ANSWERING REVIEWERS

May 5th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10515-review.doc).
We omitted one co-author whose name is Sung Soo Park. We added this c-author in this manuscript. Please let us add this co-author be included in this case report.

Title: A case of *Clostridium difficile* infection complicated by Acute Respiratory Distress Syndrome treated with fecal microbiota transplantation

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 10515

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
Reviewer1

1) in the first paragraph under case report, the authors state "Pneumonia was noted on chest X-ray" I suggest modifying this to "consolidation was noted on the chest X-ray which is consistent with the diagnosis of pneumonia" we can't see pneumonia on chest x-ray but we can see consolidation.

-> We corrected as you commented on page 6.

2) Please provide references on the dosing regimen used for FMT, and it maybe helpful to add to the discussion section a paragraph on different dosing regimens and weather they differ by method of delivery (upper endoscopy versus colonoscopy).

-> Recommended dosing regimen is >50 g of stool regardless of infusion route. We added on page 9

3) Please clarify what vancomycin dosing regimen was used to treat this patient (125 mg versus 500mg 4 times per day).

-> Because of renal insufficiency, vancomycin dosing regimen was 125 mg 4 times / day. We added on page 7

4) In the discussion section, authors describe the definition of ARDS. First, i don't think it is relevant to discuss this in this manuscript as it is out of context. Second, the definition used is old, there is a newer definition (Berlin definition) that is in use instead of the old AECC definition (Intensive Care Med. 2012 Oct;38(10):1573-82).

-> We corrected our manuscript and removed the definition of ARDS.

5) Authors may consider adding to the discussion section, other reasons not to use intra-colonic FMT like fear of perforation in a severely inflamed colon.

-> We added your comment on page 9

6) In the discussion section, the following statement need further clarification: "FMT performed via upper endoscopy has a risk of aspiration; however, we applied endotracheal intubation during the procedure and there was no aspiration" was the patient intubated for the procedure or was already intubated for ARDS? please clarify because its not clear, and it would be very unusual to intubate a patient just for this procedure. I hope that may comments were useful.

-> We performed endotracheal intubation before the FMT. We corrected as you commented on page 9; endotracheal intubation for the treatment of ARDS had been performed several days before the procedure and there was no aspiration

Reviewer2

The paper is well written and could be an important addition to the literature because it does remind clinicians of the potential extra intestinal effects of CDI.

1) However the authors fail to provide strong link between CDI and ARDS. This has been described in the literature (Sindhu S. Jacob et al HEART & LUNG VOL. 33, NO. 4 pg;267-268) and this manuscript should emphasize this more. The current structure speaks to the notion that the ARDS encountered by this patient appears to be a direct consequence of his pneumonia with very little to do with CDI.

-> Thank you for your comment. We reviewed that article and knew that ARDS could be complicated by *C. difficile* infection. However, in our case ARDS developed first and CDI developed as a complication of treatment for ARDS (ex. Antibiotics). In our opinion strong link between CDI and ARDS might not be as high as you commented. We partly corrected our manuscript and added this reference.

2) In the description of the case, stating the kind of antibiotics administered will be important and same applies for method of Cdiff testing (by ELISA?)

-> Clarithromycin and ceftriaxone was the starting antibiotic. We added this explanation on page 6.

-> *C. difficile* test was done by toxin assay and stool culture. We added this explanation on page 7.

3) Adding the dosing and frequency of flagyl and vancomycin for treatment of Cdiff will also be important

-> We corrected as you commented on page 7.

4) DISCUSSION The issue here is the development of ARDS in a patient with CDI. That the patient responded to the FMT and not broad spectrum antibiotics used to treat his pneumonia seems to imply CDI was the predominant disease entity contributing directly to the development of ARDS. ARDS in the setting of CDI has been reported. The paper should be focused on ARDS as a complication of Cdiff and thus the statement " However, the incidence of CDI in patients with ARDS has not been reported" should be revised This statement should be focused on the incidence of ARDS in patients with severe CDI and not the other way round (i.e. the incidence on CDI in patient with ARDS) This will also be consistent with the authors conclusions which states " this is the first case of CDI complictated by ARDS……"

-> As answered to your comment 1), link between CDI and ARDS was not so high as your comment. But we revised our manuscript: "this is the first case of CDI complicated by ARDS…" on discussion.

Reviewer3

1) The authors do not specify which antibiotics were administered to the patient and how long (although we understand that antibiotic treatment was administered for 13 days, prior to CDD appearance, as patient admission was because of a pneumonia) ?

-> We changed antibiotics and used it for 13 days prior to development of CDI. We revised according to your comment on page 7

2) On day 13 diarrhea developed, CDD was diagnosed and oral metronidazol was added. However the patient was under mechanical ventilation…so I imagine that metronidazol was administered through a nasogastric tube. Why did they not start with oral vancomycin? ?
According to recent clinical practice guidelines for CDD, if diarrhea does not improve in 5-6 days you should change antibiotic treatment to vancomycin if you have been using metronidzole. Why did they wait 10 days to change CD treatment? ?

➔ Thank you for your nice comment. When we started regimen for CDI, the patient was in acute kidney injury. So we could not use vancomycin. We added your comment to discussion on page 9.

3) Finally, I think that the authors should specify when antibiotic treatment administered for pneumonia was stopped. We do not know if non CD-antibiotics were administered concomitantly to vancomycin which could explain the refractoriness to conventional CD treatment.

-> We used meropenem and teicoplanin when antibiotic treatment for pneumonia was stopped. We added your comment on page 7.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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