Author's response to reviews

Title: Risk Factors for Recurrent Clostridium difficile Infection (CDI) Hospitalization Among Hospitalized Patients with an Initial CDI Episode: A Retrospective Cohort Study

Authors:

Marya D Zilberberg (MZilberb@schoolph.umass.edu)
Kimberly Reske (kreske@dom.wustl.edu)
Margaret Olsen (molsen@dom.wustl.edu)
Yan Yan (yyan@dom.wustl.edu)
Erik R Dubberke (edubberk@dom.wustl.edu)

Version: 3
Date: 7 May 2014

Author's response to reviews:

May 7, 2014

We are submitting a revised version of the manuscript entitled “Risk Factors for Recurrent Clostridium difficile Infection (CDI) Hospitalization Among Hospitalized Patients with an Initial CDI Episode” in addition to detailed responses to the referees’ comments. We hope that we have addressed all of the concerns adequately and are looking forward to the decision.

We are grateful for the opportunity to improve our work.

Respectfully,
Marya Zilberberg, MD, MPH

Reviewers

Reviewer: Lutz von Müller

This is a retrospective single centre analysis of CDI detected between 2003 and 2009 with a specific focus on recurrent CDI. The authors discriminate patients with initial (iCDI) and recurrent (rCDI) C. difficile infection according to the recordings in the clinical databank.

Although the manuscript is well written and despite the high numbers of CDI infections recorded there are some major points which might be addressed to achieve the standard for publication.

1. The restrospective data provide limited information to substantially discriminate between initial and recurrent CDI; a structured questionnaire was not introduced to discriminate between initial and recurrent CDI. Therefore, in case of recurrent infections could have been misinterpreted as initial CDI if patients were treated for the first episode in one other hospital or at outpatient base. All cases of recurrent CDI treated later on in other hospitals or at outpatient
base could not be identified by the current study design. This could be the reason why the rate of rCDI was twofold lower as compared to other studies.

AU: While the reviewer is correct in that we may have misclassified a handful of rCDI cases as iCDI, we did use a strict definition of no evidence of CDI within 60 days prior to the onset of the index episode to define it as initial. In addition, all admission and discharge summaries were reviewed to determine whether the patient had CDI at a facility other than BJH in the 60 days before admission. A statement to this effect has been added to the methods on page 6. In the Limitations paragraph on page 12 we discussed this issue extensively.

2. Analysis of retrospective data was finished in 2009; however, there is no obvious reason why more actual were not included.

AU: When we started these analyses, this was the extent of the available data. Analysis of large datasets such as done for this study, takes a significant amount of additional work aside form data collection: prior to analysis, the data need to be cleaned and validated, often requiring additional investigation, as not every variable obtained will be complete. In addition, every hospitalization of every patient was reviewed to determine if CDI had been diagnosed and determine the medications the patients received as outpatients. The data collection process for this study began in mid-2010; thus 2009 was chosen as the study end date to ensure all CDI patients had been discharged from the hospital and enough time had elapsed to determine whether the patients would develop a CDI recurrence. Since there have been no appreciable changes reported in the epidemiology of CDI following this period of time, adding more recent data is not likely to alter our results.

3. Due to these major limitations scientific novelty of this manuscript is missing and the results are pure descriptive.

AU: We respectfully disagree with the reviewer that our results are purely descriptive. There are few high quality studies on risk factors for recurrent CDI, and this is the largest study by far to examine risk factors for recurrent CDI. In addition, we have used the most relevant statistical methods (i.e. extended Cox proportional hazards modeling) to control for the time dependent nature of some predictor variables that directly impact the risk of recurrent CDI (i.e. antimicrobials), which has not previously been done.

Certainly, the quality of data is always limited in retrospective studies. However, despite these limitations retrospective data are important for longitudinal analysis due to availability of an extensive historical dataset. This information is of striking importance for clinical appearance of CDI in times of outbreaks with a new hypervirulent 027 ribotype outbreak strain.

Therefore I would recommend the authors to include also more actual data on CDI into analysis (e.g. end of 2013). This would allow to answer the question how the clinical appearance of CDI changed since 2003 and how the 027 epidemics was associated with recurrence rates. It would be of high clinical importance to obtain new independent data to confirm that the recurrent rates for CDI were increasing in recent years (e.g. Aslam et al. 2005).
AU: We agree with the reviewer that there are limitations to retrospective studies. One of these limitations is lack of data not obtained through routine patient care. Practices in the US may differ from other countries in that culture and molecular typing of C. difficile are not routinely performed as part of routine patient care in the US. Therefore we do not have strain typing data. Also, as previously noted, the epidemiology of CDI has not significantly changed from the end of the study period (2009) until today. Therefore the time and expense of collecting additional data are unlikely to significantly enhance what is already the largest study of risk factors for recurrent CDI.

Reviewer: Bryan F Curtin

1. Is the question posed by the authors well defined?
This manuscript highlights the increasing problem of Clostridium Difficile Infections (CDI) and recurrence of disease and then proceeds to identify potential risk factors for recurrent CDI. The goals and question posed by the author are clear and well defined.

