Reviewer's report

Title: Klebsiella pneumonia septic shock and death in a patient with community-acquired Clostridium difficile colitis (CA-CDI):

Version: 3  Date: 13 March 2013

Reviewer: Scott Curry

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Major Compulsory Revisions:

1. In the abstract and elsewhere, Heslop et al. repeatedly state that "toxic megacolon and bowel perforation are...unusual outcomes following community-acquired C. difficile infection." The citation provided by the authors (3) does not support this contention, as 20% of CA-CDI patients had severe outcomes compared to 31% of HA-CDI. I would hardly characterize this difference as indicating that severe CDI is "unusual" in this group. In fact, the same authors cited have argued in another paper (Aliment Pharmacol Ther. 2012 Mar;35(5):613-8. doi: 10.1111/j.1365-2036.2011.04984.x. Epub 2012 Jan 10) that 40% of CA-CDI required hospitalization, 20% were severe, and 4.4% were severe-complicated. Their original publication, like all laboratory-based surveillance studies for CDI, suffers from significant diagnostic testing and misclassification bias, as healthy outpatients in the community are likely to be misclassified as having mild CDI when they in fact are C. difficile carriers getting tested for C. difficile toxin while NOT being tested for the common causes of outpatient gastroenteritis such as norovirus, C. perfringens, etc for which clinical testing is not commonly available. This is well documented in a prospective study of outpatients with diarrhea by Hirshon et al (PMID:22000379). I would change the focus of this case report to reflect that CA-CDI, just like HA-CDI, can and does end badly. 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.

2. Missing case report elements: Why was a high-risk antimicrobial antibiotic for CDI like clindamycin used in this patient to begin with? Was she penicillin-allergic? Does this case illustrate a need for more rational use of antimicrobial therapy in outpatient settings? Why was chloramphenicol started along with metronidazole when she first developed a GI syndrome? What was her serum albumin (a proposed marker for severity of CDI) at admission? 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?

3. Did the patient have autopsy cultures of spleen and lungs? Absence of K. pneumoniae in the lungs would add more weight to the supposition that the patient had bowel translocation of KPN due to PMC.
4. What was the antibiotic susceptibility pattern of the *K. pneumoniae* isolates from blood?

5. "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. Which do you feel was the proximate cause of death and sepsis? 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? Was the diagnosis known ante-mortem? 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)?

6. "Interestingly however, these interventions including vancomycin treatment with recommended total colectomy were not indicated in the management of the present case." I disagree. This is just the sort of case for which SHEA/IDSA guidelines call for combined therapy with enteral vancomycin, IV metronidazole, +/- vancomycin enemas and surgical evaluation.

7. Regarding the molecular epidemiology in this case, I think that this bears substantially more highlighting throughout the manuscript. The genotypic features of ATCC 43255 (more commonly known by its previous strain designation from the Wadsworth reference lab, VPI10463) shared with this isolate are striking, especially its likeness by ribotyping and PFGE. However, VPI10463 was originally isolated from a surgical wound, and as far as I know this might be the first case report to describe this CD variant associated with true CDI, much less fulminant CDI. VPI10463 hyperexpresses toxin (100,000X more than most other CDI strains, including infamous ribotype 027 epidemic strains) despite an intact tcdC gene, and it would be fairly simple to see if this strain shares this phenotypic feature.

Minor essential revisions:

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.

2. The pulsotypes 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.
Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.