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EDITORIAL

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Once is not enough: clinical trials in sepsis

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Introduction

In this issue of *Intensive Care Medicine*, the steering committee members of the PROWESS-Shock trial present a balanced discussion of the controversies surrounding recombinant human activated protein C (rhAPC) and the challenges intrinsic to designing an industry-sponsored trial [1]. The investigators have taken important steps to be transparent about financial conflicts of interest, to safeguard data monitoring and to ensure the validity of statistical analysis. The purpose of the upcoming PROWESS-Shock Trial is to prospectively test rhAPC in a high-risk septic population—those patients with vasopressor-dependent shock for ≥4 h. The need for this trial, years after the regulatory approval of rhAPC for a similar indication, is a cautionary tale that contains important lessons for health care providers who manage patients with sepsis, the pharmaceutical industry and the Food and Drug Administration (FDA).

The following is an excerpt from a letter written to Dr. Jay P. Siegel, Director of the Office of Therapeutics Research and Review, FDA, on 22 October 2001 by four of the ten dissenting members of the FDA advisory panel that considered the safety and efficacy of rhAPC (Personal communication, Suffredini A for the authors, Cross AE, Munford R, Suffredini A, Warren S):

> "Despite many attempts over the last two decades, no drug in this field [sepsis] has reproducibly improved mortality. All agents have failed when tested in a second confirmatory trial. Accordingly, a drug [rhAPC] that we know to be toxic should not be released without confirming that it does, in fact, prolong lives…"

After 7 years of use and two additional randomized controlled trials (RCTs) we have finally returned to addressing the fundamental clinical concern voiced in this communication.

Since its approval in 2001, there has been mounting evidence that the incidence of serious bleeding, including cerebral hemorrhage with rhAPC is higher in clinical practice than estimated from the original PROWESS trial [2–4]. Because of this and the continued controversy about efficacy and how to select patients who may benefit, rhAPC has been under-utilized in the subpopulation of patients for whom it was approved [5]. As the PROWESS-Shock investigators and steering committee members note in this issue of *Intensive Care Medicine*, the results of this trial will hopefully resolve a disturbing paradox surrounding this therapy: the PROWESS-Shock trial may on the one hand prove that rhAPC increases the risk of serious bleeding without providing an overall survival benefit, or it may show that rhAPC is a safe, life-saving therapy which has been denied to patients due to scientific uncertainty. In either case, since the introduction of rhAPC in 2001, some septic patients have been adversely affected by the inadequacy of available evidence to appropriately guide its use in clinical practice.

In hindsight, it may seem surprising that the FDA did not heed the advice of the dissenting members of the advisory committee and require a second RCT prior to approving rhAPC. In defense of the FDA, sepsis is lethal syndrome-affecting patients of all ages and new approaches to improve outcome have been eagerly sought for the past 30 years. This has led to a sense of urgency and promising results from initial trials of new therapeutic approaches have repeatedly inflated expectations among healthcare providers. However, the history of rhAPC clearly shows the downside of approving drugs for sepsis based on a single RCT. In the case of rhAPC, the risks of severe hemorrhage and approval for a target population that was not prospectively defined further compounded the lack of confirmatory evidence demonstrating reproducibility.

In an effort to determine the importance of reproducibility in this field, we performed a MEDLINE search for therapies used for sepsis that have undergone more than one RCT of which at least one showed a significant improvement in survival. Including rhAPC, we found seven such agents: high dose corticosteroids, two anti-endotoxin therapies, human recombinant interleukin-1 receptor antagonist (IL-1ra), intensive insulin therapy (IIT) and intravenous immunoglobulin [4, 6–37]. Like rhAPC, some of the agents received initial regulatory approval or in the case of already available drugs were widely adopted into clinical practice for the management of severe sepsis. Of note, we chose not to discuss intravenous immunoglobulin as prior meta-analyses of these studies have yielded controversial and conflicting conclusions beyond the scope of this editorial [34–37].

