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### **Update on Diagnostic Value of Breath Test in Gastrointestinal and Liver Diseases**

**Subject:** Response to reviewer's comments/suggestions

Dear Editor World Journal of Gastrointestinal Pathophysiology,

Thank you for considering our mini review for publication in your esteemed journal. We have thoroughly appraised the reviewer's suggestions and comments and found them to be very helpful in order to improve the quality of our mini review. Following are the responses we have compiled.

I request you to consider its publication.

Regards,

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Professor, Department of Medicine  
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**Reviewer: 01**  
**Reviewer's code: 00158730**

**Comment: 01**

**Mention of fasting breath hydrogen values should be included in SIBO.**

**Response:**

This has been updated in the manuscript. Following is an extract for reference:

**Protocol:** Subjects are made to undergo an overnight fast. Prerequisites of the test include teeth brushing and use of disinfecting mouth wash and gargles, keeping in mind the fact that oral bacteria can lead to false increment on hydrogen peaks. With the commencement of breath hydrogen sampling basal breath hydrogen is recorded. In circumstance when basal values of breath hydrogen are recorded in excess of 16 parts per million (ppm), substrates are not given and test is abandoned as according to few researchers high basal hydrogen values are diagnostic of SIBO but this finding remains contentious. A diagnosis of SIBO is made on glucose Hydrogen breath test if there is a upsurge in breath hydrogen by 12 ppm above the base line levels. Reportedly sensitivity and specificity of this test are 62% and 83% respectively, when compared with culture from jejunal aspirate [7].

**Comment: 02**

**Several of the references need spell checks (i.e. 57, 61, 65) and are not in the correct journal format (42).**

**Response:**

This has been corrected and updated.

**Reviewer: 02**

**Reviewer's code: 00058696**

**Comment: 01**

**The authors do not provide for us a summary of the literature review that they completed prior to their preparing this review article.**

**Response:**

We selected articles from the PubMed database and Google scholar by using the search terms "breath test", "Helicobacter pylori", "Carbon breath test" and "Urea breath test".



Inclusion criteria were articles published in English, in peer-reviewed journals, between 1966 and 2011.



The articles were further filtered in a team meeting , keeping in view the ideology behind this mini review i.e the current practices, the new advancements and factors limiting the use of breath tests.

**Comment:02**

**Since sorbitol is a non-absorbed sugar, it is not clear why one would use it as a test of carbohydrate metabolism**

**Response:**

This section has been deleted due to the controversial use of this test based on additional literature review conducted.

**Comment: 03**

**The authors do not clearly demonstrate that newer analytical techniques improve sensitivity and specificity as a benefit of having a higher expense**

**Response:**

We have mentioned that newer methodologies/techniques have made the utility of breath testing less complicated and more convenient. Furthermore such developments have led to the introduction of point of care testing systems in this field. As far as increase in diagnostic accuracy is concerned more studies are awaited based on comparison with the traditional gold standard testing.

**Comment: 05**

**The lactose hydrogen breath test depends upon the lactose reaching the terminal ileum or cecum. This must be clear. If the oral-cecal transit time is up to 6 hours as suggested by the authors, patients with very slow small bowel transit are more likely to have small intestinal bacterial overgrowth, a potential cause of a false positive breath test with ingestion of lactose.**

**Response:**

The time interval between ingestion of lactulose and rise in breath hydrogen 20 ppm above basal is a measure of oro-cecal transit time. It is important to note that value of breath hydrogen to diagnose an abnormality is generally higher if fermentation of the substrate occurs in the colon rather than small intestine. For this reason, the cut-off value of hydrogen to estimate oro-cecal transit time and lactose malabsorption is 20 ppm above basal (already mentioned in the article);

in contrast, the cut-off value of hydrogen to diagnose bacterial overgrowth in the small intestine is 12 ppm above basal.

**Comment: 04**

**In the Section "Basic Mechanism of Breath Test", methane must be included.**

**Response:**

As per the suggestion this has been included under the above mentioned heading.

Following is the reference from the manuscript:

Moreover Hydrogen and Carbon breath tests are the most widely known and practice, Methane breath test are also gaining popularity based on the fact that its production is prevalent in 36-50% of healthy subjects in comparison with hydrogen which is more pervasive. Literature review has shown that a noticeable amount of subjects do not produce hydrogen in spite of having SIBO because of the presence of the bacterium Methanobrevibacter smithii which converts hydrogen into methane.

