Responds to the reviewer’s comments:

Reviewer’s code: 02650654
SPECIFIC COMMENTS TO AUTHORS

The authors can discuss the possibility of this particular treatment with pharmaceutical equivalent products.

Response to comment:

In recent years, with the deepening understanding of the pathogenesis of CDI in the medical community, great changes have taken place in the management of CDI. Initially, metronidazole was mainly used as a first-line management. Data before 2000 showed that the proportion of patients receiving metronidazole to achieve clinical cure was similar to that of vancomycin. However, recent data show that vancomycin has a significant effect on symptoms relief and a lower recurrence rate .While antibiotics have been the mainstay of CDI treatment for decades, increases in CDI frequency, severity, and treatment failures have prompted investigations into the development of alternative therapies that are less disruptive to the colonic microbiota. Fecal microbiota transplantation (FMT) is a such alternative now recommended in select guidelines due to growing evidence demonstrating efficacy. Unfortunately, because data regarding the use of FMT in initial CDI episodes are limited, FMT is currently recommended only for the treatment of recurrent CDI infections.

We had discussed the pharmaceutical equivalent products in the third paragraph of discussion part.

Paknikar R, Pekow J. Fecal Microbiota Transplantation for the Management of Clostridium difficile Infection. Surg Infect (Larchmt). 2018. 19(8): 785-791.

Reviewer’s code: 01800952
SPECIFIC COMMENTS TO AUTHORS

Authors have successfully used Fecal transplantation (FT) in a patient with CD toxin colitis. Authors did not choose to use standard of care treatment therapy for first attack of CD toxin colitis. Authors claim this is the first case of FT in china and want to get credit for this. I believe using such unconventional treatment for such a sick patient with first attack of CD toxin colitis shall send wrong message of treating such patients with FT. FT is effective in recurrent CD toxin colitis. To substantiate what authors recommend needs a carefully designed Randomized Controlled Trial, under strict supervision. Data on a single patient may be misleading.

Response to comment:

Many thanks for your review and your comments on different management approaches for this admittedly challenging case of rCDI treated by FMT in MSAP.

Various options were discussed in length with the patient and his family. We agree that choosing FMT management instead of antibiotics in primary CDI is controversial. In recent years, with the deepening understanding of the pathogenesis of CDI in the medical community, great changes have taken place in the management of CDI. Initially, metronidazole was mainly used as a first-line management. Data before 2000 showed that the proportion of patients receiving metronidazole to achieve clinical cure was similar to that of vancomycin. However, recent data show that vancomycin has a significant effect on symptoms relief and a lower recurrence rate .While antibiotics have been the mainstay of CDI treatment for decades, increases in CDI frequency, severity, and treatment failures have prompted investigations into the development of alternative therapies that are less disruptive to the colonic microbiota. This effect may be driven by resistance patterns of the bacteria. FMT is a such alternative now recommended in select guidelines due to growing evidence demonstrating efficacy. Unfortunately, because data regarding the use of FMT in initial CDI episodes are limited, FMT is currently recommended only for the treatment of recurrent CDI infections. In this background, we discussed the pros and cons with the patient and obtained Informed written consent from the patient and family. We have to think about how to choose drugs if vancomycin gradually loses its current therapeutic effect like metronidazole, which will inevitably pay a huge price, but also shows the importance of FMT. Until further high quality evidence becomes available, different management options have merits and associated risks; the ultimate decision should be taken at an individual level.

This strategy has the indisputable advantage of confirming what was strongly suspected. Retrospectively, not starting FMT at this patient was therefore a missed opportunity.

The fact that not all people at risk of or with CDI need enduring antibiotics treatment explains why FMT is a very potential and much needed additional treatment approach. We indeed need more relevant clinical studies to conquer the epidemic.

Paknikar R, Pekow J. Fecal Microbiota Transplantation for the Management of Clostridium difficile Infection. Surg Infect (Larchmt). 2018. 19(8): 785-791.

Reviewer's code: 03261315

SPECIFIC COMMENTS TO AUTHORS

Here are my comments: in the section CASE PRESENTATION Please modify the phrase: nothing to declare. Add how much quantity of alcohol per day. Physical examination: please add the macroscopic aspects of stools and findings at rectal palpation. Please erase the final diagnosis and replace it with evolution. Please write precisely what drugs did you stop. "We stopped all treatments that could induce diarrhea (which one?), ". Pay attention at the probiotics treatment in acute pancreatitis. The recent studies showed that the probiotics increase the mortality in AP and the European guidelines do not recommend probiotics in acute pancreatitis (in fact should be avoid it). Why did you perform colonoscopy in infection with Clostridium?? In the section discussion: please discuss the risk for medical staff and medical instruments and the specific measures that should be taking when a colonoscopy is made in patients with infection with Clostridium. Also, please specify if there are needed special measures when faecal transplantation via naso-jejunal tube is made.

