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EDITORIAL

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Wanted: early goal-directed therapy for septic shock—dead or alive, but not critically ill!

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The landmark prospective, randomized trial on early goal-directed therapy (EGDT) for severe sepsis and septic shock was published by Rivers et al. [1] in 2001. The trial findings included an astonishing 42% relative risk reduction (RRR)—a 16% absolute risk reduction—of in-hospital mortality. I used the word astonishing because no single therapy—other than antibiotics—has ever shown such a survival benefit in the history of sepsis research. The trial was expectedly welcomed by most clinicians and surgeons who work with critical care patients, and a sense of hope pervaded the sepsis field after almost 20 years of many failed trials. EGDT quickly became a standard recommendation by many medical and surgical societies, which also endorsed two reports by the survival sepsis campaign guidelines [2, 3]. So many observational studies evaluating EGDT have been published that I would have to ask the editors for extra space in order to cite all of them. Also expectedly, trial design problems and the possibility of EGDT being "too good to be true" attracted criticism soon after the trial publication [4–7]. Unquestionably, the EGDT trial design flaws extensively discussed over the last 8 years, and the lack of solid scientific reproducibility in another similar prospective randomized trial have raised serious questions about the validity of the original results, not to mention the possible trial misconduct issues reported in the Wall Street Journal [8].

Let's just forget all these problems for a moment and assume that this trial was among the best trials ever performed in the intensive care medicine field. In other words, this would be a truly "stand alone" type of trial—in such a case, not only the EGDT 'enthusiasts,' but even the mild or moderate 'skeptic' physicians should be easily persuaded that there are no substantial reasons to justify their skepticism, correct? Not really. In order to understand why a healthy dose of skepticism about EGDT is necessary (even when we assume it was among the best trials ever), I will start with the question that matters the most: "What is the current probability that EDGT is not better than the standard care in our patients with severe sepsis?" Surprisingly, this realistic and clinical question can be easily answered by Bayesian methodology, which allows us to think in the same way we do when we take care of our own patients with severe sepsis [9–12]. If the intensivist or the emergency department (ED) physician believes that there has been very little evidence against the use of EGDT—based on other prospective or observational studies evaluating similar hemodynamic strategies before of after the Rivers trial (a "mild skeptic" in Bayesian terms), then the current probability of EGDT being no better than standard care is 0.05 or 5%. This gives the physician weak support to use EGDT in clinical practice, because a 5% probability that EGDT would be no better than the standard care (the way many of us would like to interpret a p value 0.05) would preclude the acceptance of this therapy by most ICU and ED physicians. However, if the clinician believes that there is little to moderate evidence against the use of EGDT (a "mild-moderate skeptic" in Bayesian terms), then the probability of EGDT being no better than standard

care elevates it to 0.14 or 14%. This high probability of failure—despite a "positive" trial result—would preclude the use of EGDT by the vast majority of physicians [9]. Analogously, Bayes technology allows us to ask another essential clinical question: "What is the current probability of decreasing the RRR for death by more than 15% in our patient with severe sepsis? (The 15% represents the lowest clinical meaningful threshold for a new sepsis therapy.) The probability of EGDT achieving this 15% relative death reduction is very low for the "mild skeptic" physician: 62% [9], and inadmissibly low for the "mild-moderate skeptic" physician: 27%! Hence it is clear that the scientific evidence for EGDT to change ICU standard care is tenuous, at best. Still, the meetings and journal debates between the EGDT 'lovers' and 'doubters' appear endless. How can we resolve this conundrum about EGDT?

This journal edition brings a study by Reade et al. [13], who suggest that by the use of a prospectively designed individual patient data meta-analysis of clinical trials performed in critically ill patients, such as the EGDT trials, we would have more reliable scientific evidence to decide about its use (or not) in our medical practice, as well as a better understanding of which specific patient subsets would receive the most benefit. In the context of this article, the word "evidence" means all clinical trials that meet the prospectively defined meta-analysis inclusion criteria. By the way, what is an individual patient meta-analysis? How is that different from the conventional meta-analysis? Has individual patient meta-analysis been ever used in intensive care medicine?

