

April 3, 2014

Dear Editor,

Please find enclosed the edited manuscript in word format (file name : wjg-naser-revised.docx)

Title: Mycobacterium avium subspecies paratuberculosis (MAP) causes Crohn's disease in some IBD patients

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 9829

The manuscript has been improved according to the suggestions of reviewers

- 1) Format has been updated
- 2) Revisions has been made according to the suggestions of the reviewer
 - 1) Reviewer No. 914743
 - 2) Reviewer No. 31299
 - 3) Reviewer No. 44980
 - 4) Reviewer No. 680628
 - 5) Reviewer No. 504462
- 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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REVIEWER 1:

The information contained in Naser's article is clearly presented and allows the reader to measure the pros and cons of the controversial issue as to whether MAP has a role in the etiopathogenesis of Crohn's Disease. This article should be published with only minor changes. It should be edited for minor grammatical changes. I have listed the lines that should be looked at:

Line 30 – add commas >>> **corrected.**

Line 34 – add 's' to the word human >>> **corrected**

Line 62 – add 'of' in front of the word 'CD' >>> **corrected**

Line 93 – add 'number of' >>> **corrected**

Line 107 – add 'a' in front of the word 'patchy' >>> **corrected**

Lines 120 -122 – clarify >>> **corrected**

Line 137 – twentys – not tweens >>> **corrected**

Line 139 – to or by >>> **corrected**

Lines 142 – 160: This whole section can be reduced to a few sentences. The audience is well aware of how CD is diagnosed. >>> **reduced**

Line 162 – 'are' is needed >>> **corrected**

Lines 185-186 – revise? >>> **revised**

Line 234 – 'a few' or special' >>> **corrected**

Line 241 – reword >>> **reworded**

Lines 263 – 265 – not clear >>> **corrected**

Lines 338-339 – reword >>> **reworded**

Line 352 – humans >>> **corrected**

Line 361 – What is truly >>> **corrected**

Line 404 – an extra 'the' >>> **corrected**

Line 408 – antibiotic, not antibiotics >>> **corrected**

Line 410 – prior to submission >>> **corrected**

Lines 444-452 – needs editing for missing words >>> **corrected**

Line 352 –Clarify what the definition of a positive test in the scheme submitted. Does 1 of the 3, 2 of the 3, or all 3 (MGIT culture and then DNA extraction, direct bacterial DNA extraction and MAP antibodies). >>> **An additional figure will be added to the scheme for further clarification as to what is a positive and negative result.**

REVIEWER 2:

This review article shows the relation between Crohn's disease (CD) and MAP. It is very interesting, however, I have some comments described as follows.

1. INTRODUCTION section includes the history of CD, however, it is long. Authors should omit the history and shorten it. >>> ***I respectfully disagree with this reviewer because a detailed history provides a holistic perspective of CD and shows that it has been part of humanity for a long time and gives the reader a better understanding of the disease.***
2. In WHO IS AFFECTED BY CD? section: Authors mention prevalence of CD. If infection of MAP is related to prevalence of CD, please mention the relation. If it is not related, authors had better omit this paragraph. >>> ***This was clarified.***
3. Authors had better omit DIAGNOSIS OF CD section. >>> ***was reduced to a few sentences***
4. Please correct the form of references. >>> **corrected**

REVIEWER 3:

A casual association between Mycobacterium avium paratuberculosis (MAP) and Crohn's disease (CD) has never been proven or excluded to date. This review showed that the link between MAP and CD varied by

different studies and methods used. The major shortage in this manuscript is lack of evidence to support the casual role of MAP in CD. ***We respectfully disagree with this comment since the manuscript describes in detail published data from 60 plus articles.*** At its present for, the authors did not provided evidence to confirm that “MAP causes CD.” >>> ***Supporting evidence for a strong correlation between MAP and CD was discussed.*** The authors should address these points and extensively revise the manuscript. **done**

REVIEWER 4:

Dear Sir, the historical review, as well as the comprehensive data of Mycobacterium avium subspecies paratuberculosis (MAP) is impressive and worth reading. However, even though there seems to be a relation between CD and MAP, you seem to approach it solely from an epidemiological standpoint. ***We respectfully disagree with this comment.*** Currently, your detection PCR technique looking for the IS900 seems very promising! However you do not show whether there are any animal models that supports this pathogenic relationship, or whether there have been any successful therapeutic approaches to eradicate MAP. >>> ***We respectfully disagree with this comment about the need for the inclusion of animal models as well as therapeutic approaches that eradicated MAP – MAP in Johne’s Disease animals is present in a bacillary form which is quite different from the cell-wall deficient form seen in humans. With respect to therapeutic approach – this was not the focus of this review.*** So for the moment, the only real association between both entities is epidemiological, and unlike what your title says, you can only conclude there is a correlation, but you cannot make any conclusions about causality. Hope to hear from you soon. >>> ***The title will be revised.***