Response to comment:

Considering the Reviewer's suggestion, we have revise our article at every track changes point.

1. Response to comment: in the section CASE PRESENTATION Please modify the phrase: nothing to declare.

We modify to "His family history was unremarkable".

2. Response to comment: Add how much quantity of alcohol per day.

We add the data :（about 80g per day）.

3. Response to comment: Physical examination: please add the macroscopic aspects of stools and findings at rectal palpation.

We add the words: The macroscopic aspects of stools were yellow water-like stool. After the occurrence of diarrhea, rectal palpation was negative.

4. Response to comment: Please erase the final diagnosis and replace it with evolution.

We have made minor modifications in this section to show the

progression of diagnosis.

5. Response to comment: Please write precisely what drugs did you stop. “We stopped all treatments that could induce diarrhea (which one?), ”.

We write that “We stopped all treatments（ rhubarb and mirabilite, mannitol, oral; glycerol enema） that could induce diarrhea.”

6. Response to comment: Pay attention at the probiotics treatment in acute pancreatitis. The recent studies showed that the probiotics increase the mortality in AP and the European guidelines do not recommend probiotics in acute pancreatitis (in fact should be avoid it).

We did not use probiotics in the early stage of pancreatitis (within a week of onset), but in the treatment of diarrhea after the onset of diarrhea.

7. Response to comment: Why did you perform colonoscopy in infection with Clostridium?? In the section discussion: please discuss the risk for medical staff and medical instruments and the specific measures that should be taking when a colonoscopy is made in patients with infection with Clostridium.

The optimal role of the lower GI endoscopy in the setting of CDI remains poorly defined and controversial. In the late 1970s and 1980s, some authors stressed the importance of endoscopy as a diagnostic tool . In the 1990s, with the improvement in the speed and reliability of the microbiologic diagnostic tests, it was thought to be less useful due to the cost and the relative lack of sensitivity of endoscopy as a general screening tool. As such, lower GI endoscopy began to play a secondary role in the workup of antibiotic-associated diarrhea .

The most common indication was ruling out other colonic etiologies in 19 (42%) patients, including (a) four immunosuppressed patients where there was a need to rule out CMV colitis and/or GVHD, (b) four patients with bloody diarrhea where inflammatory bowel disease, ischemic colitis, or malignancy was suspected, and (c) eight patients with persistent diarrhea despite medical treatment for CDI.the most common indication of lower GI endoscopy in the setting of CDI was to rule out other colonic pathologies that may be coexisting with CDI diagnosis and inconclusive C. difficile studies being the second most common indication.

Our method of disinfecting endoscopes is to immerse them in glutaraldehyde to kill the spores of Clostridium difficile.

Burkart NE, Kwaan MR, Shepela C, et al. Indications and Relative Utility of Lower Endoscopy in the Management of Clostridium difficile Infection[J]. Gastroenterol Res Pract, 2011,2011:626582. DOI: 10.1155/2011/626582.

8.Response to comment: Also, please specify if there are needed special measures when faecal transplantation via naso-jejunal tube is made.

We add :Before FMT was applicated, the patient was taught relevant knowledge, and he was required to keep fasting within 1 hour before

operation and 1 hour after operation.

Reviewer's code: 02510721

SPECIFIC COMMENTS TO AUTHORS

To Authors This study is very interesting and shows a new perspectives in the management of the clinical appearance of the global intestinal dysfunction during moderate and severe acute pancreatitis, with also the development of CDI. This clinical condition is characterized by many factors as intestinal wall dysfunction, alteration of the intestinal flora, effects of the possible organ dysfunction. In summary the use of FMT in the treatment of CDI in course of MSAP is a possible therapeutic resource, but in the more severe cases should be difficult to replace or to integrate with the use of antibiotics (e.g. the classic vancomycin). Further studies, with more cases, should be useful. In conclusion this case report is very well developed and can be a valuable communication in the clinical event in progress.

Response to comment:

Special thanks to you for your good comments. We believe that more clinical studies on initial treatment of CDI will be designed and completed in the future or at present.

Reviewer's code: 00055108

SPECIFIC COMMENTS TO AUTHORS

See attached manuscript for comments, please consider them carefully.

Response to comment:

Considering the Reviewer's suggestion, we have revise our article at every track changes point.

1. Response to comment: language，

We have provide the Non-Native Speakers of English Editing Certificate by AJE as well.

