Author's response to reviews

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

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Author's response to reviews: see over
Response to editor

Reviewer: Andrew Rhodes
Comments:
1. On the whole the text is well written but the figures are too many and some are confusing. It would be helpful to have the figures order the studies in the same fashion.
   Reply: Thanks for your suggestion. We have modified the primary figures and made them more concise. We deleted some figures and created a table to summarize the data.

2. I am not sure why the Jansen study is missing as this was the only lactate clearance study against placebo.
   Reply: Thanks for your suggestion. The purpose of this meta-analysis is to evaluate the effect of EGDT on severe sepsis patients compared with usual care or lactate clearance group. So we do not include the studies with non-septic patients or no EGDT treatment. In Jansen study (Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med 2010 Sep;182 (6):752-61.), lactate group was compared with usual care group but not EGDT group, and many non-septic patients were included in this study, so it was not included in this meta-analysis.

3. I am not sure of the merits of mixing lactate clearance studies that are comparing against EGDT with the EGDT studies. This is not assessing similar methodologies.
   Reply: Thanks for your suggestion. Nowadays, since EGDT has been recommended as the standard treatment for severe sepsis, it is interesting to evaluate whether EGDT is better than any other treatments such as usual care or lactate-directed. And in subgroup analysis, we also compared the effect of EGDT on sepsis with usual care and lactate clearance respectively.

4. It is more usual to perform a random effects model when heterogeneity is present.
   Reply: Thanks for your suggestion. We have modified our draft and performed a random effects model on all results.

5. The study named 'Group' should be described by the first author like the other studies.
   Reply: Thanks for your suggestion. We have replaced “Group 2010 study” to “Jing 2010 study”.

6. The Process trial had three study arms. The second was a modified EGDT arm and hence should be included in the modified subgroup.
   Reply: Thanks for your suggestion. We have added the modified EGDT data of
Process study to the analysis of modified EGDT subgroup.

Reviewer: Qi Zhou

MAJOR COMMENTS:

1. This study evaluated the effect of EGDT in comparison to the usual care. It regarded the treatment of lactate clearance as a group of usual care. Is it a common that the lactate clearance treatment is part of usual care? Should the treatment of lactate clearance really be considered as usual care? If the answer is no, then a broader concept of “usual care” could bias the assessment of the EGDT effects over the standard usual care.

Reply: Thanks for your suggestion. In lactate clearance group, there was an early target for lactate clearance. But in usual group, there was no definite requirement of lactate clearance.

Nowadays, since EGDT has been recommended as the standard treatment for severe sepsis, it is interesting to evaluate whether EGDT is better than any other treatments such as usual care or lactate-directed. And in subgroup analysis, we also compared the effect of EGDT on sepsis with usual care and lactate clearance respectively. We have added the main components of the control group in table 2 to make it easy to understand.

2. Page 8, lines 12 and 13, the sentence should be read as ‘When statistically significant heterogeneity was detected with a p-value less than 0.10, the pooled analysis of each study was performed in the random-effects model. Also since the Chi-square Cochrane Q test for heterogeneity assessment is under powered, a p value of 0.10 should be considered as a threshold.

Reply: Thanks for your suggestion. We have modified the sentence as your suggestion:

“Heterogeneity was evaluated using the Mantel-Haenzel chi-square test and the $I^2$ statistic to assess the degree of inter-study variation. When statistically significant heterogeneity was detected with a p-value less than 0.10, the pooled-analysis of each study was performed in the random-effects model. Also since the Chi-square Cochrane Q test for heterogeneity assessment is under powered, a p value of 0.10 should be considered as a threshold.”

