Reviewer's report

Title: Early Goal-Directed Therapy in the Management of Severe Sepsis or Septic Shock in Adults: A Meta-analysis of Randomized Control Trails

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Reviewer: Waleed Alhazzani

Reviewer's report:

This is a systematic review and meta-analysis of randomized controlled trials (RCTs) that compare EGDT versus usual care or lactate clearance, the search strategy is comprehensive and the authors identified 10 RCTs, overall, the authors address an important question. However, I have the following comments and suggestions for authors to consider:

1. Is there a published protocol? or a registered protocol in PROSPERO or other systematic reviews registry? This needs to be clarified in the manuscript.

2. The authors state under “population” in the “Study selection criteria” section: “Severe sepsis or septic shock who received EGDT or sepsis bundle including EGDT”. If the population includes patients who received EGDT in both arms of the trial, then what was the intervention in the control group? I believe that this should be changed, and that not all patients in both groups received EGDT, please clarify and correct this accordingly.

3. Under “Study selection criteria” the authors need to define the control group in the PICO question section, it is not clear to me how the control group was defined. Please clarify. Authors could simply say that they used usual care as defined in original studies, or they can list criteria (if used) to define the control group.

4. The authors used the following term throughout the manuscript “modified EGDT”, Can you please define this term so that we understand what it means. I would suggest elaborating on the major components that is common with EGDT and what components that differs from EGDT.

5. The authors used “Ventilation rate” as an outcome; can they clarify further? This term is ambiguous and could be understood in different ways.

6. Authors mention in the manuscript that they followed the Cochrane Handbook recommendation for systematic reviews, why abstracts were excluded? Authors should justify their decision.

7. Authors mentioned that they excluded abstracts, however, in the search strategy they describe that they searched for abstracts, please clarify?

8. Authors mention in the manuscript that they followed the Cochrane Handbook recommendation for systematic reviews, however, they used Jadad score to
assess the risk of bias, the Cochrane Handbook recommend using the Cochrane Risk of Bias Tool instead of Jadad score.

Quote from online Cochrane Handbook “One commonly-used scale was developed by Jadad and colleagues for randomized trials in pain research (Jadad 1996). The use of this scale is explicitly discouraged. As well as suffering from the generic problems of scales, it has a strong emphasis on reporting rather than conduct, and does not cover one of the most important potential biases in randomized trials, namely allocation concealment”.

Please justify your choice. Or use the Cochrane Risk of Bias Tool to summarize risk of bias for eligible RCTs.

9. Authors mention in the inclusion criteria that they included RCTs published after 2001, subsequently in the “search strategy” section under study selection they describe no date restriction, please clarify or adjust the sentence to be consistent.

10. Under “Quantitative data synthesis” the first paragraph “We assessed study methodology using the Jadad scoring system” I suggest changing “study methodology” to risk of bias.

11. Heterogeneity was assessed using Chi-squared test which is not unreasonable, however, the I2 is a more reliable estimate for heterogeneity in meta-analyses, can authors justify why they did not use this test especially that this metric is calculated automatically when using RevMan to generate forest plots? Please clarify in the analysis section, as the use of I2 metric was not described there.

12. Sensitivity analysis by sequentially omitting trials from the analysis is not usually done; can authors support the decision to conduct this analysis with evidence? Or describe clearly that this was decided a priori and not a post hoc sensitivity analysis.

13. Authors classify studies according to risk of bias into “poor quality” and “satisfactory”, I suggest changing the terminology into “high risk of bias” and “low risk of bias”.

14. One study Wang et al. was judged to be of “poor quality” or high risk of bias because of the absence of “random sequence allocation”, does that mean the study is not a true randomized trial (i.e. pseudo-randomized or quasi-randomized)? What were the randomization methods used? If this is the case then authors need to justify why this study was included although the eligibility criteria clearly stated that RCTs are the only permitted study design.

15. The authors included amount of fluid administered as an outcome in this study. Although the amount of fluids received is directly related to the protocol used (i.e. EGDT protocol) and may actually reflect the intervention more than an outcome. It is reasonable to pool the results to inform readers if the amount of administered fluid was different between both groups. What is not clear to me is how did authors dichotomize the outcome, ideally this should be measured as a
continuous outcome, instead the authors report it as a dichotomous outcome without clear explanation how did they dichotomize this outcome, please clarify?

16. There are some important issues that need to be addressed by the authors. In order to understand the differences between EGDT and usual care in each of the RCTs more detailed description is required. If the RCTs included were after the publication of Rivers et al. Trial then it is expected that even “usual care” will not be much different from the standard of care (which is EGDT). I suggest adding a paragraph to discuss the important components of usual care in each Trial; also in Table 2 there is a need for more details on the parameters used in each control group. It will be impossible to make any inferences without knowing the nature of the intervention and control groups. The fact that there was no statistically significant difference between intervention and control in the amount of fluids, transfusions, vasopressors used highlight the importance of providing more details on what actually was different between the two groups (e.g. Scvo2 monitoring), this need to be described in details in the manuscript.

17. In Figure 3, the results for length of in-hospital stay is provided as relative risk, this does not make any sense, I ask the authors to revise and insert the correct figure.

18. In Figure 6, the authors report fluid administration as a continuous outcome which is appropriate, but in the text they reported this as a dichotomous outcome, please clarify.

19. I suggest that authors discuss why mortality rate in the control group is low (31.9%) compared to what was observed in the Rivers et al. trial. For instance, in ARISE Trial the mortality in the control group was around 18%, also the APACHE II score in both intervention and control groups was much lower than in other landmark trials, the variation in baseline risk of death between studies is also a contributing factor to clinical and possibly statistical heterogeneity that authors need to discuss in more details.

It was a great pleasure reviewing this interesting work; I hope that my comments are clear and helpful.

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests