Outcome of breath test in adult patients with suspected small intestinal bacterial overgrowth

Version 1

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Abstract

Background
Small intestinal bacterial overgrowth (SIBO) is a syndrome characterised by an increased number of bacteria in the small intestine. The clinical symptoms could be bloating, abdominal pain, nausea, constipation, and diarrhea. Breath test is used to detect SIBO. Breath test measures hydrogen and methane produced by bacteria in the small intestines. The gases diffuse into the blood and the lungs where the gases are expired.

Methods
This study was a retrospective cross sectional study that was carried out at Celiac Disease Center of Columbia University in New York. Analytical records of 311 patients who performed the lactulose breath test or the glucose breath test at Celiac Disease Center of Columbia University between 2014-02-27 and 2015-07-01 were reviewed.

Results
50 % of the patients had a positive lactulose breath test and 37 % had a positive glucose breath test ($p=0,036$). The most commonly perceived symptom in both lactulose and glucose breath test group was bloating. In total 46 % (144/311) had a positive breath test, 22 % (68/311) was positive for methane and 28 % (87/311) was positive for hydrogen ($p=0,014$). Of the patients who had a positive glucose breath test the only statistically significant symptom was gases ($p=0,028$). There was no significant association between gender and a positive breath test result ($p=0,698$). The mean age for a positive breath test was 49 years and the mean age for a negative breath test was 45 ($p=0,104$).

Conclusion
Lactulose breath test seems to be more often positive than the glucose breath test. The study participants showed more positivity for $H_2$ than for $CH_4$. There was no significant association between a positive breath test result and gender or age. The most commonly perceived symptom among all participants was bloating and the only statistically significant symptom for glucose breath test positivity was gases.
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1 Introduction

1.1 Small intestinal bacterial overgrowth
The normal small intestine usually contains few bacterial populations, however, in small intestinal bacterial overgrowth (SIBO) there is an increased number of bacteria in the small intestine. Most researchers define SIBO as the microbiological presence of $10^5$ or more colony forming units (CFU) of bacteria per millilitre of proximal jejunal aspiration [1-5]. The prevalence of SIBO is unknown, but in general, SIBO is underdiagnosed [3,4,6,7]. A reason for that could be difficulties to detect SIBO. Some patients may not have symptoms or having nonspecific symptoms and therefore not seek healthcare [7].

1.2 Symptoms
Patients with SIBO may suffer from abdominal pain, bloating, nausea, constipation, diarrhea and gases [1,8-11], but SIBO may also be asymptomatic [8,11]. Some studies have demonstrated that SIBO could mimic the symptoms of irritable bowel syndrome (IBS) [5,11,12]. SIBO can lead to impaired absorption of proteins, carbohydrates, fats and vitamins [3,5,8,13].

1.3 Etiology
The etiology of SIBO is not completely understood since there are many factors that can affect the bacterial flora in the small intestine. Diverticulosis, small intestinal obstruction, surgical interventions in the gastrointestinal tract, and other anatomical abnormalities can predispose for SIBO [3-5,7,10]. Other factors that are associated with SIBO are motility disorders, diabetes, scleroderma, pancreatic exocrine insufficiency and immunodeficiency syndromes [1,3-5,7,10]. One protective factor is gastric acid that prevents bacterial overgrowth and some studies have confirmed that prolonged use of proton pump inhibitors (PPI) may increase the risk for SIBO [14-17]. However, another study has shown no association between PPI and SIBO [18]. Inflammation in the gastrointestinal tract, such as Crohn’s disease, ulcerative colitis and IBS have all been associated with SIBO [1,12,19-23].

1.4 Endoscopy for diagnosis of SIBO
Most researchers present direct aspiration and culture of the jejunal fluid as the gold standard for diagnosis of SIBO [1,5,8,10,11]. However, endoscopy is an invasive procedure that sometimes involves sedation or general anaesthesia [1,24]. Endoscopy is expensive compared
to other methods [6,11] and there is a risk of contamination from the oropharyngeal flora that may cause a false positive result [5,6,11,25,26]. In contrast, there could be false negative outcomes because the bacterial overgrowth may be patchy [1,10,11,26] and not all bacteria are easy to culture [26].

1.5 Breath test procedure

Another procedure to diagnose SIBO is through breath test, which measures hydrogen and methane [7,10,27]. Several studies declare that breath tests are the most common diagnostic method for SIBO, since they are cheap and non-invasive [7,10,27].

In preparation for the breath test the patients need to have a special diet and some restrictions in their daily life. The patients drink a sugar solution of lactulose (lactulose breath test) or glucose (glucose breath test). The bacterial fermentation of carbohydrates in the intestine produces hydrogen [5,7,27-29] and about 15-30% of the population are colonized with Methanobrevibacter smithii, which converts hydrogen and carbon dioxide to methane [30]. Hydrogen and methane diffuses into the blood and the lungs where the gases are expired [5,27,28].

The patients breathe into a breath analyser every 20 minutes for three hours (10 times) [5,7,27]. If either hydrogen or methane appear in the expired air, it is a signal that bacterial fermentation of carbohydrates has taken place [7,28] and excess of hydrogen or methane is supposed to be caused by SIBO [7,27,28].