High dose corticosteroids: 1963–1989

In late 1976 and in contrast to an abstract published earlier that same year [29], a single center, single author RCT which enrolled 172 consecutive patients over 8 years demonstrated a 28-day mortality benefit in septic shock with short courses of high dose corticosteroid therapy (38 vs. 10%) [27]. While aspects of this trial should have given clinicians pause and led to the design of confirmatory studies, there were no appropriately powered RCTs of high-dose corticosteroids in septic shock for the next 7 years. Meanwhile, this therapeutic approach was widely incorporated into the care of patients with septic shock in many intensive care units including our own at the National Institutes of Health (NIH) Clinical Center [38]. Beginning in 1984, however, five successive RCTs failed to show a mortality benefit from this approach, even though several different treatment regimens were investigated in various patient populations with septic shock [6, 15, 22, 23, 28]. Meta-analysis of these studies showed that high dose corticosteroid treatment actually increased mortality in septic shock and that the single, early trial showing benefit was in fact a statistical outlier (Fig. 1) [39].

Anti-endotoxin antibody therapy: 1982–1992

The first generation of anti-endotoxin therapies included plasma obtained from volunteers immunized against J5-*E. coli* endotoxin or intravenous immunoglobulin preparations derived from donors selected for high titers of anti-endotoxin antibody [7, 8, 10, 17, 25, 33]. The first RCT testing plasma from J5-immunized subjects in patients with gram-negative sepsis was published in 1982 and showed significantly improved survival [33]. The accompanying editorial concluded that this study had "…greatly enhanced our ability to treat successfully a large number of very sick patients [40]." Despite the positive result of this initial study and the expectations it raised, five subsequent RCTs using either J5 antiserum or immunoglobulin preparations containing high titers of anti-endotoxin antibodies failed to demonstrate a mortality benefit [7, 8, 10, 17, 25]. Meta-analysis of these 5 RCTs (841 patients) not only showed that J5 antiserum and polyclonal anti-endotoxin antibodies were not beneficial in patients with gram-negative sepsis, but that the original published trial was a statistical outlier (Fig. 1) [41].

Monoclonal antibody preparations including murine (E5) and human (HA-1A) IgM preparations represented the second generation of anti-endotoxin therapies. After a single RCT demonstrated a survival benefit in patients with culture proven gram-negative sepsis, HA-1A was approved for use in Europe and parts of Asia [32]. Despite the initial unanimous vote by its own advisory committee in favor of approval, serious concerns about HA-1A [42], in combination with results of a large animal sepsis model showing harm [43], led the FDA to call for a second clinical trial of HA-1A before granting licensure. This subsequent trial was terminated early because of excess mortality among HA-1A treated patients without gram-negative bacteremia (41 vs. 37% mortality rate among placebo treated patients) [24]. Consequently, HA-1A was never approved for use in the US and shortly thereafter, the manufacturer removed HA-1A from markets worldwide. Although not harmful, E5 was also not beneficial in two RCTs (Fig. 1) [14, 20].

IL-1 receptor antagonist, a mediator specific anti-inflammatory agent: 1994–1997

IL-1ra is an anti-inflammatory cytokine that inhibits IL-1 signaling and its potentially harmful inflammatory effects.

