January 13, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name:15216-review.doc).

**Title:** Gastrointestinal Behçet's Disease: A Review

**Authors:** Wasseem Skef, Matthew J. Hamilton, Thurayya Arayssi

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 15216

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

**Reviewer 02732214:**

1. Page 6, paragraph "Diagnosis": "positive and negative predictive values of 98.6%, 83%, 86.1% and 98.2%, respectively [57]." Please clarify on what prevalence (a priori probability) the predictive values were based.
    a. We thank the reviewer for the query. In their study, 145 of 280 patients were confirmed to have intestinal BD. Therefore, the prevalence (a priori probability) was 51.8%. We included a sentence in the manuscript detailing the prevalence upon which these calculations were made.
2. Table 2, serologic markers: What are the numbers in brackets stand for?
    a. The numbers in the brackets stand for prevalence of positive ASCA and IgM AAEA antibody in confirmed cases of CD and Intestinal BD respectively. This has been updated in the table.
3. I would like to see more information on involvement of large intrabdominal vessels (vasculitis).
    a. We thank the reviewer for the recommendation. We created a separate section on visceral cavity vasculitis and included a section about medical and surgical management.

**Reviewer 02998119:**

1. There appears to be scattered mention of surgical and medical management under organ specific involvement subparts. These need to be removed and lumped under the medical and surgical therapy sections.

a. We thank the reviewer for this suggestion. We have removed mention of surgical and medical management under organ specific subparts and lumped them under the medical and surgical therapy sections.

2. There is a table discussing differences between Crohn's and BD. This needs to be discussed better in the body of the text and not just in the table.
a. We thank the reviewer for the suggestion. We included a section discussing the differential diagnosis and elaborated further on the differences between Crohn's and BD.

3. IgM Anti-Alpha Enolase antibody is mentioned in the table differentiating Crohn's and BD. However this needs to be discussed in the body for differentiating from Crohn's along with references.
a. We thank the reviewer for the suggestion and elaborated further on the use of AAEA in differentiating CD from intestinal BD. The authors of one of the studies suggested that AAEA may help differentiate between CD and intestinal BD. However, we found another study that demonstrated that AAEA is positive in 50% of patients with CD. We conclude that serologic testing, including AAEA cannot be reliably used to differentiate between CD and intestinal BD.

4. Epidemiology: 1. Please mention the actual prevalence and/or incidence in Asian and Mediterranean countries.
a. We thank the reviewer for this suggestion and have mentioned actual prevalence rates in specific Asian and Mediterranean countries.

5. Esophagus: 'Serious complications such as erosions, perforations, and stenosis may occur', erosion is not a serious complication.
a. Erosions was removed from the manuscript

6. Esophagus: 5-ASA and mesalazine are the same thing.
a. We thank the reviewer for pointing out our error - corrections have been made.

7. Please ensure that table numbers in the body are accurate and similar to the actual numbers of the tables.
a. The table numbers in the body are now similar to the actual numbers of the tables

8. Prognosis: 'Cumulative rates of surgical interventions are 20% at 1 year, 27-33% at 5 years and 31-46% after diagnosis'. Here 31-46% is at what time period?
a. The time period was 10 years after diagnosis - the omission has been updated in the final copy of the manuscript.

**Reviewer 02530930**

MAJOR

1. Page 5, line 18-19. These are features suggestive of Crohn's disease.
    a. We reviewed the study results and concur that blood in stool, sigmoid involvement and focally enhanced colitis were suggestive of CD. We edited the text to reflect these changes.

2. Page 8, Medical management. First, refer to the conventional medical therapies used for BD, such as CS, IMs, Colchicine, anti-TNF, IFNalpha, Thalidomide, etc. And then mention that not all have been studied in intestinal BD.
    a. Generally speaking, most classes of medications that have been used to treat systemic BD have been used/attempted in the treatment of gastrointestinal BD. We included a prelude to address this and subsequently highlighted the classes of medications with the highest available evidence.

MINOR

1. Page 2, Epidemiology. Add the actual prevalence in Asian and Mediterranean countries.
    a. We thank the reviewer for this suggestion and have mentioned actual prevalence rates in specific Asian and Mediterranean countries.