All adequately performed meta-analyses are based on the systematic (and exhaustive) review and critical appraisal of available evidence, abstraction of the effect size and variance from each study that meet prospectively defined inclusion/exclusion criteria, then the calculation of a weighted mean of these effect sizes, and finally the exploration of the reasons for potential heterogeneity among different study subgroups [14]. When the data collection is based on the "study level" results, e.g., each treatment effect such as absolute and relative risks, or odds ratios—from each trial, the study is defined as "aggregate" patient data (APD) meta-analysis, whereas when the data collection is based on "patient level" results, e.g., each patient's outcome from each trial, the study is defined as an "individual" patient data (IPD) meta-analysis. The potential advantages of IPD over APD meta-analysis are numerous: ability to use common definitions; ability to assess adequacy of randomization; allows data checking and updating, as well as adjustment for the same variables across studies; undertakes time-to-event analysis in a more direct way; undertakes subgroup analyses for important hypotheses with increased power; and facilitates heterogeneity analyses at the patient level [15–17]. One of the classical examples of the advantages with IPD meta-analysis was demonstrated by the meta-analyses of angiotensin-converting enzyme inhibitors for acute myocardial infarction (MI): the APD meta-analysis showed similar benefits for all patients with MI, but the IPD meta-analysis with over 98,000 patients showed that the survival benefit was significantly larger for patients with anterior MI compared to other MI sites [18].

Known and important limitations of IPD meta-analysis include the lack of standardized analysis methods [19] and the frequent unavailability of individual patient (raw) data from clinical trials secondary to several issues as described by Reade et al.: authors' willingness, proprietary interests, original data destruction and patient confidentiality. The problem with the common lack of availability of patient-level data is that trials without these data would have to be excluded from the IPD meta-analysis; in addition, individual patient data would not be adequately meta-analyzed in conjunction with aggregate level data. In that case, the IDP meta-analysis would run the risk of study selection bias and the generation of questionable conclusions due to the exclusion of potentially important clinical trials. That is why APD (i.e., conventional) meta-analysis remains the most common type of meta-analysis and arguably the most appropriate to answer questions related to binary outcomes, especially when the outcomes are comparable across the studies [19]. Notably, the reasons for why meta-analyses are considered high-level evidence are similarly relevant for both IPD and APD study designs [16]. In fact, new ICU/ED trials involving, for example, EGDT, intensive insulin therapy, drotrecogin alfa activated, or low-dose steroids, should explicitly be interpreted in the context of all previous trials; in other words, new trial reports should begin and end with an up-to-date systematic review of all available evidence [20]. If it is not possible for an IPD meta-analysis to be done after the completion of a new trial, at least an updated APD meta-analysis should be performed in order to interpret the new results (positive or negative) in light of all existing evidence. Further, I expect that the authors of each of these already published pivotal trials, Rivers et al. in the current case, will be willing to provide their raw database to research groups such as Reade et al. in order to perform the most inclusive and comprehensive IPD meta-analyses. These robust and updated meta-analyses encompassing all available and relevant evidence will be the best scientific and ethical way to finally move ICU/ED research from the twentieth to the twenty-first century.

Reade et al. provided an extensive description of the pros and cons of IPD meta-analyses, as well as a review of IPDs in the intensive care field—unfortunately, they located only ten IPD meta-analyses up to this date (see Reade et al., Table 2). The paucity of studies using this technique in our field is likely due to difficulties inherent to the statistical methodology and considerable logistic barriers, as noted above, or both. The meta-analytic

methodology has made impressive advances in the last decade, which will certainly facilitate the use of IPD meta-analysis. Thus, what is mostly missing at this time to increase the utilization of IPD meta-analysis in intensive care medicine is a more transparent and cohesive collaboration among clinical trialists, principal investigators, industry and governmental institutions.

Reade et al. are to be congratulated for such a great collaborative effort to resolve important therapeutic issues such as the use of EGDT for patients with severe sepsis and septic shock. Their prospective and multinational cooperation to perform a unique and powerful individual patient data meta-analysis of several large clinical trials [Protocolized Care for Early Septic Shock (ProCESS); Australian Resuscitation in Sepsis Evaluation (ARISE); Protocolised Management in Sepsis (ProMISe)] will unquestionably bring EGDT to its final destiny: dead or alive, but not critically ill!

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