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EDITORIAL

James A. Russell
Morten Hylander Møller
Djillali Annane

Early goal-directed therapy: from discovery through enthusiasm to equipoise?

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J. A. Russell (✉)
Centre for Heart Lung Innovation, St. Paul's Hospital, 1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada
e-mail: jrussell@mrl.ubc.ca

M. H. Møller
Department of Intensive Care, 4131, Copenhagen University Hospital Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark
e-mail: mortenhylander@gmail.com
Tel.: +45 22 55 53 43

D. Annane
Service de reanimation medicale, Hopital R. Poincare (APHP), Laboratory of Cell Death, Inflammation and Infection, UMR1173, University of Versailles SQY, INSERM, 104 Bd Raymond Poincare, 92380 Garches, France

The original Rivers trial [1] of early goal-directed therapy (EGDT) discovered that a process of EGDT that guided fluids, vasopressors, inotropic agents and transfusions in the first 6 h of sepsis dramatically reduced mortality (relative risk reduction, RRR of 42 %) compared to usual care in an emergency department (ED) setting. That discovery ushered in an exciting era of early identification, resuscitation and monitoring of patients with sepsis. Since 2003, EGDT has been recommended in international sepsis guidelines [2–4], and implementation in routine care has been associated with benefits [5]. Likewise, many observers suggested that prompt recognition and treatment of sepsis may partly explain declining mortality from sepsis [6, 7].

Some have suggested that EGDT as described in Rivers' trial may not apply to the intensive care setting, because it was a single-centre trial conducted in the emergency department, the control mortality rate was higher than expected, and baseline central venous oxygen saturation ($ScvO_2$) was remarkably low (about 50 %)—an observation thought to be rare in septic ICU patients. Accordingly, many argued that there was clinical equipoise about the role of EGDT in ICU patients with sepsis, and several subsequent multicentre RCTs [8–10] did not find survival benefits from EGDT (mortality was actually slightly higher in EGDT than the usual care group in ProMISe).

In this issue of *Intensive Care Medicine*, Peake and colleagues [11] report a systematic review with meta-analysis of five RCTs [1, 8–12] showing no difference in mortality between ED-initiated EGDT versus usual care groups. However, the ED-initiated EGDT group had significantly more use of vasopressors and duration of stay in the ICU. Peake and colleagues [11] also reviewed six RCTs of non-ED-initiated EGDT, again finding no difference in mortality between EGDT versus usual care. The systematic review adheres to current standards for the conduct and reporting of a systematic review [13, 14], including a pre-experimentally published protocol, a comprehensive search strategy, adequate conventional cumulative meta-analyses, relevant sensitivity and subgroup analyses, and adequate assessment of risk of bias. Conventional cumulative meta-analyses are at risk of producing random errors because of sparse data and repetitive testing of accumulating data [15–17]. The risk of random errors can be assessed by trial sequential analysis (TSA), where trial sequential monitoring boundaries are applied to the conventional meta-analysis. The underlying assumption of TSA is that significance testing and calculation of the 95 % confidence interval are performed each time a new trial result is published or available. TSA depends on the accrued information

