable from any of the endpoints, and the survival graphs look much the same for both treatment groups.

Children with sepsis should be an ideal population to test the efficacy of new antisepsis agents because these patients commonly have acute life-threatening infection without major underlying comorbidities. Furthermore, children have a greater capacity for tissue repair than do adults, and such physiological reserve should translate into a greater potential for reversal of severe sepsis. However, the favourable outlook for children with sepsis creates an unintended but major impediment to the development of new antisepsis drugs. A low number of deaths in placebo groups forces investigators to do very large studies to identify significant differences in outcome, or to have no mortality endpoints and rely on measurement of morbidity for drug efficacy.

Several scoring systems to assess morbidity in children with sepsis have been proposed, the most recent of which[2] was used in RESOLVE. However, these scores generate abstract numbers that lack clear clinical applicability, and they are substantially affected by early mortality events and by the particular management of organ dysfunction (eg, ventilator-weaning protocols, use of blood product, removal of renal replacement therapy). Without specific protocols that standardise the management of organ support in these children, the heterogeneity of the population and the widely disparate management strategies make it difficult to find a signal of modest efficacy with any antisepsis drug.

RESOLVE has some intriguing findings. First, patients with sepsis who had the most severe coagulation abnormalities seemed to benefit from drotrecogin alfa. Similar findings, independent of APACHE (Acute Physiology And Chronic Health Evaluation) II score, have been recorded for adults with sepsis who were treated with activated protein C[3,4] or with antithrombin in the

absence of heparin.[5] Second, during the trial, intracranial bleeding was more common with drotrecogin alfa than with placebo (five events during infusion, four of which occurred in those younger than 2 months, *vs* one event during infusion). Future trials of drotrecogin alfa, and probably other anticoagulants, should avoid treatment in the neonatal period. Third, the possible role of so-called first-patient effect needs consideration because of the excess mortality noted for the initial patients who were enrolled in placebo-controlled trials of drotrecogin alfa. This effect was striking in the ADDRESS (ADministration of DRotrecogin alfa in Early Severe Sepsis) trial,[6] for which mortality was higher for the first patient given drotrecogin alfa than for the first patient given placebo at every study site (22·3% *vs* 14·5%, p=0·04). After enrolment of the first patient at every site, the number of deaths did not differ between drotrecogin alfa and placebo. Patients treated at experienced centres where drotrecogin alfa is used regularly are less likely to have adverse events than are patients treated at centres where the drug is used sparingly or for the first time. In RESOLVE, 477 patients were enrolled at 104 study sites, and the first-patient effect might have adversely affected the entire study.

The disappointing results of RESOLVE raise important questions about the overall efficacy of drotrecogin alfa in adults with severe sepsis. Could the salutary findings of the initial PROWESS (recombinant human PROtein C Worldwide Evaluation in Severe Sepsis) trial[3] have been due to chance alone? The actual mechanism of action of drotrecogin alfa remains contentious. The mechanism of protection afforded by activated protein C probably extends beyond its well-documented antithrombotic effects. That drotrecogin alfa protects endothelial cells and limits interactions between endothelial cells and neutrophils in sepsis is a consistent experimental finding.[7–9] Production of new recombinant forms of activated protein C with greater endothelial protective effects and fewer bleeding complications than those associated with drotrecogin alfa may be possible.

We seem to be at a crossroads with the indications for drotrecogin alfa in severe sepsis: either the optimum population of patients for treatment with drotrecogin alfa needs to be defined more clearly, or calls for a repeat placebo-controlled trial of drotrecogin alfa in severe sepsis in adults will become increasingly difficult to ignore.

Steven M Opal
Department of Medicine, Brown Medical School, Memorial Hospital of Rhode Island, Pawtucket, RI 02860, USA
Steven_Opal@brown.edu

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Tracking inequity: assessments of poverty-related outcomes

See **Articles** page 850

In today's issue of *The Lancet*, Patama Vapattanawong and colleagues[1] present additional analyses of routine census data for Thailand from 1990 and 2000, and show that the impressive reduction in child mortality rates and socioeconomic status has been accompanied by a narrowing of the mortality gap between various socioeconomic quintiles. Despite some methodological limitations, these findings suggest that incorporation of equity measurements into censuses or comparable routine surveys is feasible. These findings are important. Although the authors present only indirect supportive information and coverage data from programmes and relevant interventions from the period in question, their findings suggest that it is possible to reduce child