November 14, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (SCHATZ_ESPS_Manuscript_NO_13899) according to the very helpful suggestions by our assigned reviewers.

(Old Title): Predisposing factors for the development of small intestinal bacterial overgrowth (SIBO) using the D-Xylose Breath Test

New Title (per peer-review): Predisposing factors for a positive D-Xylose Breath Test: a retrospective study of 932 patients.

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13899

ESPS-Columns Scope: Retrospective Study

The manuscript has been improved according to the following suggestions by reviewers:

[1] Format has been updated

A. All formatting recommendations in the right-hand column of the manuscript returned to us by the Editor have been made. All reference citations within the manuscript reflect the proper [x-x] according to WJG publication guidelines. The references at the end of the text have been formatted appropriately to reflect **bold** or *italics* as instructed.

B. Changed the Title:

We agree with reviewer 02458583 who noted the old title was a bit difficult to understand. Have updated this in accordance with their recommendation: "Predisposing factors for a positive D-Xylose Breath Test: a retrospective study of 932 patients."

C. Added '*Key Words*' from Index Medicus to reflect the content of the study

D. Added the '*core tip.*'

E. Added *Conflict of Interest Statement*

F. Added *IRB-approval Statement*

G. Added Data-Sharing Statement

H. Added section at the end of the *Materials and Methods* affirming that the statistical review was performed by a biomedical statistician

I. Added a brief *Acknowledgements* section

J. Added *COMMENTS* section at the end of the manuscript per WJG guidelines.

K. Deleted *Appendix 1* from the main text. Included this as a supplementary document and updated to include substrate manufacturers as recommended by the peer-review.

[2] Content: Revisions have been made according to the thoughtful suggestions of all reviewers. All changes and clarifications requested by the reviewers were graciously accepted and made. Additions to the manuscript are highlighted as instructed by the Editor.

A. In specific response to the comments proposed by reviewer 00058104

1. As authors state, there are several bias due to the retrospective design of the study. These should be clearly described

We appreciate this comment. Study design limitations are explicitly and comprehensively detailed in the conclusion. We have fortified this section to include possible referral bias as the patients evaluated in our study were seen in a tertiary care center which may not adequately represent the general community population. Furthermore, we discussed how the absence of certain associations may have been due to the lack of statistical power for certain factors, specifically the overall lack of males in the study population.

2. There is not enough information provided to support the accuracy of the D-xylose test to predict SIBO, as well as, which are the conditions that adversely affect the sensitivity and / or the specificity of the test

Thank you for this critique. We have added an entire section to the beginning of the methods devoted to addressing the D-xylose test in great detail. Specifically, we have discussed the premise and physiologic basis of this test, substrate used, manufacturer, utility of the test in the evaluation of both SIBO and other GI conditions, test limitations and conditions that can adversely affect the results of the test, and the sensitivity and specificity of the test (citing multiple studies).

3. Data about the manufacturer of the test should be provided

We have included this as part of the above discussion per #2. The manufacturer was (Amersham Biosciences, Arlington Heights, IL)

4. This is not a case-control study

Thank you for highlighting this for us. We have corrected it accordingly in the manuscript to the correct, *cross-sectional* design.

5. A multivariate model analysis would more accurately describe associations than the univariate, sub-categories, and 2 by 2 analyses used

Thank you for this comment which we have reviewed at length with our statistician. We address the above comment in the statistical section of the Methods. Our analyses are large sample but otherwise assumption-free. While future investigations might look at the joint association of markers with XBT, via for example logistic regression, our predefined scope of work was to concentrate on subsets to see how consistent the overall associations were. It is important to note Tables II and III are subset analyses which are useful to readers who may ask what is the odds ratio for patients with condition 'X.' Table III illustrates the odds ratios when the condition is present to when the condition is absent, and the analysis does not take gender into account. By definition, the hysterectomy subset is all female.

