

Dear Editor,

Thank you very much for your letter and for the reviewers' comments concerning our manuscript entitled "The beneficial effect of probiotics supplements in reflux esophagitis treated with esomeprazole: a randomized controlled trial" (Manuscript NO.: 45680). We have studied the comments carefully and have revised our manuscript which we hope meet with their approval.

All changes are highlighted in yellow in the revised version of the manuscript. Point-by-point replies are listed below. We have included the page numbers in the revised manuscript to help the reviewers identify our changes.

We hope that this revised version is acceptable for publication in Medicine. We are looking forward to hearing from you soon.

Best Regards,

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**Manuscript NO.: 45680**

**Reviewer's code: 02992691**

***SPECIFIC COMMENTS TO AUTHORS***

*The issue of this study is interesting and remarkable. This study presents that intestinal bacterial overgrowth strongly affects the recurrence of reflux esophagitis. Esomeprazole could improve the reflux symptoms successfully. Moreover, the probiotics which added to PPIs in reflux esophagitis treatment can reduce bacterial growth and inflammation increasing motility in gastrointestinal system. Probiotics conversely affect on intestinal bacterial overgrowth and reduce the rate of recurrence in reflux esophagitis. There are some questions needed reply; Firstly, basic RDQ scores and LHBT results should be given to comparing findings. It is not clear why the follow-up period was completed at 48 weeks. How do probiotics using only 8 weeks stay effectively for a long period of time? Why do the authors talk about 5% and 25% percentiles? This kind of details giving information make your study confusing. Please correct them. On the other hand, this study needs some corrections: In RESULTS; Statistical methods should not be mentioned in results. Please, write statistical analysis sections below sentences: (1) The t-test was used for comparison of age, body mass index (BMI), and waist circumference between the probiotics and placebo groups. The Chi-squared test was used for comparison of sex, RE grade,..... (2) Whereas the Kaplan-Meier method offered a descriptive view of the time-to-relapse curve, Cox regression was.... There are some spelling mistakes (e.g. METERIALS; this results). Please check carefully and correct them.*

## **Response**

We thank the reviewer for the valuable comments.

1. The basic RDQ scores and LHBT results have been shown in the article on page 11.
2. The follow-up period was 12 weeks. The probiotics were used to regulate gut microbiota and prevent SIBO. Studies showed that the relapse rate of SIBO was 12.6% at 3 months after successful antibiotic treatment. We assumed the gut microbiota status might remain stable for 12 weeks<sup>11</sup>. Meanwhile, we would like to observe the lasting efficacy of live combined *Bacillus subtilis* and *Enterococcus faecium* enteric-coated capsules (Hanmi Pharmaceutical Co., Ltd) after the withdrawal.
3. Statistical methods have been corrected on page 10.
4. Many thanks for identifying the spelling mistakes. They have been amended.

**Reviewer's code:** 02992693

### ***SPECIFIC COMMENTS TO AUTHORS***

*In this study, a combination of proton pump inhibitors and probiotics have been used to treat GERD. The Authors have assumed that the addition of probiotics may decrease the recurrence of GERD symptoms. This is a relatively novel hypothesis. The therapeutic effects of RE patients treated with a combination of esomeprazole and probiotics were evaluated. The samples are big, and the methods are described in detail. The findings are interesting, and the results are well discussed. The manuscript is required a minor language revision, and an editing of the format is also required.*

## **Response**

We thank the reviewer very much for the encouraging comments. The editing of format and language polishing has been done according to the guidelines for authors.

**Reviewer's code:** 02943706

### ***SPECIFIC COMMENTS TO AUTHORS***

*Very interesting study about the therapeutic effects of RE patients treated with a combination of esomeprazole and probiotics. In my opinion, only some minor language polishing should be revised. Thank you.*

### **Response**

We very much appreciate those comments. The editing of format and language polishing has been done according to the guidelines for authors.

1. Lauritano EC, Gabrielli M, Scarpellini E, et al. Small intestinal bacterial overgrowth recurrence after antibiotic therapy. *Am J Gastroenterol* 2008;103:2031-5.