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Column: Editorial

Title: Hydrocortisone, Ascorbic Acid and Thiamine (HAT Rx) for Sepsis: Is the jury out?

Authors: Paul Ellis Marik, Joseph Varon and Salim Surani

Dear Sir,

Attached, please find the revised manuscript based on the reviewer comment addressed point by point. We hope that your readership will find it interesting and will benefit from it. We like to take the opportunity to thank the reviewers, editorial staff and editor for their time and patience. Please feel free to let us know with any questions or comments.

Warm regards

Paul Marik, MD, Joseph Varon, MD, Salim Surani, MD,

Reviewers Comments & Response

Reviewer #1: I would like to mention the following comments: 1- First and second sentence need reference.

Response: We have added the reference in both first and second sentence as suggested.

2- Type of diabetes is not known.

Response: Regarding type of diabetes it is true for both type 1 and type 2 diabetes. We like to thank the reviewer for this query.

3- For drugs, FDA (USA) and EMEA (Europe, Middle East and Africa) will decide, not jury of a court. 4- The reference(s) of table 1 is missing.

Response: We appreciate the reviewer comments. Agree with the reviewer comment with the drug decision. We have added the reference for the table 1. We like to thank the reviewer for their vigilance.

5- Vitamin C and thiamine have less (or no) side-effects; however, hydrocortisone has different potential side-effects. How would be the related ethical issue? 6- Is there any evidence of potential antagonist effect of combination or all are synergist effect? Good Luck

Response: We appreciate the reviewer comments. We have added the additional references to justify the adverse effect related issue. We are not aware of any potential antagonist effect of the combination therapy.

Reviewer #2: This editorial focuses on a promising strategy for the management of sepsis through the combination of ascorbic acid, hydrocortisone and thiamine. It reports a pure speculation and a point of view of authors. Moreover argue the conclusion that may derive from randomized controlled trial. In my modest point of view, it is little bit risky reach such conclusion. I suggest to soften the language used to avoid bias of interpretations and misunderstanding as well as criticizimes.

Response: We appreciate the reviewer positive feedback. We have soften our comment in the conclusion section.

Reviewer #3: Very amusing and well written work. In the perspective of the most complete work, authors should dedicate time and spaces to describe the synergic properties of the three elements, more in detail; extend the role of thiamine , in the shadow of very recent work (Osiezagha K, Ali S, Freeman C, et al. Thiamine deficiency and delirium. *Innov Clin Neurosci*. 2013;10(4):26–32. ; Moretti R, Peinkhofer C. *Int J Mol Sci*. 2019 Nov; 20(22): 5797; Moretti et al. 2017, *Current Drug Abuse Reviews Continued as Current Drug Research Reviews Volume 10 , Issue 1 , 2017 DOI : 10.2174/1874473711666180402142012*) and devote more attention to the synergic property of the HAT combination.

Response: We appreciate the reviewer input. The manuscript has been modified to reflect those changes and the suggested reference (17,18) has been added in the manuscript.