6. Table II is not well understood; for example, what is the meaning of a percentage above 100%

We apologize to this reviewer for any confusion. Upon further review, we did not have any percentages above 100%. However, to prevent any further confusion or misinterpretation, we have changed the format of Table II to reflect the following example:

	***n* [+XBT], %**	***n* [-XBT], %**	***P*-value**	**Odds Ratio (95% CI[d])**
GERD[a]	[171], 33% M: 22 F: 149 +PPI=112 -PPI=59	[113], 27% M: 39 F: 74 +PPI=91 -PPI=22	**0.04**	1.35 (1.02-1.80)

- 'n [+/- XBT]' refers to number of patients with the specific condition/medication who had a positive or negative D-Xylose breath test, respectively. '%' is the percentage of those subjects with a positive or negative D-Xylose breath test.

7. It is not clear what was the missing values management

We only had some missing data for BMI - this has been detailed accordingly in the methods section.

8. The word "predictors" in the title/conclusion is not supported by the data and their analysis

Thank you for this comment. We have changed the title accordingly per section #1 above and removed the word 'predictor' entirely from the manuscript.

B. In response to Reviewer 00050232

1. It is necessary to further the discussion to explain the limits of the methodology used

We appreciate this comment from the reviewer. We have addressed this accordingly per above from Reviewer **00058104 (#1).**

C. In response to Reviewer **02905121**

1. Virtually no information is provided on XBT. What is it? Why is it used? What is the reliability and validity? Who is the manufacturer? What is the history of its use and in which conditions?

   This was a very helpful critique of our manuscript and important to be discussed in depth since one of the strengths of this paper was the use of the D-Xylose breath test. This has been emphasized above in the methods section as described in response to reviewer 00058104 (#2).

2. Did XBT outcomes influence diagnosis? If no, why is it performed in the first place? Please detail its role in pt diagnosis

Thank you for this comment.

This is a retrospective study with the current analysis done from an existing XBT database at the University of Florida. As such, any patient with a diagnosis of SIBO based on the positivity of the XBT was subsequently treated for SIBO using one or a combination of several different antibiotics depending on the patient's medical and allergy history. The most commonly used antibiotics were amoxicillin, metronidazole, Bactrim, ciprofloxacin or levofloxacin, tetracycline and rifaximin. If patients tested negative for SIBO, they were not usually treated by the clinician for bacterial overgrowth syndrome and other workup was then performed to evaluate the cause of their diarrhea, malabsorption, weight loss or abdominal pain. Our next paper will evaluate whether subsequent treatment of these patients with the different antibiotics led to the resolution of symptoms and which antibiotic more effectively improved each of their GI symptoms.

We have summarized the above in a newly added topic sentence at the beginning of the discussion.

3. The identification of variables that are associated with XBT+ is mildly interesting, but what do you do with that information (as it relates to overall clinical importance)?

Again, a very astute point here by our reviewer. In our opinion, the clinical importance of discovering variables more commonly associated with SIBO helps the clinician determine which patient population is more vulnerable to development of overgrowth and therefore which population to test for this condition and perhaps which to avoid using PPI therapy, steroids or narcotics unless absolutely necessary. Interestingly, as some others have shown, independent

PPI use was not associated with SIBO based on our analysis of patients who tested positive with the XBT.

The above has been detailed in the 'COMMENTS' section under *Innovations and Breakthroughs.*

D. In response to Reviewer **2458583**

1. As the authors appreciated there is a sampling bias due to referral problems, as usually patients with the symptoms of SIBO are referred for such a test, if they couldn't find any relation between +XBT and some potential predicting factors, it might be due to sampling problems as well as lack of statistical power for including that specific factor as a predictor. This should be discussed in the limitation. For instance, not observing significance in male might be due to small sample size for male gender in this study.

We appreciate and agree with this helpful critique and suggestion as it relates to the limitations of our analyses. We have included the above essentially verbatim as discussed above in response to Reviewer 00058104 (#1).

2. I think the title is difficult to understand. Something like " Predisposing factors for positive D-Xylose Breath Test: a retrospective study of 932 patients" would be much informative here.

We thank the reviewer for this suggestion. We have changed the title of the manuscript to this.

3. This is not a real case-control study. This is a Cross-sectional study

Per similar comment from Reviewer 00058104 (#4), we have enacted this change.

4. What is the sensitivity and specificity of the XBT for SIBO?

Thank you for this comment. We have discussed in great detail both the sensitivity and specificity of the XBT as part of a detailed discussion of the test in the Methods Section. Specifics were discussed above in response to reviewer 00058104 (#2).

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology.*

Sincerely yours,

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