

July 18, 2014

Dear Editor,

Thank you for considering our manuscript 11655 for publication on the World Journal of Gastroenterology. We modified our manuscript according to the Referees' comments.

We like to take this opportunity to thank the reviewers and the Editorial Board for dedicating their time to review our manuscript and for raising some important and appropriate comments. Please find below a point-by-point response to the Reviewers' comments.

#### Reviewer 1

The MS 11655 provides critical review of the literature on the relationship between Hp atopy and allergic diseases. The conclusion supports the well-entrenched concept that childhood infections (not only wit Hp) may be necessary to induce the proper maturation of the immune system. There are several points that require your additional attention;

**Q 1:** The author quotation by name should be followed in each case by the number, and this is not the case here.

**A:** As correctly suggested by the reviewer, in the revised manuscript the author quotation by name has been followed in each case by the number.

**Q 2:** The country of the university hospital on p.18 should be listed, otherwise to most readers this is a big unknown.

**A:** This has been done in the revised manuscript.

**Q 3:** The Hp signaling through TLR4 requires some additional elaboration and referencing (see Inflammopharmacology 21(2013)67-78 and vol.22(2014) 169-177).

**A:** This has been done in the revised manuscript (page 4, lines 13-21, ref #13); please note that as suggested by reviewer #3, we modified our manuscript as a systematic review and meta-analysis according to the PRISMA guidelines. This the reason why some parts of the original manuscript have been deleted in the revised manuscript including the paragraph describing the immune response to HP; therefore we could have added only few sentences on this topic.

#### Reviewer 2

This is a very well written systematic review and meta-analysis paper concerning the relationship between Helicobacter pylori infection and atopic diseases. The authors give the extensive overview about the present outlook of the hygiene hypothesis, about the possible inverse association of H. pylori infection with allergic diseases. The authors present detailed description of host immune response by H. pylori infection. A very accurate analysis of the case-control as well as cross-sectional studies give a good overview about the evidences pro and contra the relationship between allergy and H. pylori infection which prevalence show the tendency to reduction with increasing prevalence of atopic diseases in developed and

industrialized countries. The authors have reviewed and analyzed an ample amount of literature (59 references). The review is supplied with 2 Tables and 6 figures. However, the following points need to be considered:

**Q 1:** In the list of References are absent two references cited on the p. 5: no 19 and no 20.

**A:** The reviewer is correct; however, as suggested by reviewer #3, we modified our manuscript as a systematic review and meta-analysis according to the PRISMA guidelines. This is the reason why some parts have been deleted in the revised manuscript including references cited on the p. 5: no 19 and no 20.

**Q 2:** The abbreviation of Hepatitis A virus (HAV) appears at the first time on the p.14, but is used already on p. 11.

**A:** The abbreviation of Hepatitis A virus (HAV) has been reported on the first time of citation in the revised manuscript (page 10, lines 6).

**Q 3:** In all presented Figures (Fig. 1 to Fig. 6) the authors use the abbreviation TB+ and TB-. For me it is not clear what does it mean? Should it be H. pylori + and H. pylori -?

**A:** We thank the reviewer for pointing this out. The description of the tables has been improved in the revised manuscript.

### Reviewer 3

The study titled 'Helicobacter pylori infection and atopic diseases: is there a relationship? A systematic review and meta-analysis' from Lionetti E and co. is an interesting review about the relationship between Hp infection and atopy/atopic diseases. A meta-analysis of data is also showed in the text. My comments are listed below.

**Q 1:** On page 5, line 19 it is stated that 'phylogeographic studies assume that the ancestors of the bacteria have begun to populate the human stomach 4 million years ago'(ref. #16). In the paper of Bodo Linz et al. I have not find this information. Moreover, references jump from 18 to 21 making difficult to follow the citations.

**A:** As suggested by the reviewer in the following comment, we modified our manuscript as a systematic review and meta-analysis according to the PRISMA guidelines. This is the reason why some parts have been deleted in the revised manuscript including the statement "phylogeographic studies assume that the ancestors of the bacteria have begun to populate the human stomach 4 million years ago" and references 18-21.

**Q 2:** Six meta-analyses were conducted on the cited literature that suggests the inverse relationship between Hp infection and atopic diseases. The description of the tables is not straightforward. For example, it is not clear that cases are the subjects with atopy/allergic diseases and that TB+ are those with Hp infection. I am really surprised that the meta-analyses were performed without any indication about the method or the software used. To perform a meta-analysis there are many points that must be monitored and described in detail. For example, how were the criteria used for considering studies for this review? How was the search strategy for identification of studies? What about data extraction? Study quality? How

was the statistical method used? How was measured the heterogeneity? Without these indications everyone may construct a meta-analysis without any scientific value.

**A:** We thank the reviewer for this important comment that allows us to better report our data. As suggested, we modified our manuscript as a systematic review and meta-analysis according to the PRISMA guidelines including how were the criteria used for considering studies for this review, how was the search strategy for identification of studies, data extraction, study quality, how was the statistical method used, how was measured the heterogeneity (page 5-7). Moreover, the description of the tables has been improved in the revised manuscript. Please note that this is the first meta-analysis reporting the association between “H. pylori and atopy or allergic diseases”, and that previous studies focused on one specific allergic disease (i.e. asthma).

Once again we want to thank the reviewers and the Editorial board for their thoughtful comments and suggestions that assisted us in improving the quality of our manuscript that we now hope is suitable for publication in the World Journal of Gastroenterology.

Sincerely,

Elena Lionetti