The Editor

BMC Infectious Diseases BioMed Central

236 Gray's Inn Road London WC1X 8HB United Kingdom

Dear Editor,

Re: Manuscript “A unique strain of community-acquired Clostridium difficile in severe complicated infection and death of a young adult”.

Please note that several changes have been made to the manuscript in accordance with the reviewer’s observations and comments. The change of title is to reflect salient points in the case report. Other major changes include 1) C. difficile progressing to complicated clinical outcome as the most probable cause of death; 2) Highlighting the potential risk of community acquired infection progressing to severe disease and should be treated with equal importance as with hospital acquired infection and 3) The need for more meaningful molecular epidemiological studies on C. difficile and for health care providers to be more alert to the likely critical outcome of C. difficile infection.

The following are included as attached files:

1. Responses to the reviewers queries/comments
2. Written informed consent signed by the parents for the publication of the case study

3. The revised manuscript

Sincerely,

Orville Heslop, PhD
Corresponding Author/Principal Investigator

April, 2013

Response to Reviewer’s Report (Scott Curry):

Questions/comments from section 1

1. “Heslop et al. repeatedly state that "toxic megacolon and bowel perforation are...unusual outcomes following community-acquired C. difficile infection."

Response:

We agree with the reviewer’s observation. However, our concern was with “severe complicated CDI” occurring in a young adult (22 years) which was well below the median age of 80 years in CA-CDI (Reference 8 of manuscript). We have reworded the paragraph to reflect a true characterization of CA-CDI as opposed to HA-CDI.

2. “Changing the focus of this case report to reflect that CA-CDI, just like HA-CDI, can and does end badly”.

Response:

We have made the change in the manuscript.

3. “There is no evidence to support that Gram-negative septic shock is rarely seen in CA-CDI, as data about this were not given in the provided citation".
We have adjusted the related sentence referring to “Gram-negative shock” to the correct expression of “Gram negative sepsis” as there was no evidence of “shock” as originally stated in the case history.

Questions/comments from section 2

4. Why was a high-risk antimicrobial antibiotic for CDI like clindamycin used in this patient to begin with?

Response:

Despite the excellent coverage of clindamycin as a broad-spectrum antibiotic, one should be cautious considering the risks involved. We were unable to determine the reason for clindamycin usage in this case and we can only presume that the patient was allergic to penicillin or the dentist was unaware of the potential risk of this patient acquiring CA-CDI. This case certainly highlights the need for a more rational use of antimicrobial therapy in outpatient settings.

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5. Why was chloramphenicol started along with metronidazole when she first developed a GI syndrome?

Response:

We presume that the apparent use of chloramphenicol in empiric therapy was to prevent the potential risk of other enteric bacteria causing diarrhoea. The introduction of metronidazole was apparently for the suspected case of C. difficile associated diarrhoea.

6. What was her serum albumin level (a proposed marker for severity of CDI) at admission?

Response
There was no record that the serum albumin level was determined on this patient at admission.

7. What does "a subsequent diarrheal stool specimen was positive for C. difficile? mean, i.e. was one sent at admission that was negative?" "At what hospital day was the positive EIA sample sent?"

Response:

Only one stool specimen was sent the second day after the patient's admission. A positive ELISA for C. difficile toxins A/B on this single sample was used for confirmation of CDI. The original statement was removed from the text to avoid confusion.

Questions/comments from section 3 & 4

8. Did the patient have autopsy cultures of spleen and lungs?

Response:

No autopsy cultures of spleen and lungs were done.

9. What was the antibiotic susceptibility pattern of the K. pneumoniae isolates from blood?

Response:

The antibiotic susceptibility pattern of the isolate (K. pneumoniae) was as follows:- Susceptibility testing on K. pneumoniae by the Kirby Baeur method showed susceptibilities to ceftriaxone, co-trimoxazole, ceporin, amikacin, gentamicin, ceftazidine, augmentin and resistance to chloramphenical, piperacillin and ampicillin. These results are now included in the manuscript.

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Questions/comments from section 5
10. "Haematogenous dissemination of C. difficile is rare and toxemia was more likely to have been due to the toxicity of the C. difficile toxins and the induction of proinflammatory cytokines by the toxins (8), hence the septic presentation was entirely due to disseminated K. pneumoniae." This sentence makes little sense.

Response:

The above statement was removed from the manuscript. Your comment/observation has been addressed in the manuscript.

11. Which do you feel was the proximate cause of death and sepsis?

Response:

We agree with the observation made. It was an unacceptable oversight by us to suggest that the primary cause of death was Gram negative septic shock seeing that K. pneumoniae was cleared from the blood at least 5 days post death.

