

Format for ANSWERING REVIEWERS



April, 23, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9429-review.doc).

Title: Impact of Clostridium difficile infection on inflammatory bowel disease outcome: a review

Author: Anca Trifan, Carol Stanciu, Oana Stoica, Irina Girleanu, Camelia Cojocariu

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 9429

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. The changes are highlighted in red within manuscript.

(1) Reviewer #000682787: There are limited data on the impact of CDI on IBD. A well written review. The reviewer did not raise any suggestion for revision.

Response: Thank you for the positive opinion.

(2) Reviewer #02861620: This is an excellent review, and draws appropriate conclusions while carefully highlighting the limitations of the included studies as retrospective or observational. Minor points: a) Were all articles included?; b) Were major international GI and infectious disease meetings proceedings surveyed given potential publication bias of negative results?; c) The authors may wish to comment on the role of fecal transplant in CDI management in IBD patients.

Response:

a), b) We included only English written studies reporting outcome of IBD patients infected with *C. difficile* (please, see page 6, methods, second sentence).
c) We believe that this is a very interesting topic, but perhaps beyond the scope of the current review. Thank you for the positive comments to the manuscript.

(3) Reviewer #00036648: This is a worthwhile topic for review given its clinical relevance and increasing incidence.

Thank you for the detailed review and helpful suggestions.

Minor points:

1) a. How the studies reviewed in this paper diagnosed an episode of CDI (or whether there was significant variations between studies)?

b. Were the negative outcomes associated with failure of first line antibiotics therapy such as metronidazole or the type/degree of immunosuppression cohorts

c. How long is the duration of effects of one episode of CDI on IBD on the risk of outcomes such as colectomy or deaths? Does the risk of colectomy pertain to that particular admission or within 30 days

or, is there evidence that an episode of CDI has a longer term impact, with more adverse course of the disease even distantly 1 or 2 years?

d. If a patient with IBD has an episode of CDI which is properly treated, is there risk for subsequent CDI episodes greater than an IBD patient with otherwise similar disease characteristics who has never been diagnosed with CDI?

e. Does the type of treatments of an episode affect future subsequent outcomes-i.e., does treatment with metronidazole or vancomycin have a different bearing on outcomes compared with other newer therapies such as newer anti-CDI pharmacotherapy or fecal transplantation?

Response:

a) "It should be underlined that most of analyzed studies relate to hospitalized IBD patients in the early 2000s, when enzyme immunoassay of stool for *C. difficile* toxins A and B has dominated the laboratory diagnosis of CDI, despite its low sensitivity". This sentence has been added at the end of first paragraph in Discussion section.

b) ", probably due to changes in the treatment regimen (use the vancomycin as a primary antibiotic, and a rapid decrease in steroid dosing) ". This sentence has been added at the end of 6th sentence, second paragraph, page 8.

c) The definitions of short- (30-90 days of index admission) and long-term (at least 1 year following index admission) outcomes are given. Please, see page 12, 1st paragraph, last two sentences.

d) Approximately 20% of patients have recurrence of CDI despite successful treatment of initial episode. Studies analyzed in our review did not include IBD patients with recurrent CDI.

e) There are no published studies comparing treatment with metronidazole or vancomycin with newer therapies such as fecal transplantation, in patients with IBD + CDI.

2. Why the final section entitled "CDI in IBD patients following surgical interventions" is placed after the Discussion just before the Conclusions.

Response:

Most if not all reviews place CDI in special conditions in IBD as we have done. The reason is that both elective colectomy and restorative proctocolectomy with ileal pouch-anal anastomosis are commonly performed surgical procedures for the management of UC patients who have no prior episodes of CDI. Thank you again for your comments.

3. The Discussion section contains too many repetitions of the results of the review, the authors should provide more interpretation of the literature as it stands.

Response:

The interpretation of the results of analyzed studies is provided in the Discussion section page 12 last line, continuing on page 13 with first two paragraphs.

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

Sincerely yours,



Carol Stanciu MD, PhD, FRCP