2. Response to comment: Why this treatment as primary approach? The

treatment is experimental in this patient group – AP. Explain.

Various options were discussed in length with the patient and his family. We agree that choosing FMT management instead of antibiotics in primary CDI is controversial. In recent years, with the deepening understanding of the pathogenesis of CDI in the medical community, great changes have taken place in the management of CDI. Initially, metronidazole was mainly used as a first-line management. Data before 2000 showed that the proportion of patients receiving metronidazole to achieve clinical cure was similar to that of vancomycin. However, recent data show that vancomycin has a significant effect on symptoms relief and a lower recurrence rate .While antibiotics have been the mainstay of CDI treatment for decades, increases in CDI frequency, severity, and treatment failures have prompted investigations into the development of alternative therapies that are less disruptive to the colonic microbiota. This effect may be driven by resistance patterns of the bacteria. FMT is a such alternative now recommended in select guidelines due to growing evidence demonstrating efficacy. Unfortunately, because data regarding the use of FMT in initial CDI episodes are limited, FMT is currently recommended only for the treatment of recurrent CDI infections. In this background, we discussed the pros and cons with the patient and obtained Informed written consent from the patient and fmt。We have to think about how to choose drugs if vancomycin gradually loses its current therapeutic effect like metronidazole, which will inevitably pay a huge price, but also shows the importance of FMT. Until further high quality evidence becomes available, different management options have merits and associated risks; the ultimate decision should be taken at an individual level.

This strategy has the indisputable advantage of confirming what was strongly suspected. Retrospectively, not starting FMT at this patient was therefore a missed opportunity.

The fact that not all people at risk of or with CDI need enduring antibiotics treatment explains why FMT is a very potential and much needed additional treatment approach. We indeed need more relevant clinical studies to conquer the epidemic.

3. Response to comment: Did the patient receive any antibiotic treatment during this period of 9 days? Ref…we stopped all treatments that could inducue diarrhea…..

He did not receive any antibiotic , we stopped all treatments (rhubarb and mirabilite, mannitol, oral; glycerol enema） that could induce diarrhea.

4. Response to comment:This is not a typical used name for the substans

We use “montmorillonite (MMT) ” instead of “smectite” right now.

5. Response to comment:Generic and brand name?

“live combined bacillus subtilis and enterococcus faecium” is the drug’s generic brand,and brand name is “Medilac-s”,we have revised it.

6. Response to comment:Did you do a confirming laboratory test – to rule out carrier state

We did not do a confirmation test which might be toxigenic culture(TC) because the patient had a very particular diarrhea symptom and endoscopic findings and positive toxin detection. According to ESCMID, A two-stage test [glutamate dehydrogenase(GDH) or nucleic acid amplification tests(NAATs) for toxin genes followed by a highly sensitive toxin test or GDH in combination with a toxin test] is recommended to diagnose CDI. We did the NAATs(Xpert) and Toxin B EIA test，both of which were positive，so we believed CDI is likely to be present.

Crobach MJ, Planche T, Eckert C, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2016. 22 Suppl 4: S63-81.

7. Response to comment:This paragraph would be presented clear if divided in several section – supportive treatment – FMT treatment – the donor information can be presented nicely in a own paragraph

We have revised this paragraph as reviewer's suggestion.

8. Response to comment:When was this performed?

The Colonoscopy was performed concurrently with fecal toxin examination during follow-up.

9. Response to comment:Please consider to make your discussion short, focus on your case,

We have revised as the reviewer's suggestion.

10. Response to comment:At this point not a valid statement – to early

We delete this inappropriate expression.

11. Response to comment:This is background – introduction information – please consider to move it.

We have revised as the reviewer's suggestion.

12. Response to comment:This is a combination of background – introduction information – please consider to move it. Be strict to your case – discuss why you chose FMT and not AB. Why is FMT especially good treatment in this patient group?

We have revised as the reviewer's suggestion.

13. Response to comment:This figure need some arrow and explanatory text to be readable – please provide

We add red arrow to mark the necrotic region of pancreas.

14. Response to comment:See comment on figure 4

We have revised as the reviewer's suggestions.

15. Response to comment:This is not need – a description in the manuscript is enough. Suggests it to be rejected

We reject the figure 3 and describe it in the final diagnosis part.

16. Response to comment:Combined figure 2 and 4 – only one picture from each fig. gives the reader sufficient information.

We have revised it as reviewer's suggestion.

17. Response to comment:This is not easy to read – please consider a different layout or reject.

Focus on our case, we have deleted some columns(Fecal material/Quantity and times of FMT/Donor) of the form for easily reading.