Author's response to reviews

Title: B. anthracis Associated Cardiovascular Dysfunction and Shock: The Potential Contribution of Both Non-toxin and Toxin Components

Authors:

Kenneth E Remy (kenneth.remy@nih.gov)
Ping Qiu (qiup@cc.nih.gov)
Yan Li (yli3@cc.nih.gov)
Xizhong Cui (cxizhong@cc.nih.gov)
Peter Q Eichacker (peichacker@cc.nih.gov)

Version: 6 Date: 14 August 2013

Author's response to reviews: see over
Confidential comments to editors

Title: B. anthracis Associated Cardiovascular Dysfunction and Shock: The Potential Contribution of Both Non-toxin and Toxin Components

Authors:

Kenneth E Remy (kenneth.remy@nih.gov)
Ping Qiu (qiup@cc.nih.gov)
Yan Li (yli3@cc.nih.gov)
Xizhong Cui (cxizhong@cc.nih.gov)
Peter Q Eichacker (pelchacker@cc.nih.gov)

Version: 5 Date: 2 August 2013

Comments: see over
Responses to the editor

1. I have compared the overlap between this review and the 2011 review and we think this should be changed to a mini-review. Thus can (you) expand the sections on the cardiovascular effects of lethal and edema toxin on the articles published since 2011 and condense the other sections of the manuscript and focus on the recent publications since 2011. There are 23 references that you cite since 2011 and in the literature there are about 10 references using keywords such as anthrax, toxin and cardiac. Thus it would be good to include these as appropriate. *In the revised manuscript we have included references from 2011 which we feel are appropriate to the topic at hand. To put this work in the proper context however, it was necessary to include some earlier references as well.*

2. I have done a developmental edit on your manuscript and will send this as an attachment in a separate email message. *We have addressed the comments in the prior attached version of our manuscript from the e-mail of 5/31/13.*

3. Start by describing all known features of *B. anthracis* infection, then focus on shock as an indicator of poor prognosis and a little-understood feature.

   *Discussing “all known features of *B. anthracis* infection” would require a major review at the least and likely something even larger. We have noted that the development of shock in during *B. anthracis* infection is associated with a poor prognosis and that understanding its basis is important (p 3, Ins 2-7).*

4. Everything apart from the sections highlighted by reviewer 1 should be condensed as much as possible, which could be achieved by removing experimental detail
and simply describing the current understanding in more general terms. The present review has been reduced to less than 1900 words from the prior 3443 words and experimental detail have been removed where appropriate.

5. The highlighted sections should be expanded to explain how the new findings do or don’t fit with what was known before and what insights they give to mortality specifically and anthrax infection more generally. Newer findings are discussed in the context of prior beliefs and of the mortality associated with B. anthracis infection where appropriate.

6. It is probably worth stating explicitly just how high mortality in recent outbreaks has been, and what the cause or causes of mortality have been. Recent mortality rates are noted in the revised manuscript (p 3, ln 2-7).

7. I would also like to see the difference between injurious and ?normal? inflammatory response spelled out briefly with an emphasis on those features most relevant to this paper ? this seems to be taken for granted generally, not just in this article, and I’m not sure it should be but it shouldn?t take up a lot of room. I would love to know whether these injurious features are similar to other immune overreactions ? is this a cytokine storm? Might there be broader significance to this than just learning how to treat anthrax? The adaptive and maladaptive aspects of host inflammation are addressed briefly in the revised manuscript but with references if the reader is unfamiliar with the concepts (p4, lns.2-3). Addressing these concepts in any detail would itself require a major review.

8. It will help readers a great deal if each paragraph and section can be linked to the next, but it?s difficult to suggest how to do this until the revisions have been
made. Generally, simply using things like ?therefore?, ?as a result? and similar terms that link concepts goes a long way to doing this. Where appropriate, such terms have been applied.

9. We would be grateful if you could address the comments in a revised manuscript using track changes or a different color. Please provide a cover letter giving a point-by-point response to the concerns and clearly indicate where the changes have been made in the manuscript i.e. page, paragraph and line etc. The manuscript has been edited extensively to condense it as requested and track changes were too cumbersome to apply throughout (see response to comment #4). However, track changes have been employed in the revised version where possible to highlight specific points requested by the editor and reviewers as well as other changes incorporated during the revision. A cover letter and responses to the editor and reviewers are provided.
Responses to Reviewer 1

1. Has the author used logical arguments and sound reasoning? No. The review is merely a collection of facts.

10. Have similar reviews been published recently? Yes, a very similar review has been published in an open access MDPI journal “Toxins” in 2011 [“Hicks CW, Cui X, Sweeney DA, Li Y, Barochia A, Eichacker PQ. The potential contributions of lethal and edema toxins to the pathogenesis of anthrax associated shock. Toxins (Basel). 2011 Sep;3(9):1185-202. doi: 10.3390/toxins3091185”]. Essentially the current review that is under revision and the published review have more or less similar content with only a few additional facts. The few new findings added in the review submitted to BMC Medicine are: (a). “A more recent study in the same rat model showed that challenge with purified B. anthracis peptidoglycan alone produced lethality associated with inflammatory mediator release and changes in coagulation and fibrinolysis consistent with DIC.” The reference given for this statement is “In Press”. (b). “However, as noted by Guichard et al, endothelial impairment is not entirely consistent with EFs recognized action as a potent adenyl-cyclase [71]. There is a substantial literature showing that increased cellular cAMP levels have a protective effect on endothelial barrier function [72, 73]. Consistent with this, ET has been noted to increase endothelial barrier resistance in some investigations [68, 74].” (c). “In subsequent studies this group showed that the metalloproteases Npr599 and InhA cleaved host structural and regulatory proteins important in endothelial function..."
including plasma ADAMTS13, von Willebrand factor (VWF) substrate FRETS-VWF73, and VWF itself [95, 96].” The prior review has been condensed and emphasizes data published from 2011 on as requested by the editor.

2. The flow of information between paragraphs is not entirely smooth and is difficult to grasp at times. The authors, at times, have used long sentences and the complexity of sentences often makes the implied meaning obscure. The manuscript has been condensed and sentences shortened and clarified.

3. Mild typographical errors, need to be checked, like, “nucleotide-binding oligomerization”, “vascular resistance”, “a gram-positive bacterium”, “define LTs injurious” and like. The manuscript has been further edited.

4. At places the usage of words can be improved, e.g, “bioterrorism agent” and not “bioterrorist agent”, “several bacterial components likely play an important role in pathogenesis.” and not “several bacterial components likely play an important pathogenic role.”, “important for improving the management of B. anthracis infection associated shock in the future.” and not “important for improving the management of shock with B. anthracis in the future.”, “Purified whole B. anthracis cell wall” and not “Purified whole anthrax cell wall”. The manuscript has been further edited.

5. Needs some language corrections before being published. The manuscript has been further edited.
Responses to Reviewer 2

1. One did feel though that there was, at times, a somewhat uncritical lumping of many observations, including a large number of rodent challenge findings that appear, in many respects, extremely distant from the findings in humans. Perhaps more caution would be warranted in these areas. *Discussion of findings from rodent models has been reduced.*

2. While it is for the editors to make the final aesthetic decisions, one felt that Figure 1 might benefit from a little more artistic input! *We will take the editor’s guidance on this point.*