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Early goal-directed therapy in the treatment of sepsis: the times have changed but not the therapy and benefit to patients.

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Dear Editor,

A review and meta-analysis published by Angus and colleagues [1] concludes: "EGDT (early goal-directed therapy) does not decrease mortality but increases costs" and suggests: "EGDT should not be part of the Surviving Sepsis Campaign (SSC) guidelines". This conclusion, while interesting, is incorrect for numerous methodological reasons. EGDT was the result of a series of studies over two decades identifying poor care, early sepsis mortality, early identification (SIRS), risk stratification (lactate), cultures and antimicrobials, identifying cryptic shock and early hemodynamic optimization to treat global tissue hypoxia in the emergency department (ED) [2]. While considered standard care in the ICU setting, these principles were applied to the most proximal part of hospitalization as ischemic stroke, acute myocardial infarction, or trauma was treated. EGDT is more than optimizing central venous pressure (CVP) and oxygen saturation ($ScvO_2$) as hypothesized by Angus et al.

EGDT was a prospective randomized trial where resuscitation was conducted in the ED and blinded to the ICU team. Angus et al. incorrectly labels the EGDT unblinded. The trial Trilogy, completed a decade later, was unblinded and included as

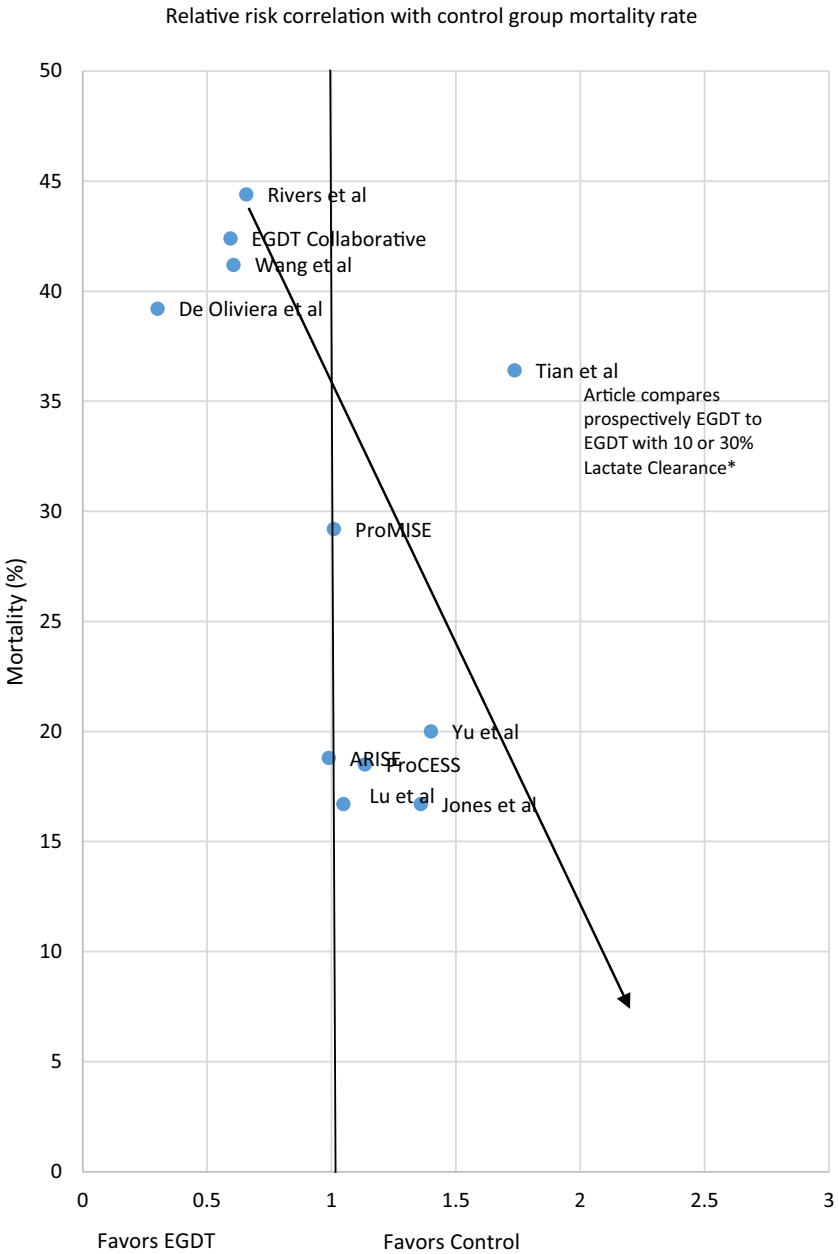

Fig. 1 Relative risk correlation with control group mortality. In studies with higher mortality treatment with EGDT leads to a more pronounced reduction in the relative risk of mortality than studies with lower mortality. *Lactate clearance formula: $[(Lactate_{Initial} - Lactate_{Repeat})/Lactate_{Initial}) \times 100\ \%$

standard care all elements of EGDT except CVP and $ScvO_2$ in all groups. Before and during the conduction of the Trilogy numerous publications incorporating EGDT (SSC guidelines) have shown a consistent mortality reduction over the last decade. It is no surprise that mortality was diminished and little difference exists between groups in the Trilogy of trials.

