

ANSWERING REVIEWERS

Name of journal: World Journal of Gastroenterology

Manuscript NO: 66092

Title: Helicobacter pylori infection: how does age influence the inflammatory pattern?

Reviewer's code: 05844467

Position: Anonymous

Academic degree: Anonymous

Professional title: Anonymous

Reviewer's Country/Territory: Anonymous

Dear reviewer,

We are glad for the great evaluation and for your comments about our manuscript. No adjustments were requested, but some changes were made to improve the quality of the text.

Best regards,

Fabício Freire de Melo

Professor, PhD

Reviewer's code: 00073423

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Full Professor

Reviewer's Country/Territory: Lithuania

Dear reviewer,

Thank you for your evaluation of our manuscript. Your suggestions were followed and made **green** in the file:

- 1- The title is more limited to what was covered in our text; Helicobacter pylori infection: how does it influence the inflammatory pattern?
- 2- Data linked to the population of Eastern/Central Europe were entered.
- 3- An objective excerpt has been added to the conclusion so that the main theme is addressed more clearly.

Best regards,

Fabrcio Freire de Melo

Professor, PhD

Reviewer's code: 05072111

Position: Peer Reviewer

Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Poland

Dear reviewer,

We greatly appreciate your comments. All suggestions were followed and are listed below. In the file, they are marked in **blue**.

1. In the sentence "During childhood, it is possible to observe the predominant regulatory response, evidenced by several studies when they found high concentrations of key cytokines for the maintenance of this type of response such as TGF- β 1 and IL-10..."; we add the type of response that is observed so that it is clearer to the reader of the Abstract.
2. In the excerpt "... the high levels of TGF- β 1 and IL-17 found in that context, ..."; we changed "in that context" to "in this infectious scenario", so that it is easily observed that such alterations are noticed in a context of infection by *Helicobacter pylori*.
3. In the sentence "This can be explained based on the gastric inflammatory pattern against the disease, which changes as long as the infected individual gets older; favoring, initially, the persistence of the infection and then the gastric damage.". We replace the word "initially" with "during childhood" and, later after "then", insert "in adulthood"; making the exposure of events during infection more objective.
4. In the excerpt "*Helicobacter pylori* is a microaerophilic, gram-negative, bacillus-shaped, mobile bacterium of great clinical importance and capable of colonizing an extremely hostile environment, due to its low pH, the stomach"; we replace "bacillus-shaped" with "rod-shaped" and the end of the sentence as requested.
5. In the introduction, a part of the pointed paragraph was moved to "Prevalence" and the other remained in "Introduction" to bring only an overview of the approached axis.
6. In the sentence "H. *pylori* are part of Group I of carcinogens ..."; we replaced "are part of" with "belongs to a" as requested.
7. In the sentence "This predominantly regulatory pattern makes the gastric mucosa of children more easily colonized with H. *pylori*, but with less

- inflammation, when compared to what occurs in the mucosa of infected adults.”; the word “easily” was replaced by “easy to be” as required.
8. The sentence “Interestingly, the pattern of immune response against the pathogen observed in children is not able to eliminate the infection, and the bacterium persists in the gastric environment if left untreated.”; has been replaced as suggested.
 9. In the excerpt “a lower concentration of TGF- β 1, which, despite participating in the Treg and Th17 responses”; “Th17” has been removed from the sentence.
 10. We bring a brief sentence with possible explanations for the observed difference in the prevalence between men and women presented in the excerpt “A higher prevalence of disease is usually observed among male subjects than in females”, as suggested.
 11. In the sentence “The analysis of the expression of cytokines in the gastric environment evidenced that IL-10 and TGF- β 1 are expressed in higher levels in the former group than in the latter”; we dropped the "Than in the latter" as requested.
 12. “In” has been removed from the phrase “Taken together, the aforementioned results show that act, indeed, influences in the immune response”, as requested.
 13. “T regulatory cell” has been replaced with “Treg cells” in the phrase “enhanced levels of Foxp3 and Latency Associated Peptide by T regulatory cell”, as requested.
 14. The sentence “Therefore, we hope that, along with the advances in the clinical analysis of genetic and epigenetic backgrounds, the future approaches of H. pylori infections and the decisions on the necessity of bacterial eradication were carried out in a more individualized manner, instead of the generalized, but necessary, treatments preconized by current guidelines." it was split to not be so extensive.

15. In the sentence “In a study that added neutralizing antibodies to IL-12 in gastric biopsy cultures, he observed”, the word “he” was replaced by “authors” as requested.
16. In the sentence “As aforementioned, gastric environment colonization by H. pylori leads to a polarization of Th1/Th17 responses whereas Treg cells are responsible for regulating the inflammatory process”; “of” was replaced by “toward” and “regulating the inflammatory process” was replaced by “an induction of anti-inflammatory responses”, as requested.
17. In the sentence “Along with the cytokine pattern in children previously discussed in this paper ...”; the word “children” was replaced by “pediatric patients”.
18. We made a new legend, assigning different colors to the arrows corresponding to adults (orange) and children (purple).

Best regards,

Fabício Freire de Melo

Professor, PhD

Reviewer’s code: 00058453

Position: Editor-in-Chief

Academic degree: FRCA

Professional title: Professor

Reviewer’s Country/Territory: United States

Dear reviewer,

Thank you very much for your comments. The changes suggested by the reviewers were carried out and the requested documents were also provided.

Best regards,

Fabrício Freire de Melo

Professor, PhD

Reviewer's code: 05844467

Position: Science Editor

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Japan

Dear reviewer,

We really appreciate your comments. The Conflict of Interest Disclosure Forms and the Copyright License Agreement have been provided and will be attached. A PowerPoint file with the figures was also provided, as requested.

Best regards,

Fabrício Freire de Melo

Professor, PhD