

October 5, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5433-review.doc).

Title: Clostridium Difficile and Inflammatory bowel disease: role in pathogenesis and implications in treatment

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Name of Journal: *World Journal of Gastroenterology*

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

1 Format has been updated

2 Revisions have been made according to the suggestions of the reviewers

Reviewer no 1:

(1) In reply to the first suggestion: " When the authors describe Clostridium difficile is more often observed among IBD patients than the general population, they should consider if surveillance of this population in out-patient clinics might be a confounding factor? In this respect the authors should also keep an eye to make the presentation of their results in a more balanced way which definitely will improve the quality. Thus, the authors should comment that Clostridium difficile infections do not seem to trigger exacerbation of IBD (check for instance PubMed PMID 23267869). ", we made the following changes: In page 5 lines 127-133 we wrote "It is possible, though, that the seemingly increased risk of CDI in patients with IBD is due to increased surveillance of this population for CDI. There are studies that question the role of CDI in IBD. A recent prospective Dutch study found a low prevalence of *C. difficile* in IBD patients and did not find any association of *C. difficile* with disease activity, disease subtype (CD or UC), gender, antibiotic, and immunosuppressive therapy^[48]. " With reference no 48 being the suggested article. We also changed "there is a clear association between IBD and *C. difficile*" to there is a possible association between IBD and *C. difficile*" in page 6, line 152.

(2) In reply to the comment: " When writing about treatment (p. 11) the authors should primarily check if any Cochrane recommendations exist in their area ((they do)), as Cochrane data is the closest we come to evidence based medicine. I do, however, not find any Cochrane references.", we added in page 11, lines 305-308 the following: " A Cochrane systematic review from 2011 found no statistically significant difference in efficacy between vancomycin and other antibiotics including metronidazole, fusidic acid, nitazoxanide or rifaximin^[83]", while adding a Cochrane reference.

(3) Regarding the comment: "The authors seem to be very enthusiastic about fidaxomicin and even suggest it should be "a first line agent" (top of p. 13). I wonder if any well performed RCT's exist to substantiate such a statement? In the respect the authors should also check PMID 23704121." , we removed the words "first line agent" and added the following in page 12 lines 337-341: " fidaxomicin might be a promising treatment for patients with risk factors known to portend relapse and severe infection^[87], though two different

economical analyses reported conflicting results of the cost effectiveness of using fidaxomicin as first-line treatment for CDI [88,89]. ", while referencing the suggested article.

(4) In reply to the comment "regarding faecal transplantation mentioned on p. 14 the authors could comment on for instance PMID 24018052.", we added the following: " A recent review of FMT[99] notes that though there are no guidelines concerning FMT for treatment of CDI in patients with IBD, after FMT and eradication of *C.difficile*, the severity of IBD is gradually reduced with improved responses to medications for IBD." Lines 380-383, while using the suggested reference.

(5) Due to the comment that " Key words should be listed alphabetically" we changed the order of the key words, page 2, line 52.

(6) Due to the comment " Abbreviations should be defined the first time they appear in the manuscript (check for instance IBD in "Introduction", p. 4, line 4 vs. line 6?)" , we corrected in page 3 line 60 "inflammatory bowel disease (IBD)".

(7) In reply to the comment : " Ulcerative colitis should not be capitalized ("u" on p. 5).", we made that change in page 4, line 105.

(8) Regarding the comment "Do the authors have any competing interest (e.g. supported by the drug company producing fidaxomicin)?" we highlight that we have mentioned on page 1, line 23 " No potential conflict of interest or disclosures declared".

Reviewer no 2:

(1) In reply of the comment " The abstract needs to be largely modified. It contains too many details. It should not discuss about the conflicting data or emphasize the need of further studies to understand better the role of CDI in IBD. In contrast, it should introduce the main information of the review and highlight the aim of the work.", we changed and shortened the abstract, removed the sentences on conflicting data and need for further studies, and added the aim of this work.

(2) Concerning the comment " Full names of several abbreviations should be cited at the first time used and not repeated thereafter. For example, full name for IBD should be cited at at line - but not line 8 in page 4, Introduction part" , we corrected in page 3 line 60 "inflammatory bowel disease (IBD)".

(3) In response to the comment: "A figure summarizes the current knowledge on CDI implication in IBD could be added." We added table 1: Unique features and clinical implications of CDI in patients with IBD that summarizes the current knowledge on CDI implication in IBD.

Reviewer no 3:

(1) In reply to the comment: " In the diagnosis section some reference to the ECCO guidelines (PMID 21172195) should be made, since specific recommendations on when and when not to test for CDI infections are made, both at initial diagnosis and at disease flares.", we added " Also, the European Crohn's and Colitis Organization guidelines recommend testing for Clostridium difficile infection in patients with severe or refractory UC[68]." Lines 249-251, while citing the ECCO guidelines.

(2) In reply to the comment " I am not sure about the relevance of the unpublished data reported. More details should be provided (ve. Sample size)", we added in page 7 line 176: " on 115 patients with CDI ".

(3) Concerning the comment : " The statement on the role of fidaxomicin as a first- line therapy seems risky because there are still only a few randomized trials, and data about cost-effectiveness are somewhat conflicting (PMID 23704121, 23538181), we added the following in page 12 lines 337-341 "fidaxomicin might be a promising treatment for patients with risk factors known to portend relapse and severe infection[87], though two different economical analyses reported conflicting results of the cost effectiveness of using fidaxomicin as first-line treatment for CDI [88,89]. ", while referencing the suggested article.

(4) In reply to the comment : " From a practical point of view it should be advisable to summarize recommendations on diagnosis and management of CDI on IBD patients, perhaps in a table. " we added table 1: Unique features and clinical implications of CDI in patients with IBD that summarizes the current knowledge on CDI implication in IBD.

Reviewer no 4:

(1) In reply to the comment : " The authors point out that *C. difficile* is nowadays considered a risk factor for IBD exacerbation. However, the latest study reported that *C. difficile* is not a common trigger for exacerbations of IBD in clinical practice (In?amm Bowel Dis 2013;19:2125-2131) . Please cite the important reference and clarify the conflicting conclusions." we made the following changes: In page 5 lines 127-133 we wrote "It is possible, though, that the seemingly increased risk of CDI in patients with IBD is due to increased surveillance of this population for CDI. There are studies that question the role of CDI in IBD. A recent prospective Dutch study found a low prevalence of *C. difficile* in IBD patients and did not find any association of *C. difficile* with disease activity, disease subtype (CD or UC), gender, antibiotic, and immunosuppressive therapy^[48]. " With reference no 48 being the suggested article. We also changed "there is a clear association between IBD and *C. difficile*" to there is a possible association between IBD and *C. difficile*" in page 6, line 152.

(2) In answer to comment: " Make sure to provide the full form of all abbreviations that they appear in the manuscript for the first time (For example, line 6 in Introduction). After appearance of abbreviations, authors should adopt the abbreviations in the following manuscript (Line 3 and 7 in Abstract)." , we corrected in page 3 line 60 "inflammatory bowel disease (IBD)".

(3) In reply to the comment "Please carefully check the spelling. For example, Running title: *Clostridium difficile* and inflammatory bowel diseaas." We rechecked the spelling in the whole paper and fixed the spelling in the running title.

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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