On the contrary, multiple discrete plaques of yellowish exudate on the mucosal surface of the entire large bowel, typical of pseudomembranous colitis (PMC) that was florid would more strongly suggest the cause of death. The change has been made in the manuscript to reflect the most probably cause of death.

12. “To my view, in light of the sterilized blood cultures, it seems more probable to have been from fulminant CDI with SIRS. I would state explicitly that her CDI treatment departed substantially from the standard of care (no escalation to enteral vancomycin, no surgical intervention) and comment on why this may have been?”

Response:

The apparent rapid progression to serious clinical outcomes and failure to act judiciously and in good time could be from several factors. a). The apparent advanced stage of CDI in this patient when she was referred to the UHWI;

b) A community acquired CDI of this nature presumably being seen for the first time together with the likely inexperience of the clinician appropriately managing this case which was unresponsive to metronidazole; c) Being preoccupied in
treating Klebsiella sepsis while awaiting the antimicrobial susceptibility report, apparently eluded the bigger picture of severe complicated CDI.

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13. Was the diagnosis known ante-mortem?

Response:

The presumptive diagnosis at admission was pseudomembranous colitis and the early use of metronidazole would suggest knowledge of CDI

14. What was the turn-around time on the EIA testing? Did clinicians totally discount the possibility of CDI because of the onset of disease in the community on chart review? Was no initial CDI testing done for this reason (seems unlikely)?

Response:

The turn around time for the ELISA was within the hour of performing the test. We believe that the clinician/s did not discount the possibility of CDI occurring in the community but apparently did not act judiciously with the correct approach to treatment, which we feel needed aggressive treatment with combination antibiotic therapy of metronidazole and vancomycin administered directly into the colon. There was also the option for surgical intervention in the management of this patient. Initially there might have been a lack in clinical suspicion of the extent of severity of the clinical outcome initiated by overgrowth and production of toxins by C. difficile.

13. Was no initial CDI testing done for this reason (seems unlikely)? Response:

No initial laboratory testing for CDI was done except after admission at the UHWI. The ELISA testing was carried out the following day after admission. It is important to note however, that the patient was apparently in an advanced stage of CDI.

Questions/comments from section 6

14. "Interestingly however, these interventions including vancomycin treatment with recommended total colectomy were not indicated in the management of the
present case." I disagree.

Response:

The severity of CDI in this case indeed indicated that intra-colonic therapy was needed.

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It is however noted that this was not done. Moreover intra-colonic vancomycin might have made a significance difference in the patient’s recovery. Changes in the manuscript have been made to reflect this observation.

MINOR ESSENTIAL REVISIONS:

Questions/comments from section 1 & 2

1. The authors repeatedly misuse the term "indicated" to mean "was noted" throughout the manuscript. At the top of page 6, for instance, the authors note that "no previous history of hospitalization....was indicated in this patient." I presume this to mean that the patient had no known hospitalizations in the 12 weeks prior to her falling ill. Please clarify.

Response:

The related sentences of the above comments were revised to clarify that there was no history of hospitalization of this patient over 12 weeks prior to falling ill.

2. “The pulsortypes in the PFGE figure 1 are obviously Canadian designations not corresponding to the CDC NAP types. I would delete this from the figure to avoid confusing the audience. Also, please remove "hypervirulent” re the reference strain. For reasons specified above, the strain has not been observed to be hypervirulent in vivo”.

Response:

We have deleted the pulsed-field type designations from the figure. “Canadian and Hyper-virulent” were removed from those sentences in the manuscript as
1. How do the authors conclude that the death was presumably resulted from Kp sepsis but not CDI?

Response:

We agree with the observation made. It was an unacceptable oversight by us to suggest that the primary cause of death was Gram-negative septic shock seeing that K. pneumoniae was cleared from the blood at least 5 days post death.

On the contrary, multiple discrete plaques of yellowish exudate on the mucosal surface of the entire large bowel, typical of pseudomembranous colitis (PMC) that was florid, would more strongly suggest the cause of death. The change has been made in the manuscript to reflect the most probably cause of death.

2. Do the authors have the susceptibility and genotype data for the Kp strain?

Response:

Antimicrobial susceptibility testing was done on the K. pneumoniae strain but no genotyping was done on this isolate

Susceptibility testing on K. pneumoniae by the Kirby Baeur method showed susceptibilities to ceftriaxone, co-trimoxazole, ceporin, amikacin, gentamicin, ceftazidine, augmentin and resistance to chloramphenical, piparacilin and ampicillin. These results are now included in the manuscript.

3. The software and parameters used to generate the dendrogram should be given.

Response:
We have added a sentence to describe the software and parameters used in Fig 1 legend.

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