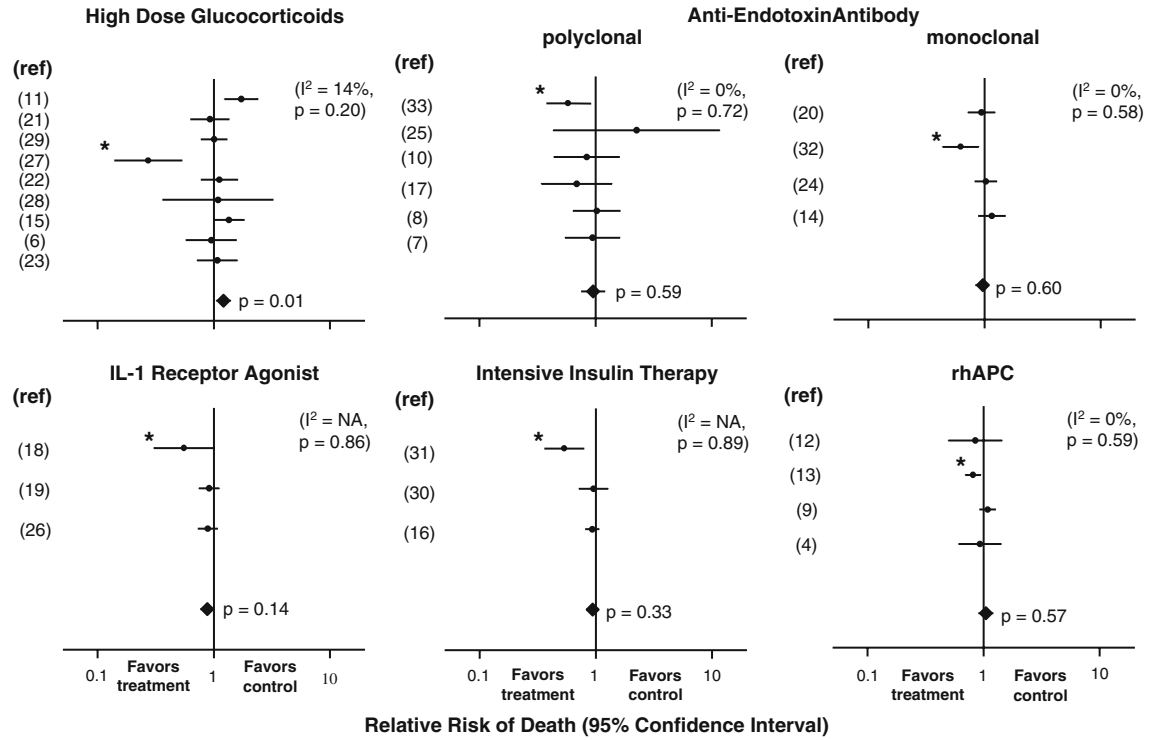

Fig. 1 Each panel represents one of six therapies. The relative risk of death (RR) is shown for each randomized controlled trial (RCT) by a *closed circle* and the *horizontal lines* represent the 95 percent confidence interval. Significantly beneficial RCTs ($P < 0.05$) are denoted by an *asterisk*. In each panel, all RCTs except the initial significantly beneficial trial are included in the summary statistic (shown as a *diamond*). A test for heterogeneity (I2) of these RCTs is shown in the *upper right hand corner* of each *panel*. For each therapy, RCTs performed, excluding the beneficial trial, were either overall harmful or showed no effect. When examined across the 6 interventions, there was a significant shift in the RR from the early beneficial trial to the final one showing no effect ($P = 0.003$). *ref* reference, *Il-1* Interleukin-1, *rhAPC* recombinant human activated protein C

A human recombinant preparation of IL-1ra was tested in three clinical trials beginning in 1994. The initial randomized but unblinded phase 2 trial ($n = 99$) of IL-1ra showed a dose-dependent significant survival benefit [19]. Unfortunately, this beneficial result was not reproduced in two subsequent large RCTs ($n = 1{,}589$ combined) (Fig. 1) [18, 26].