**Comment: 05**

**In Practical application of Carbon Breath Testing: the weaknesses of the H. pylori test including patients' use of H,K-ATPase inhibitors, the need for metabolic activity of the bacteria, and the effect of rapid gastric emptying (which can be induced by H. pylori itself) should be clearly summarized as limitations .**

**Response:**

Under the heading: **Urea Breath Test (UBT) for Helicobacter pylori (H. Pylori) Infection**

We have already mentioned the limitations of UBT. Following section is extracted from the manuscript for reference.

Points to consider: High cost of substrate is a drawback of this test. The use of bismuth-based preparations, drugs including proton pump inhibitors several antibiotics can affects the results of this test [47]. Gargles or mouth wash are routinely advised before the commencement of the test as oral contamination could lead to false positive results.

**Comment: 06**

**This breath test is simply a different type of bioassay. The authors do not describe the lack of enthusiasm among GI physicians to use tests (e.g. breath tests) which provide minimal reimbursement.**

**Response:**

We have mentioned the lack of use of breath test among GI physicians in comparison with invasive diagnostic modalities.

**Reviewer: 03**

**Reviewer's code: 02445772**

**Comment: 01**

**There are many errors in the reference list (I think "copy and based" errors with wrong letters and signs)**

**Response:**

This has been corrected and updated

**Comment: 02**

**Table 1 should be better organized; intersections of Carbon breath tests are not clear**

**Response:**

**Table 1 has been revised.**

**Table 1: List of Breath tests available for Clinical utilization**

<b>INDICATIONS:</b>
<b><u>Tests for Small intestinal bacterial overgrowth</u></b>
a. Glucose hydrogen breath test
b. Lactulose hydrogen breath test
c. 13C-Glycocholate breath test
d. 13C-Xylose breath test
<b><u>Tests for Carbohydrate malabsorption</u></b>
a) Fructose hydrogen breath test

b) Lactose hydrogen breath test

c) Saccharose hydrogen breath test

d) <sup>13</sup>C-Lactose breath test

e) <sup>13</sup>C-Fructose breath test

f) <sup>13</sup>C-Saccharose breath test

g) Methane breath test

**Tests for Helicobacter pylori infection**

a. <sup>13</sup>C-urea breath test

b. <sup>14</sup>C-urea breath test

**Tests for the evaluation of gastric emptying**

a. <sup>13</sup>C-Octanoic acid breath test

**Tests for the evaluation of exocrine pancreatic insufficiency**

a. <sup>13</sup>C-mixed triglycerides breath test

b. <sup>13</sup>C-starch breath test

c. <sup>13</sup>C egg protein breath test

**Tests for the evaluation of hepatocellular function**

a. <sup>13</sup>C Aminopyrine breath test

b. <sup>13</sup>C Methacetin breath test

*Abbreviations: UBT: Urea breath test, <sup>14</sup>C:14 Carbon, <sup>13</sup>C:13 Carbon*

**Comment: 03**

- **Table 3 should be deleted, this is not a classical table (if necessary a description in the text would be preferable)**
- **Figure 3 should be deleted (no information!)**

**Response:**

Table 3 and Figure 3 have been deleted keeping the valuable suggestions in mind.

**Comment: 04**

- **The authors do not clearly demonstrate that newer analytical techniques improve sensitivity and specificity as a benefit of having a higher expense.**

**Response:**

We have not explored the diagnostic accuracy of newer analytical techniques as part of this mini review however we have mentioned that these techniques have made the utilization of breath test easier and even can be introduced at smaller centres.

**Comment: 05**

- **Table 4: Consider "Representative diagnostic accuracy"**

**Response:**

This has been incorporated in the main text.

**Comment: 06**

- **My minor comments include: Abstract line 1: "intermittently" for "hesitantly"? Abstract, final paragraph: "has got" should be "has an". Introduction, line 2: should be "carbon dioxide". Basic Mechanisms of Breath Test, final line: "are enlisted in" could be "are summarized in Table 1". Hydrogen Breath Test, line 4: "becomes part of" should be "is absorbed into". Page 11, Points to consider: "still bounds the wide spread" should read "still limits the widespread". Page 13, paragraph 3: "asses" is assess. Page 19, paragraph 2: "a must need" could be "an important requirement".**

**Response:**

These suggestions have been incorporated in the main text.

**Reviewer: 04**

**Reviewer's code: 00050564**

Well written review but is trying to do too much and should be more selective and deal with those tests in more detail. What the reader will relay seek is guidance on the commonly performed test (for SIBO and food intolerance). What are the best tests, how should they be optimally performed and how should they be analyzed.

**Response:**

Thank you for your suggestion we tried to make the review as precise as possible and emphasize on the tests as you suggested. However for a review of this nature we thought that describing the other tests although briefly is necessary for the completion of the review. We have modified Table 03 in order to emphasize the common tests in use.