3. The interpretations of the I-square values were inconsistent across the manuscript, for example:

Page 11, line 6, I-square=75% - moderate
Page 11, line 8, I-square=12% - no evidence
Page 11, line 15, I-square=43% - no evidence
Page 11, line 17, I-square=95% - marked
Page 12, line 2, I-square=69% - marked
Page 12, line 8, I-square=85% - moderate
Page 12, line 21, I-square=76% - marked

Suggest using the following guideline based on Cochrane:
0% to 40%: might not be important
30% to 60%: may represent moderate heterogeneity
50% to 90%: may represent substantial heterogeneity
75% to 100%: considerable heterogeneity

Reply: Thanks for your suggestion. We have modified all the I-square values as your suggestion.

4. I suggest using the forest plot to present Table 3-sensitivity analysis, to increase the visibility on the outcomes.
Reply: Thanks for your suggestion. Sensitivity analysis was conducted by sequentially deleting a single study each time. I am afraid that there might be too many figures (10 figures) if using forest plot to present.

5. In figure 3, the forest plot for ‘Length of in-hospital stay’ was incorrectly placed. It was from the result of ‘In-hospital mortality’.
Reply: We are sorry for the mistake. I have corrected it.

MINOR COMMENTS:
1. Page 2, line 11: you need to specify what “parameters” you referred here, physiological, clinical or something else.
Reply: Thanks for your suggestion. We have modified it that:
“The primary outcomes were mortality among severe sepsis or septic shock patients. Length of ICU and in-hospital stay, mechanical ventilation support, vasopressor and inotropic agents support, fluid administration and red-cell transfusion rate in first 6h, were also analyzed.”

2. Page 9, lines 12 and 13: it is unclear on how the ”no imbalances“ was assessed, in visual or by analytical method? I assume this is based on visual judgment. It becomes uncommon to report the p-values for the baseline characteristic comparison since people could get significant result(s) by chance from multiple comparisons.
Reply: Thanks for your suggestion. We admit that it was based on visual judgment. We have deleted this confusing sentence.

3. Page 10, line 8: 3838 should read 3738.
Reply: We are sorry for the mistake. I have corrected it.

4. Page 11, lines 4, 10 and 19: RR should read MD.
Reply: We are sorry for the mistake. I have corrected it.

5. Page 12, line 15: RR should read MD
Reply: We are sorry for the mistake. I have corrected it.

6. Page 13, line 1: If the control group is not different from the usual care, you need to
consistently word it as usual care to avoid confusion from the readers.

Reply: Thanks for your suggestion. In this meta-analysis, control group is the total one, which includes usual care group and lactate clearance group.

Reviewer: Waleed Alhazzani

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.
   
   Reply: Thanks for your suggestion. We have not registered protocol in anywhere. We have clarified it 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.

   
   Reply: Thanks for your suggestion. We added some information on “Data extraction” to clarify it:

   “The following exclusion criteria were used: (a) EGDT was performed in all patients or studies of compliance with EGDT; and (b) EGDT not based on published protocol [4]; and (c) pediatric patients; and (d) nonhuman studies.”

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.

   
   Reply: Thanks for your suggestion. We have defined intervention of control group as that:

   “The intervention of control group was usual care or other strategies that described in original studies.”

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.

   
   Reply: Thanks for your suggestion. We have defined the modified EGDT as that: “We defined modified EGDT as a similar or simplified 6h protocol that based on standard 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.

   
   Reply: Thanks for your suggestion. We have replaced “Ventilation rate” to “mechanical ventilation support (rate and days).”
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.

Reply: Thanks for your suggestion. We excluded the studies published just in abstracts. We have modified the draft as “We excluded non-randomized studies, studies published in abstracts, reviews, commentaries, and editorials.”

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

Reply: Thanks for your suggestion. After title screening, we evaluated all the abstracts for relevance and identified as included, excluded or requiring further assessment, and then we excluded the studies only published in abstracts.

8. Authors mention in the manuscript that they followed the Cochrane Handbook recommendation for systematic reviews, however, they used Jadad score to 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.

Reply: Thanks for your suggestion. We have modified the draft as your suggestion. We used risk of bias tool instead of Jadad score.