If a patient suffers from SIBO the glucose breath test will show a peak of hydrogen or methane excretion. Glucose is normally absorbed in the proximal portion of the small intestine, and if the patient has bacterial overgrowth, there will be bacterial fermentation before glucose is absorbed, showing rise of hydrogen or methane in the breath test. SIBO may be underdiagnosed when using the glucose breath test because it fails to detect bacterial overgrowth in the distal part of the small intestine, the test will be false negative [7,27,28].

A positive lactulose breath test will present two peaks. Under physiological conditions lactulose is metabolized in the proximal colon, and is not absorbed at all in the small intestine. Therefore, a positive lactulose breath test will result in an early hydrogen or methane peak, representing the bacterial fermentation of lactulose in the small intestine, and the late peak is due to exhaled hydrogen or methane as a consequence of colonic bacterial metabolism and is completely normal [7,27,28]. A normal mouth-to-ecum transit time is about 65-85 minutes
so if there is just one late peak, the test is considered to be negative because one late peak only represents the normal physiological process in colon [28]. If the patient has a rapid orocecal transit time SIBO may be overdiagnosed when using lactulose breath test [26,27].

Both glucose breath test and lactulose breath test requires a bacterial flora that can metabolize carbohydrate to hydrogen, otherwise the test can be false negative. The tests can also be false positive if the oral bacterial flora is producing hydrogen [29].

1.6 Treatment of SIBO

The treatment for SIBO first needs to address any predisposing conditions [3,9,31,32], and if there is an underlying anatomical cause it must be surgically corrected [5]. Wide-spectrum antibiotics are used because of the presence of many different bacterial species [3,9,31,32]. Another treatment is relevant symptomatic medication against e.g. diarrhea [5], and nutritional supplementation should be administrated in case of malnutrition [3,31,32].

1.7 Aim of the study

The aim of the study is to investigate the outcome of breath test in adult patients with suspected SIBO. The aim is also to find out which symptoms the referred patients have and if any of the symptoms are more likely to be indicative of SIBO, by using breath test.

2 Material and Methods

2.1 Study design and setting

This study was a retrospective cross sectional study and it was carried out at Celiac Disease Center of Columbia University in New York.

2.2 Study subjects

The study included 311 patients who underwent the breath test for evaluation of SIBO at Columbia University during a period from 2014-02-27 to 2015-07-01. Patients that were included in the study had gastrointestinal symptoms and they had all had a doctor’s appointment where the doctor had a clinical suspicion for SIBO and therefore recommended the breath test. The study participants were from 18 to 91 years old and the mean age was 47 years. Of all the 311 patients 74% (n=230) were women and 26% (n=81) were men.
2.3 Data collection

Analytical records of 311 patients who performed the breath test at Celiac Disease Center of Columbia University between 2014-02-27 and 2015-07-01 were reviewed. The patients were divided into two groups depending on if they performed the lactulose breath test or glucose breath test. Demographic information about gender and age was collected. In the analytical records the patients had reported their symptoms and from the records we also got information about the given substrate (lactulose or glucose) and the outcome of the breath test. The reported symptoms were the patients’ subjective experiences. The weight loss and weight gain were defined as unexplained during the last six months and the rest of the symptoms (nausea, vomiting, diarrhea, constipation, bloating, abdominal pain and gases) were defined as a period of one month.

2.4 Breath test

The breath test was performed at Columbia University. Before the performed breath test the patients had some restrictions in their daily life. They should not have had antibiotic for 30 days before and no probiotic 10 days before the test. The patients needed to fast for 12 hours before they started the breath test and 24 hours prior to test the patient could not eat whole grain products, vegetables, fruits, nuts, seeds, beans, all dairy products except eggs, dessert, or artificial sweeteners. The morning of the test the patients were not allowed to brush their teeth with toothpaste and they should not have any PPI-medication. No smoking and no sleeping or vigorous exercise one hour prior to the test.

Before the breath test began the patients had to rinse their mouth with antiseptic alcohol-free mouthwash to make sure that they had no oral bacteria affecting the breath test. The breath test started by collecting a baseline sample where the hydrogen and methane levels in patient’s breath were examined, then the patients drank a sugar solution of lactulose (lactulose breath test) or glucose (glucose breath test). The patient’s physician decided if either glucose or lactulose should be used. For lactulose breath test the patient had 10 gram of lactulose mixed into 6-8 oz. of water and for the glucose breath test the patient had 1 gram of glucose for each kg of patient’s body weight (max of 100 gram) mixed into 6-8 oz. of water.

The patients breathed into a breath analyser (QuinTron) every 20 minutes for three hours (10 samples total) and the breath samples were examined. During these three hours the patients were not allowed to eat or drink anything and they could not smoke, exercise or sleep.
A positive lactulose breath test was defined as an increase of either hydrogen or methane at least 20 ppm (parts per million) within the first hour (small intestine) followed by a larger peak (colonic) and the glucose breath test was positive if hydrogen or methane was increased at least 12 ppm over the lowest preceding value within the test period.