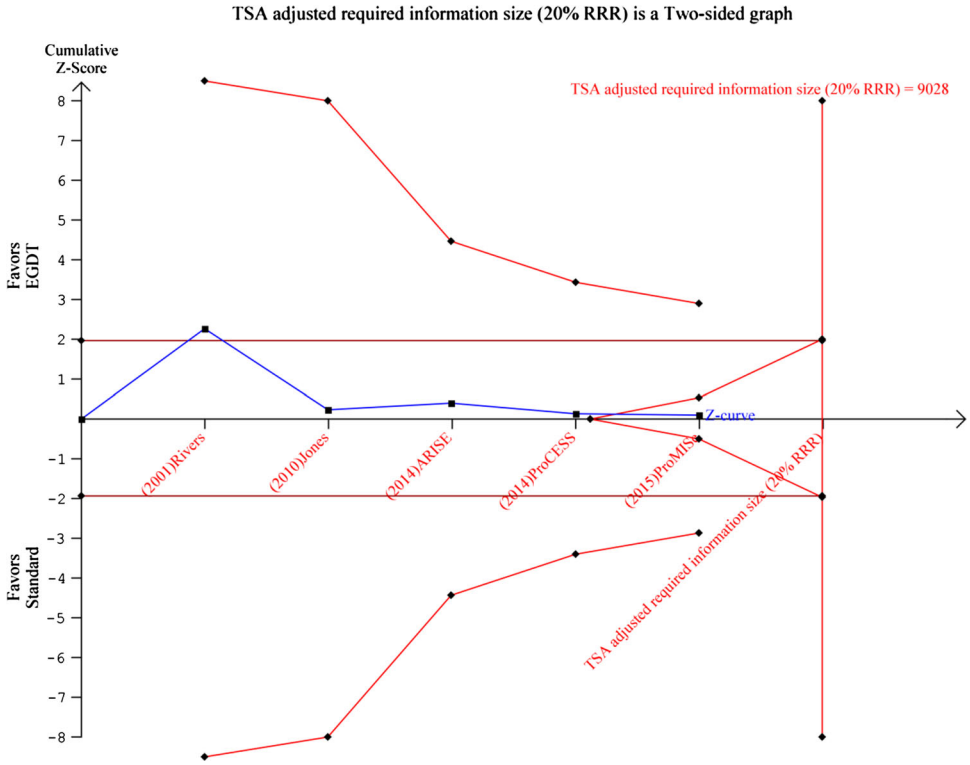

Fig. 1 Trial sequential analysis of all-cause mortality (five trials [1, 8–11]). The *upper* and *lower red boundaries* are trial sequential monitoring boundaries for benefit and harm. The TSA adjusted required information size of 9028 patients was calculated using $\alpha = 0.05$ (two sided), $\beta = 0.10$ (power 90 %), an anticipated relative risk reduction of 20 % (as in the original sample size calculations of the three recent trials [8–10]), and an event proportion of 22 % in the control arm (mean value of the included trials). The *blue cumulative z curve*, constructed using a random effects model, crosses the boundary for futility

available and the required information size needed to detect or reject a reasonable clinically relevant intervention effect. Applying TSA to the present meta-analysis yields that the area for futility has been reached (Fig. 1), suggesting that a 20 % or greater relative risk difference in mortality (as used in the original sample size estimations in [8–10]) between EGDT and usual care is unlikely (risk of type II error 10 %). Consequently, TSA is consistent with the results of the conventional cumulative meta-analysis.

Several striking differences are obvious when comparing the estimated vs. the actual mortality. First, usual care group mortality rates were overestimated by 5.1 % [8], 19.4 % [9] and 10.8 % [10], similar to previous overestimates in septic shock trials [18]. Finally, care prior to inclusion and randomization in both groups was at the discretion of the treating physician, and could include elements of aggressive fluid resuscitation which could have dampened the efficacy of EGDT. The mean times from ED admission to randomization were very short, about 3 h in ProCESS [8], 1.5 h in ARISE [9] and about 2.5 h in ProMISe [10]. The 90-day mortality rate of the usual care groups, using very similar inclusion criteria and over the same time frame, was 10.6 % higher in ARISE [9] than in ProMISe [10].

Why were the results of the three recent RCTs of EGDT so different from Rivers' trial? It is quite likely that there is systematic "contamination" of the principles of EGDT in usual care in most EDs and ICUs now, so it was likely impossible to have a usual care group that did not have early recognition and early resuscitation, which may account for the remarkably low usual care mortality rates. Second, the main difference between EGDT and usual care groups was the use of $ScvO_2$ measurement and targeting therapies to achieve $ScvO_2$ greater than 70 % [1]. Use of continuous $ScvO_2$ monitoring was done in 87 % of EGDT patients in ProMISe and about 93.2 % in ProCESS. Finally, the requirements and methodological quality of clinical trials have increased over the years, resulting in an a priori lower risk of bias and subsequently less pronounced intervention effects [19]. Another important difference between Rivers' RCT [1] and the ProCESS [8], ARISE [9] and ProMISe [10] trials was the delay in adequate and full resuscitation in Rivers' control arm. ProCESS, ARISE and ProMISe were run in settings of high levels of care in ED and ICU. The results of ProCESS, ARISE and ProMISe may not be generalizable in emerging countries with evolving health care systems.

What should clinicians do now? The confluence of low usual care mortality rates confirms that early recognition and intervention are effective. Use of sepsis bundles to enhance early recognition in the ED and guide therapies are effective and easily applied processes of care. However, resuscitation based solely on $ScvO_2$ monitoring cannot be recommended. Thus, Rivers' improved process of care (early recognition and intervention) that is now an integrated part of sepsis bundles and guidelines around the globe has ironically led to lower mortality rates

without the need for the original algorithm. Does that mean clinicians should never measure $ScvO_2$? Of course not; patients with inadequate response to standard resuscitation might merit advanced hemodynamic monitoring, including use of $ScvO_2$ or cardiac output monitors.

To summarize, the present high-quality systematic review with meta-analysis, and the TSA suggest that routine use of EGDT including $ScvO_2$ in adult patients with severe sepsis in the developed world is not warranted. New RCTs of EGDT may be warranted in children, emerging countries, or with different targeted endpoints and algorithms. Continued improvements in processes of care that enhance early recognition and resuscitation with appropriate doses of fluids, vasopressors and inotropic agents are critical to further improvements in outcomes of sepsis.

Conflicts of interest Dr. Russell reports patents owned by the University of British Columbia (UBC) that are related to PCSK9 inhibitor(s) and sepsis and related to the use of vasopressin in septic shock. Dr. Russell is an inventor on these patents. Dr. Russell is a founder, director and shareholder in Cyon Therapeutics Inc. (developing a sepsis therapy). Dr. Russell has share options in Leading Biosciences Inc. Dr. Russell reports receiving consulting fees from Cubist Pharmaceuticals (formerly Trius Pharmaceuticals) (developing antibiotics), Ferring Pharmaceuticals (manufactures vasopressin and is developing selepressin), Grifols (sells albumin), MedImmune (regarding sepsis), Leading Biosciences (developing a sepsis therapeutic), La Jolla Pharmaceuticals (developing a sepsis therapeutic), CytoVale Inc. (developing a sepsis diagnostic) and Sirius Genomics Inc. (now closed; had done pharmacogenomics research in sepsis). Dr. Russell reports having received grant support from Sirius Genomics, Ferring Pharmaceuticals that is provided to and administered by UBC.

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