“Independently and in duplicate, reviewers assessed risk of bias using the Cochrane collaboration tool. For each included trial, a description, a comment, and a judgment as “high”, “unclear”, or “low” risk of bias was provided for each of the following domains: adequate random sequence generation; allocation sequence concealment; blinding for objective outcomes; incomplete outcome data; free of selective outcome reporting; and free of other bias. Trials with high risk of bias for any one or more key domains were considered as at high risk of bias. Trials with low risk of bias for all key domains were considered as at low risk of bias. Otherwise, they were considered as unclear risk of bias.”

And we also modified the results of risk of bias:

“Assessment of methodological quality

The details of risk of bias are summarized in Figure 2. Seven studies were judged to be at low risk of bias, and other three studies were judged to be at unclear risk of bias. Nine trials generated adequate randomized sequence and reported appropriate allocation concealment [4, 8, 13, 14, 20-22]. Among all RCTs, none of them were double-blinded. However, blinding of patients and clinicians was extremely difficult in these studies to evaluate a complex intervention such as EGDT protocol, and the authors judged that the primary outcome (mortality) is not likely to be influenced by lack of blinding.”
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.

Reply: Thanks for your suggestion. There was no date restriction in our searching and 10 RCTs were included from 2001 to 2014. We have modified the sentence.

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.

Reply: Thanks for your suggestion. We have modified the sentence as your suggestion.

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.

Reply: Thanks for your suggestion. We have modified the draft to use I² for heterogeneity evaluation based on Cochrane recommendation:
- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

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.

Reply: Thanks for your suggestion. We are sorry to say that we are not sure whether sequentially omitting trials would be a suitable method for sensitivity analysis. In our opinion, sequentially omitting trials can establish the contribution of each study to the effect size, which can avoid arbitrary or unclear decisions. We used it mainly according to some references which used it for 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”.

Reply: Thanks for your suggestion. We have modified the draft as your suggestion.

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.

Reply: Thanks for your suggestion. Wang 2006 study reported it was a “randomized” study, but the method for random sequence generation and allocation concealment was not clear. However, after contacting the original author, we learnt that the random sequence was generated through computer software, but we were not sure about selection bias.

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?

Reply: We are sorry for the mistakes, and we already corrected it:

“A total of 7 studies including 3204 patients provided information on fluid administration (L) in first 6h with considerable heterogeneity ($\chi^2 = 788.12$, I$^2 = 99\%$). There was no significant difference between EGDT and control group (MD 0.88 L, 95% CI: -1.07 to 1.93; $P = 0.10$). In subgroup analysis, EGDT was associated with more fluid administration in first 6h in comparison with usual group (MD 1.24 L, 95% CI: 0 to 2.48; $P = 0.05$), whereas result between EGDT group and early lactate clearance group was not significant ($P = 0.27$).”

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.

Reply: Thanks for your suggestion. We have added the main components of the control group in Table 2 to make it easy to understand. We absolutely agree that Scvo2 monitoring is the key method differing from usual care, and we put some discussion on that point:

“Compared with usual care, continuous monitoring of Scvo2, which requires invasive central vena catheterization and special equipment, is the key method of EGDT. However, its effectiveness is still uncertain [37]. In contrast, it is convenient to monitor lactate levels, and early goal lactate clearance may be more effective for severe sepsis or septic shock than EGDT in the present meta-analysis. Thus, future studies should focus on comparing EGDT with early lactate clearance as a therapeutic option in severe sepsis or septic shock.”

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.

Reply: We are sorry for the mistakes, and already corrected it.

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.

Reply: We are sorry for the mistakes, and already corrected it in the text.

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.

Reply: Thanks for your suggestion. We have added the discussion in part of “Strengths and limitations”:

“Forth, the variation in baseline among studies might be also a contributing factor to clinical and possibly statistical heterogeneity. For instance, APACHE II score and total mortality in ARISE study and River’s study were 15, 18.7% and 20, 45.6% respectively. In addition, the intervention in control group (usual care group) was not clear and might be different among studies.”