

Editorial Office,

World Journal of Gastroenterology

March 25, 2023

Dear Editor,

I, along with my coauthors, would like to re-submit the attached manuscript titled "**Safety and effectiveness of vonoprazan-based rescue therapy for *Helicobacter pylori* infection**" to the *World Journal of Gastroenterology*. The manuscript ID is 84138.

The manuscript has been carefully rechecked, and appropriate changes have been made in accordance with the reviewers' suggestions. The responses to the comments have been prepared and are attached herewith.

We thank you and the reviewers for your thoughtful suggestions and insights, which have enriched the manuscript and produced a more balanced and better account of the research. We hope that the revised manuscript is now suitable for publication in your journal.

As before, this manuscript is not under consideration for publication by any other journal or medium, and all authors have agreed to its publication.

I look forward to your reply.

Sincerely,

Xiaoyong Wang

Department of Gastroenterology, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, 29 Xinglong Lane, Tianning District, Changzhou 213000, Jiangsu Province, China

Email address: [wxy20009@126.com](mailto:wxy20009@126.com)

Reviewer #1:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:**

The main purpose of the original article entitled "Safety and effectiveness of vonoprazan-based rescue therapy for *Helicobacter pylori* infection" was to determine the effectiveness of dual therapy (amoxicillin + vonoprazan) combined with the probiotic strain of *S. boulardii*. In general, I believe that the results obtained are presented in a clear way and are of great importance to clinicians (especially in the context of increasing resistance to antibiotics in *H. pylori*). Nevertheless, there are some issues that require further clarification and/or correction.

The list of suggested amendments is presented below:

Major: - In the subsection "H. pylori culture and antimicrobial susceptibility testing", there is information about bacterial storage. It was mentioned that the bacteria were stored in BHI but nothing was said about the presence of glycerol (whereas 20% or 30% is added as standard). Has this substance been added?

**Answer:** The brain-heart infusion broth which we used to store the bacteria in our study contained 20% glycerol.

- Where did the MIC values for antibiotic resistance classification of *H. pylori* strains come from? According to commonly used EUCAST recommendations, resistance to antibiotics is: amoxicillin > 0.125 mg/L, tetracycline > 1 mg/L, levofloxacin > 1 mg/L, clarithromycin > 0.5 mg/L and metronidazole > 8 mg/L. Taking these modifications into account will

certainly have a significant impact on the interpretation of the obtained results.

**Answer:** The MIC values for *H. pylori* resistance classification were obtained from the fourth edition of the National Guide to Clinical Laboratory Procedures, China.

- I believe that the number of people with anxiety (only 5) is far too small to draw conclusions about the effectiveness or ineffectiveness of antibiotic therapy.

**Answer:** Due to the small number of patients with anxiety in our study, we only preliminarily found an association between anxiety and eradication failure, suggesting that this regimen may need to be adjusted for patients with anxiety. We intend to further investigate this in our future studies.

- A big loss for the quality of the manuscript is the lack of a control group in which a supplementation with *S. boulardii* was not used. On this basis, better conclusions could be drawn regarding the need or lack of need for probiotic supplementation during the amoxicillin + vonoprazan therapy.

**Answer:** Thank you for your valuable suggestions. We will conduct further research that includes a group treated with amoxicillin + vonoprazan and a group treated with amoxicillin + vonoprazan + *S. boulardii*. We agree that this study design will allow us to draw better conclusions regarding the need or the lack of a need for probiotic supplementation.

Minor: - Problem with page numbering, e.g. 4/27 and 8/27 appear twice, and some pages are missing

**Answer:** The page numbering has been corrected.

- Subsection "H. pylori culture and antimicrobial susceptibility testing" should be numbered as 2.4

**Answer:** Thank you for pointing this out. We have made the corresponding modification in the revised manuscript.

Reviewer #2:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:**

My comments to the Authors: This study has shown that the 14-day VAS regimen is a safe and effective rescue therapy for H. pylori. This regimen achieved an eradication rate of > 90%, with good patient compliance, especially in patients without anxiety. The results of this study suggest that the 14-day VAS regimen can be recommended as a treatment for H. pylori infections.

## MATERIALS AND METHODS

1. I wonder if the authors also evaluated medication compliance using a questionnaire administered within three days of treatment. Since two weeks is long, I thought it would be underestimated unless the medication diary was evaluated daily.

**Answer:** In our study, all patients were asked to keep the remaining drugs after treatment and fill out the relevant questions in the questionnaire within 3 days after treatment. Adverse events and patient compliance were assessed using the questionnaires and the patients' medication diaries. Patients who felt unwell during the treatment or forgot to take their medication were advised to contact the investigators immediately.

2. This study was a pilot study. However, the authors should present the hypotheses and target number of cases in the Methods section.

**Answer:** In section 2.5 (Sample-size calculation and statistical analysis), we assumed a 93% eradication rate with vonoprazan-based rescue therapy. The 95% confidence interval was 86.6%–99.4%, and the sample size was 64

patients. Assuming a 5% follow-up loss, at least 68 patients would be required.

## DISCUSSION

1. I am interested in the finding that patients with anxiety disorders are a risk factor for eradication failure. I wondered if they had some drugs for anxiety disorders that could affect the eradication of drug metabolism. In addition, they tend to have more medication. Can polypharmacy affect drug compliance?

**Answer:** Thank you for your question. The patients with anxiety continued to take flupentixol/melitracen (Deanxit) during rescue treatment. Currently, Deanxit has not been found to affect the metabolism of the drugs/supplement in our regimen (vonoprazan, amoxicillin, or *Saccharomyces boulardii*). In addition, the number of patients with anxiety disorder in this study was small, and relevant conclusions and potential mechanisms need to be further explored in future studies. Nonetheless, all the patients with anxiety in this study had taken >80% of all the medications prescribed, and their compliance was good.

Reviewer #3:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:**

- Abstract was too long, Please provide shorter abstract while focusing on results as well as conclusion.

**Answer:** Thank you for pointing this out. We have provided a shorter abstract focusing on the results and conclusions.

- Core tip should be covered the present findings.

**Answer:** Thank you for pointing this out. We have made the corresponding modifications in the revised manuscript.

- Please highlight the rationality of this work. the authors should discuss about novelty of this work than previous published relevant papers.

**Answer:** Thank you for your valuable suggestions. We have highlighted the rationale of this work in the Introduction and Discussion sections. We have also discussed the novelty of this work in the Discussion section. To our knowledge, this study is the first to determine the safety and efficacy of 14-day VA-dual plus *S. boulardii* supplementation as a rescue therapy for *H. pylori* infection. The 14-day VAS regimen used in this study offers certain advantages over previous rescue therapies.

- The inclusion and exclusion criteria and the section of Study design and outcomes should be specified with more details.

**Answer:** We have provided more details on these parts in the revised manuscript.

- Figure quality was low.

**Answer:** Thank you for pointing this out. We have provided new figures.

- Discuss regarding study limitation.

**Answer:** The limitations of the study have been further discussed in the revised manuscript.

- Conclusio was missed. the authors should stated objective conclusion with further perspectives.

**Answer:** Thank you for pointing this out. We have made the corresponding modifications in the revised manuscript.



(1) Science editor:

The manuscript has been peer-reviewed, and it's ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search

results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

**Answer:** Thank you for your helpful advice. We have made the corresponding modifications in the revised manuscript.