Reviewer's report

Title: Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial

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Reviewer: Derek Wheeler

Reviewer's report:

The manuscript submitted by Maitland and colleagues is an important follow-up analysis to the surprising results of the FEAST trial, which showed that early and rapid fluid resuscitation in African children presenting with severe febrile illness increased 48-hour mortality compared to control (no bolus group). In this follow-up, secondary analysis of the FEAST trial, the authors show hypothesized that excess deaths in the fluid resuscitation group were likely due to neurological or respiratory events (specifically, cerebral edema and/or pulmonary edema secondary to fluid overload). Given the growing body literature on the adverse effects of fluid overload in both critically ill children and adults, this would seem to be a reasonable hypothesis. However, the secondary analysis showed that:

1. Excess mortality occurred in all subgroups of children (with respect to pre-defined presentation syndromes)

2. Cardiovascular collapse, rather than fluid overload, appeared to contribute to the excess mortality in the fluid resuscitation group.

Major Compulsory Revisions:

1. While the overall analysis seems to support the conclusions above, the authors take the stance that the results of the current analysis, when considered with the results of the FEAST trial itself, should "prompt a re-evaluation of evidence on fluid resuscitation for shock and re-appraisal of the rate, composition and volume of resuscitation fluids." I do not think that one single clinical trial should necessarily change the practice on such a widely used and "time-honored" therapy as fluid resuscitation for shock. See for example the conflicting results of several follow-up randomized, controlled clinical trials to the use of activated protein C, tight glucose control, etc. I absolutely agree 100% that the results of the FEAST trial and this secondary analysis should prompt further research in this area. However, I think the authors need to temper their comments somewhat - recall that this particular trial was performed in completely different circumstances than most of the industrialized world. This needs to be taken into consideration before throwing out the concept of "fluid resuscitation" altogether.

2. In the Methods Section, under the heading "Analysis" - can the authors explain (or at least reference) what is meant by "landmark analysis"?
3. In relation to my comment in #1 above, the first paragraph of the Results section details the demographic and clinical characteristics of the cohort in the study - I think it needs to be emphasized (in the Discussion at least, and especially if the authors take the stance that fluid resuscitation should be re-considered) that this particular cohort is not very representative of the types of critically ill patients seen in industrialized countries.

4. Given the controversial findings and implications of this study, I think it would be important to at least offer a hypothesis on how early fluid resuscitation could lead to excess mortality through cardiovascular collapse. The authors offer several alternative explanations arguing against electrolyte changes, worsening acidosis, fluid overload, etc, but offer no potential physiologic explanation for cardiovascular collapse per se.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

No competing interests to declare.