2. Page 4, line 8. Erosions are not serious complications.
    a. Erosions was removed from the manuscript

3. Page 4, line 15-16. 5-ASA and mesalazine are the same.
    a. We thank the reviewer for pointing out our error - corrections have been made.

4. Page 5, line 28. Table 2, not 3
    a. The table numbers in the body are now similar to the actual numbers of the tables

5. Page 8, line 12. Etanercept. Mention that there are case reports of its use for conventional BD.
    a. We added a section detailing the use of etanercept in conventional BD and the absence of data supporting its use in adults with refractory intestinal BD. We did however find an isolated case report of a 6 year old Japanese girl successfully treated with Etanercept (although she was also treated with tacrolimus, prednisolone and mizoribine).

**Reviewer 02998298**

1. The sentence "Cumulative rates of surgical interventions are 20% at 1 year.." is missing the amount of years after "31-46%". According to the source 89 it should say "10 years after

diagnosis". The citation for respective data should contain the original sources (Jung et al. "Influence of age at diagnosis and sex on clinical course and long-term prognosis of intestinal Behcet's disease." Inflamm Bowel Dis. 2012; Kim et al "Clinical manifestations and course of intestinal Beh?et's disease: an analysis in relation to disease subtypes." Intest Res. 2005).

a. We thank the reviewer for the correction. We also made sure to cite the original sources.

2. What source is the statement "Patients with a chronic, relapsing course tend to do worse than patients with CD and similar intestinal involvement." based on? Jung et al. in "Long-term Clinical Outcomes of Crohn's Disease and Intestinal Behcet's Disease" Inflamm Bowel Dis. 2013 did not see any difference and sources 86,87,88 did not compare the clinical courses of CD and BD.

a. We thank the reviewer for their suggestion. We have revised that segment and included the results from the aforementioned study. The available literature suggests that there is no difference in cumulative probability of disease-specific surgery, disease-specific hospital admission or postoperative prognosis (ie. clinical recurrence or reoperation rates).

**Reviewer 02984706**

1. As there are separate sections for medical and surgical management, it should be discussed in those sections and not in the organ-specific descriptions.

a. We thank the reviewer for this suggestion. We have removed mention of surgical and medical management under organ specific subparts and lumped them under the medical and surgical therapy sections.

2. Differentiation between Crohn's, ITB, and BD should be better organized in the text.

a. We thank the reviewer for the suggestion and concur. A separate section has been created for differential diagnosis which discusses ITB, BD and CD.

3. As the paradigm for IBD treatment has become endoscopic / histologic remission, discussion for this paradigm in BD should be addressed.

a. We thank the reviewer for the comment. Although we are well aware that the paradigm for IBD treatment has become endoscopic/histologic remission, there is insufficient literature currently to make the same recommendation for intestinal BD. We added a sentence in the conclusion to address this point.

4. Much of the highly relevant data from the tables should be incorporated in the text. For example, discussion of the IgM Anti-Alpha Enolase antibody should be in the body of the text and warrants further elaboration.

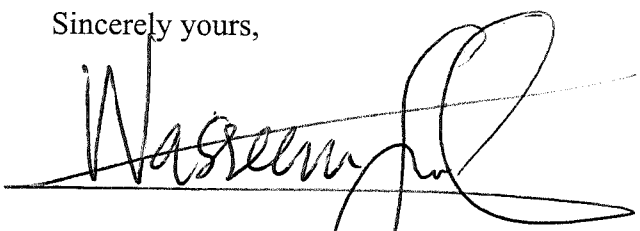
a. We thank the reviewer for the suggestion and elaborated further on the use of AAEA. The authors of one of the studies suggested that AAEA may help differentiate between CD and intestinal BD. However, we found another study that demonstrated that AAEA is positive in 50% of patients with CD.

5. Further descriptions of strictures, fistulae, and abscesses should be in the text. It is only in the management section and in the tables.

a. We thank the reviewer for the suggestion and have elaborated further on complications of intestinal BD including fistulas, strictures, abscesses and perforations. We found a study that stated that strictures, fistulas and abscesses were less common in intestinal BD. It appears that intestinal perforation is more common in intestinal BD and typically occurs in the terminal ileum, ileocecal region or ascending colon.

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

Sincerely yours,



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January 20, 2015
Answer to Journal editor Chief:
The references have been checked, newer reference has been added. Thank you!