

## Peer Review File

**Article information:** <http://dx.doi.org/10.21037/tp-21-1>

### **Reviewer A**

#### **Comments to the authors:**

*The article is fairly difficult to follow. It starts off with a nicely crafted background, followed by a useful paragraph on hydrocortisone in humans with sepsis. I'm not quite clear why there is an entire section on in vitro and animal models of ascorbic acid, especially since there is a preponderance of human data. The following portion on HAT therapy then seems out place (it is introduced after a section on steroids but before a section on safety of high dose ascorbic acid). Then there is a section on vitamin C safety, but no dedicated sections to hydrocortisone or thiamine safety. This is all concluded with a review of adult studies of septic patients receiving HAT therapy, followed by the single piece of retrospective pediatric data.*

*For the sake of the reader, a better format might be:*

- 1. Background*
- 2. HAT therapy*
- 3. Components of HAT data per component (hydrocortisone, vit C, thiamine)*
  - a. Background*
  - b. Safety*
  - c. Human data*
- 4. Longer discussion of the adult data (the narrative review would benefit from a bit more detail than just what is in the table for the large JAMA-level studies on HAT)*
- 5. Pediatric data*
- 6. Implications for future research*

REPLY: We thank the Reviewer for the suggestions on how to improve the structure of the manuscript, which has been thoroughly revised. We have edited the manuscript accordingly as suggested by the Reviewer. We have added a section on thiamine and have aligned the respective sections on hydrocortisone, thiamine, and vitamin C to reflect on rationale/pathophysiology, safety, and human data. We feel that keeping the in vitro and animal data on ascorbic acid is relevant to guide the reader and to build the rationale for clinical studies.

Finally, we have expanded the description of the adult trials on HAT therapy.

**Reviewer B**

**Comments to the authors:**

*This manuscript takes on a very challenging topic that currently has limited robust literature support in the pediatric population. The authors have done a great job collating and describing the available literature of metabolic resuscitation in adults and pediatrics as well as the favorable safety profile. I would ask the authors to consider the following:*

- 1. The authors should consider review of the article for grammatical and syntax changes to improve readability*

REPLY: We have revised and proof-read the manuscript.

- 2. The authors could consider changes to the paper's order and flow to increase reader comprehension. Certain background or mechanism sections, such as "the concept of metabolic resuscitation" may make more of an impact if provided earlier in the article for context moving forward*

REPLY: We have revised the manuscript as suggested, see as well comments from Reviewer A.

- 3. On page 3/line 73 – authors can consider if the sentence "in the near future.." adds value to the subsequent conclusions. Although it is an important point, it may be better to make a general statement regarding the potential future state of phenotype driven care in a just-in-time manner.*

REPLY: We have changed the section and added a similar statement to the research perspective at the end, rather than at the start of the manuscript.

- 4. On page 5/line 103 – authors can consider changing title of section to be more reflective of content. Although you do review an animal model in the section, the really great information included in this section includes the pathophysiology and mechanism of the intervention.*

REPLY: We have changed the section title as suggested.

- 5. The authors could consider a more in depth discussion of mechanism and proposed indication for use for all resuscitation agents discussed throughout the article. Ascorbic acid and hydrocortisone are briefly reviewed, but not thiamine. Adding the proposed mechanism for thiamine and its role as a metabolic resuscitator on its own or as an adjunctive agent with vitamin C could give the reader a stronger understanding on why these therapies are*

*being explored.*

REPLY: We have added a section on thiamine as suggested.

6. *On page 8/Line 195 – authors can consider adding dosing strategy used for metabolic resuscitation in pediatric patients presented by Wald et al.*

REPLY: We have added further detail on dosing strategy, and reference to Wald et al AJRCCM.

7. *On page 9/Line 215 with sentence starting “the pediatric critical care community” the authors can consider simplifying statement. The authors make an excellent justification for caution in embracing interventions with low quality evidence, but the message is lost in the complication of the syntax.*

REPLY: We have reworded the sentence.

8. *Table 1 – authors should consider visually separating the pediatric study from the adults study. Additionally the table is only referenced once in the manuscript body and not in reference to any adult studies.*

REPLY: Table 1 has been updated, and references have been added in the manuscript body.

9. *Table 2. Section 1- Authors can consider including thiamine research into this section, including importance of dosing and duration*

REPLY: We have updated Table 2 as suggested.

10. *Table 2. – authors include mega-dose vs. high-dose therapy in relation to vitamin C which is a new term being referenced in this chart. Consider addressing and defining those terms before inclusion into this table.*

REPLY: We have changed the wording to “Optimal dosing of high-dose ascorbic therapy”/

### **Reviewer C**

#### **Comments to the authors:**

*This is a well written review and I have only a few minor comments:*

1. *On line 79, “pragmatic, safe, and economic interventions” should be changed to “pragmatic, safe and economically viable interventions”.*

REPLY: We have changed the wording as suggested.

2. *Line 83 says “steroids exerts” and should say “steroids exert”*

REPLY: We have changed the wording as suggested.

3. *Line 85 “At the same time glucocorticoid therapy has been associated with side effects such as hyperglycaemia, hypertension, critical illness neuropathy, and, possibly, increased risk for hospital-acquired infections”. This should be referenced.*

REPLY: We have referenced the statement.