Author's response to reviews

Title: The EUPHRATES Trial (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized Controlled Trial of Adults Treated for Endotoxemia and Septic shock): Protocol and Rationale for a Blinded Theragnostic Multi-centered Randomized Controlled Trial

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Author's response to reviews: see over
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Dear Editor-in-Chief,

We are grateful to the editor and the reviewers for their interest in our manuscript and for their help in improving it. We are resubmitting herein our revised version entitled ‘The EUPHRATES Trial (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized Controlled Trial of Adults Treated for Endotoxemia and Septic shock): Protocol and Rationale for a Blinded Theragnostic Multi-centered Randomized Controlled Trial’. We have responded to the reviewers thoughtful suggestions directly in our comments below and have included the relevant sections of edited text in this letter. All changes are also indicated with the “Track Changes” feature in the attached file.

Editor Comments
1. Please include the names of all ethical bodies that approved your study in the various centres involved, along with the references given. If you do not wish to list them all in the methods section, please include the list as an additional file and refer to this in the methods section.

   - Thank you. A list of all ethical bodies that approved the protocol has been added as Appendix 1. The following sentence has been included in the Methods section p. 7, second paragraph. “A list of all ethical bodies that reviewed and approved the trial is listed in Appendix 1.”

2. Please modify your Authors Contributions section to demonstrate that each author meets all three of the following criteria to qualify for authorship:

   - Substantial contributions to: the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
   - Drafting the work or revising it critically for important intellectual content; AND
   - Final approval of the version to be published
• We thank the editor for this important comment. This section has now been updated and reads as follows:

“DK: conception and design, manuscript writing and final approval of the manuscript. DF: conception and design, manuscript writing and final approval of the manuscript. CAS: conception and design, data collection, manuscript editing and final approval of the manuscript. KK: statistical design, data analysis, manuscript writing and final approval of the manuscript. PMW: conception and design, critical revision of the manuscript, and final approval of the manuscript. RPD: conception and design, critical revision of the manuscript, and final approval of the manuscript. All author’s agree to be accountable to all aspects of the work.”

Editor Comments

1. MAJOR COMPULSARY REVISIONS
METHODOLOGY

Patients. – How patients will be collected and selected is not clearly described; for example, it is not reported if the cases will be consecutive or not, which is very important in regards to representativeness.

• Thank you for this important comment. Indeed it is the intent to screen patients consecutively for the purpose of representativeness. On page 7, last paragraph under “Study Design”, the following revision has been made: “Consecutive patients with evidence of septic shock as indicated by initiation of intravenous antibiotics and on vasopressor therapy for hypotension will be screened and those eligible will be consented for a blood draw for measurement of EAA.” We hope that this addresses the concern satisfactorily.
2. MAJOR COMPULSARY REVISIONS

METHODOLOGY

Intervention and co-interventions. – Compliance is not defined and how will be checked compliance is not described.

- Thank you for this comment. We have added a full section on compliance and monitoring to the methods section of the manuscript. This can be found on pages 13 and 14. It reads as follows: “Monitoring: The trial is fully monitored by the contract research organization responsible for trial operations. A trial monitoring plan has been established and is on file with the FDA. One hundred percent source data verification is done for all data points in the case report forms (CRF). Protocol violations are predefined. Adherence to treatment as defined by number of treatments delivered versus prescribed as well as total time of each delivered treatment is compiled in the CRF and tabulated for analysis. All co-interventions are captured including concurrent medications. A detailed policy on co-enrollment in other studies has also been developed and approved by the DSMB.”

3. MINOR ESSENTIAL REVISIONS (not for publication).

References
- These have all been updated in a corrected version of the manuscript.

Thank you very much.

Sincerely yours,

David J. Klein MD FRCP(C)