AU: Thank you.

2. Are the methods appropriate and well described?
The methods for the most part are comprehensive and well described. One area I think needs more detail is the definition of the high-risk and low-risk antibiotic choices. The authors define which antibiotics they consider high and low risk and cite two papers that appear to have been published by the same group. I think the authors could address this by acknowledging that their antibiotic classifications are based on studies done at the same institution, or by including other studies that have looked at classifying antibiotics by their risk of CDI.

The following paper was recently published and has similar findings of which antibiotics are high risk:

AU: We appreciate the reviewer’s comments. Although not all classifications of high risk antibiotics for CDI are identical, they in general are similar. We used clinical as well as statistical methods based on our observations and real-world data to come up with our classification of antimicrobials in regards to risk for CDI. We do note in the discussion section the greatest limitation of this study is the generalizability of the findings. We feel the reviewer’s comment is adequately covered by this statement. However, if the editors would like an additional statement to this effect but with specific reference to this issue, we are happy to include such.

This is a Minor Essential Revision and should be addressed prior to publication.

3. Are the data sound?
The data collected from retrospective review the authors performed appears
sound and well stratified.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   The discussion and conclusion sections are well balanced and supported by their data. However, I think the discussion section is conspicuously lacking a paragraph suggesting possible interventions as a result of their findings, aside from a few sentences at the very end in the conclusions section. While it is important to recognize the importance of modifiable risk factors in the development of rCDI, which of these risk factors can we realistically modify on a large scale. It would be interesting to hear the authors' viewpoints on specific intervention strategies regarding their findings. At minimum the importance of educational initiatives or antibiotic stewardship should be at least mentioned.

   AU: The reviewer makes a good point. We have added the following sentence to the first paragraph of the Discussion section on page 10:
   “This may serve as yet another reason for institutions to engage in aggressive antimicrobial stewardship programs.”

   In addition, while the authors mention that they found no difference between PPI and H2 blocker and the development of CDI in their preliminary data and past work, there have been multiple studies released in the past few years that suggest H2 blockers may be safer, and this should be acknowledged. Examples include:


   These are Minor Essential Revisions and should be addressed prior to publication.

   AU: We are grateful to the reviewer for this suggestion. We have included the following sentences to the Discussion on page 10, and added the Tleyjeh meta-analysis as citation #24:

   “Similarly, Tleyjeh et al. in a meta-analysis of 33 studies focusing specifically on H2RB exposure reported a smaller, albeit still significant, association between receiving H2RBs and development of CDI (24). Both meta-analyses suggested that gastric protection in conjunction with antibiotic administration carries a higher risk of CDI development than exposure to PPIs or H2RBs alone (23, 24).”

6. Are limitations of the work clearly stated?
   The authors clearly and effectively state the limitations of their work in the context
of a retrospective observational study.

However, while the authors cite the updated 2010 SHEA/IDSA guidelines on multiple occasions, including discussion about the hyper-virulent strain of Clostridium Difficile and our current knowledge on the risk of acid suppressant therapy, they do not acknowledge one of the most essential elements of those guidelines, which was the stratification of CDI into mild-moderate, severe, severe-complicated cases and the new recommendation of oral vancomycin as a sole first line agent in more severe cases. The patient population they observed was between 2003 and 2009, which would not have been treated according to updated guidelines and thus represents a significant limitation.

AU: The goal of this study was to determine risk factors for recurrent CDI. To date, no study has found severity of an initial episode of CDI or preferential use of vancomycin for severe CDI to decrease the risk of recurrent CDI (including the studies upon which the treatment recommendations are based). Therefore we did not feel that a statement in reference to the study period, publication of the SHEA/IDSA guidelines, and lack of data indicating risk of recurrent CDI is impacted by CDI severity or management of severe CDI was warranted.

This is a Minor Essential Revision and should be addressed prior to publication.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

The authors clearly acknowledge work their are building upon, which is in multiple cases their own published work from prior retrospective studies. As mentioned in my earlier comments, in such occurrences other studies should be mentioned in these cases to give the reader more broadened perspective.

AU: We appreciate the reviewer’s suggestions, and have incorporated them into the Discussion.

8. Do the title and abstract accurately convey what has been found?

Yes, although I would re-word the Background portion of the abstract so that (rCDI) is preceded by the words "Recurrent Clostridium Difficile infection" and not "Clostridium Difficile Infection recurs" with according changes to the rest of the sentence to make it grammatically appropriate.

AU: We have now changed the sentence to the following:

“Recurrent Clostridium difficile infection (rCDI) is observed in up to 25% of patients with an initial CDI episode (iCDI).”

This is a Discretionary Revision and the authors can choose to ignore it.

9. Is the writing acceptable?

The writing is acceptable and is of high quality.

Overall this study provide a through and very interesting retrospective observation look at a wide variety of risk factors. While I think that some sections can be further expounded upon (see my previous comments), I would say that the entire body of work is quality and worthy of publication.
AU: We are grateful for this reviewer’s thorough critique of our work and the opportunity that he has provided for us to improve it.