Intensive insulin therapy: 2001 to present

In 2001, IIT (maintaining blood glucose between 80 and 110 mg/dL) was reported to significantly improve survival in critically ill surgical patients [31]. Based on this single center, unblinded RCT, IIT was quickly embraced and introduced into the care of a wide range of critically ill patients in the United States including those with sepsis. Although not conducted in septic patients, this trial was the primary evidence that supported the inclusion of insulin-based glucose control in sepsis guidelines and management bundles [44]. However, two subsequent RCTs of IIT, including one, which specifically tested IIT in severe sepsis, failed to demonstrate a survival benefit while finding a 16–18% increase in severe hypoglycemia [16, 30]. In septic patients, this severe hypoglycemia was associated with a significantly increased incidence of serious adverse events [16].

rhAPC: 2001 to present

In the original PROWESS study, severely septic patients experienced an overall reduction in mortality with rhAPC therapy (30.8 vs. 24.7%; $P = 0.005$) [13]. However, a retrospective analysis by the FDA suggested that the benefit was limited to patients with a high risk of death. Based on this post hoc analysis, the FDA approved rhAPC only for patients with APACHE II scores $\geq$25 or other indicators of high mortality [45]. Similarly, the European Medicine Agency approved rhAPC only for patients with severe sepsis and multiorgan failure. As discussed in this issue of *Intensive Care Medicine* by the authors of the PROWESS-Shock Steering Committee, two follow-up controlled trials involving children (RESOLVE) and adults with sepsis and a low risk of death (ADDRESS) were both stopped early for futility as it was highly unlikely that rhAPC would be

superior to placebo [4, 9]. Together, these two trials enrolled 3,039 patients and, both showed an increased risk of serious bleeding with rhAPC compared to controls (2.4 vs. 1.0% and 2.4 vs. 1.2%; $P = 0.02$ for both comparisons) that exceeded the risk of bleeding in the original PROWESS trial [46]. In addition, patients with APACHE II scores ≥ 25 ($n = 324$) or two or more organ failures ($n = 872$) showed no benefit from rhAPC in the ADDRESS trial, raising concerns about efficacy and whether these criteria identified a population of septic patients who were likely to benefit from the drug [47].

Conclusions

In an effort to streamline the process of approving medical therapies without compromising safety, the US Congress passed The FDA Modernization Act of 1997 [48]. Included in this document was a clarification of the number of required clinical investigations needed for approval:

> "If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence…are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of [approval]."

However, in the case of sepsis therapies, the history of this field argues that two beneficial RTCs are necessary with at least one being a confirmatory trial for the regulatory approval of any new drug. Confirmatory trials are particularly germane if new therapies have life-threatening risks and inconsistent benefits across subpopulations of patients. For the six sepsis therapies reviewed here, an early beneficial trial was later eclipsed by subsequent trials that were either unable to confirm efficacy or ultimately demonstrated harm; this shift in treatment effect was statistically significant across the six interventions ($P = 0.003$) (Fig. 1). Four of the therapies (high dose corticosteroids, HA-1A, rhAPC, and IIT) received either broad clinical acceptance, governmental licensure or both. Based on a subsequent trial, one of these therapies, HA-1A, was removed from the markets worldwide after it was shown to be harmful. Another, high dose corticosteroids, was shown in later trials to have risks that outweighed any potential benefit in septic shock and use was abandoned. IIT has been shown in a study of septic patients to have no benefit and to increase the risk of severe hypoglycemia. A recent meta-analysis including trials employing more liberal blood glucose goals (<150 mg/dL) than IIT also found no survival benefit and an increased risk of hypoglycemia in critically ill patients [49]. We await the results of the PROWESS-Shock trial in high-risk patients to help guide future care. However, this will not change the paradox described above that patients were potentially harmed because a high risk and controversial therapy was approved for sepsis without a confirmatory trial.

This pattern of inconsistent findings between trials serves to remind us of the limits of the single RCT. Namely, while the RCT design minimizes selection bias within a trial, it is still only a single experiment. Moreover, performing one or more RCTs does not guarantee the internal or external validity of the results [50]. In sepsis research, patient population heterogeneity, high background mortality rates, and an incomplete understanding of the pathogenesis have made progress slow and costly. As such, reproducible and highly consistent evidence of benefit in a clearly defined and easily identifiable group of septic patients is essential before conferring regulatory approval or changing clinical practice—*primum non nocere.*

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