An acceptable alternative to randomized controlled trials (RCTs) are prospective observational trials (POTs). POTs importantly reflect the reality of implementation and the bedside clinical scientist's contributions to the literature rather than large institutional funded trials. In POTs using EGDT comprising over 62,260 patients, a mortality reduction of 13.3 % [from 40 ± 11 to 26.7 ± 11 % ($P < 0.001$)] has been shown, which compares to the original EGDT trial of 46–30 %. Multiple investigators, including the Cochrane Collaborative, have shown that there is little evidence that estimates of treatment effects in POTs reported after 1984 are either consistently larger than or qualitatively different from those obtained in RCTs [3, 4].

Re-examination of the RCTs analyzed by Angus reveals a significant benefit in patients of greater illness severity (Fig. 1). The focus of the analysis should reflect whether invasive monitoring is necessary to realize the mortality benefits of EGDT in various hemodynamic subgroups. Limitations of these studies (heterogeneity in enrolled patients, pediatric and adult populations, unblinded care, influences of existing sepsis protocols, and central venous catheterization rates greater than 50 % in all groups) need to be methodically examined. These and other systematic biases need to be addressed [5] along with assessment of validity, informativeness, and limitations of the review process. The conclusion should be a general interpretation of the results in the context of other evidence, and implications for future research as described by the PRISMA statement (Supplement 1).

The analysis should be a celebration of an all-time low in sepsis mortality and the success of SSC with EGDT. The retreat to embrace another repeat negative study with serious systematic biases is not in the best interest of patient care. EGDT is not a noun which is to be liked or disliked; it is a verb or a series of actions. These actions have been shown to be successful and are amendable to change not removal.

References

1. Angus DC, Barnato AE, Bell D, Bellomo R, Chong CR, Coats TJ, Davies A, Delaney A, Harrison DA, Holdgate A, Howe B, Huang DT, Iwashyna T, Kellum JA, Peake SL, Pike F, Reade MC, Rowan KM, Singer M, Webb SA, Weissfeld LA, Yealy DM, Young JD (2015) A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med. doi: 10.1007/s00134-015-3822-1
2. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. New Engl J Med 345:1368–1377
3. Benson K, Hartz AJ (2000) A comparison of observational studies and randomized, controlled trials. New Engl J Med 342:1878–1886
4. Anglemyer A, Horvath HT, Bero L (2014) Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. Cochrane Database Syst Rev 4:MR000034
5. Tang JL, Liu JL (2000) Misleading funnel plot for detection of bias in meta-analysis. J Clin Epidemiol 53:477–484

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