2.5 Statistical analysis

All the data were analysed using IBM SPSS Statistics 23. Comparisons of breath test results, positivity for hydrogen and methane, glucose vs. lactulose breath test and symptoms were performed using a Pearson Chi-square test or a Fisher’s exact test. T-test (Sig 2-tailed) was used to compare ages. P-values of less then 0,05 were considered statistically significant.

3 Results

3.1 Baseline characteristics

The study participants (n=311) were divided into two groups, 72 % (n=224) performed the lactulose breath test and 28 % (n=87) performed the glucose breath test. Table 1 shows the gender and ages in both groups.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Glucose breath test (n=87)</th>
<th>Lactulose breath test (n=224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>47±17</td>
<td>47±17</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>74/87 (85)</td>
<td>156/224 (70)</td>
</tr>
<tr>
<td>Male</td>
<td>13/87 (15)</td>
<td>68/224 (30)</td>
</tr>
</tbody>
</table>

3.2 Symptoms

The most commonly perceived symptom in both lactulose and glucose breath test group was bloating (80-87 %). Other symptoms that many patients reported were abdominal pain (54-57 %), constipation (51-53 %), gases (47 %) and diarrhea (39-47 %). See figure 1.
Figure 1. Reported symptoms for patients that were performing the glucose breath test or the lactulose breath test.

3.3 Breath test result

3.3.1 Hydrogen and methane

The breath test considered being positive if either hydrogen or methane or both gases were positive. In total 46 % (144/311) had a positive breath test, including 4 % (11/311) that was positive for both CH₄ and H₂, 18 % (57/311) that was positive for CH₄ and 24 % (76/311) that was positive for H₂ (p=0.014). Figure 2 illustrates the positivity for CH₄ and/or H₂.

Figure 2. Positivity for methane and hydrogen, (n=311).
3.3.2 Glucose breath test and lactulose breath test

In total 50 % (112/224) had a positive lactulose breath test and 37 % (32/87) had a positive glucose breath test ($p=0.036$). Of all the patients who did the lactulose breath test (n=224), 31 % (n=70) was positive for H$_2$ and 20 % (n=17) of all the patients who did the glucose breath test (n=87) was positive for H$_2$, ($p=0.039$). Of all the patients who did the lactulose breath test (n=224), 23 % (n=52) was positive for CH$_4$ and 18 % (n=16) of all the patients who did the glucose breath test (n=87) was positive for CH$_4$, ($p=0.356$).

Table 2. Comparison between lactulose and glucose breath test and positivity for H$_2$ and CH$_4$.

<table>
<thead>
<tr>
<th></th>
<th>Lactulose breath tests (n=224)</th>
<th>Glucose breath test (n=87)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$ positivity, n (%)</td>
<td>70/224 (31)</td>
<td>17/87 (20)</td>
<td>0.039</td>
</tr>
<tr>
<td>CH$_4$ positivity, n (%)</td>
<td>52/224 (23)</td>
<td>16/87 (18)</td>
<td>0.356</td>
</tr>
</tbody>
</table>

3.3.3 Symptoms correlated to the breath test results

Table 3 demonstrates the number of patients with positive and negative glucose breath test result correlated to the symptoms. Of the patients who had a positive glucose breath test 63 % experienced gases and of the patients who had a negative glucose breath test 38 % experienced gases ($p=0.028$).

Table 3. Symptoms correlated to the outcome of the glucose breath test.

<table>
<thead>
<tr>
<th></th>
<th>Glucose breath test (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive breath test result (n=32)</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>8/32 (25)</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>0/32 (0)</td>
</tr>
<tr>
<td>Weightloss, n (%)</td>
<td>3/32 (9)</td>
</tr>
<tr>
<td>Weightgain, n (%)</td>
<td>1/32 (3)</td>
</tr>
<tr>
<td>Diarrhea, n (%)</td>
<td>12/32 (38)</td>
</tr>
<tr>
<td>Constipation, n (%)</td>
<td>19/32 (59)</td>
</tr>
<tr>
<td>Bloating, n (%)</td>
<td>28/32 (88)</td>
</tr>
<tr>
<td>Abdominal pain, n (%)</td>
<td>15/32 (47)</td>
</tr>
<tr>
<td>Gases, n (%)</td>
<td>20/32 (63)</td>
</tr>
</tbody>
</table>
Table 4 demonstrates the number of patients with positive and negative lactulose breath test result correlated to the symptoms. Of the patients who had a positive lactulose breath test 5% experienced weightloss and of the patients who had a negative lactulose breath test 13% experienced weightloss ($p=0,039$).

Table 4. Symptoms correlated to the outcome of the lactulose breath test.

<table>
<thead>
<tr>
<th>Lactulose breath test (n=224)</th>
<th>Positive breath test result (n=112)</th>
<th>Negative breath test result (n=112)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, n (%)</td>
<td>38/112 (34)</td>
<td>44/112 (39)</td>
<td>ns</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>7/112 (6)</td>
<td>8/112 (7)</td>
<td>ns</td>
</tr>
<tr>
<td>Weightloss, n (%)</td>
<td>6/112 (5)</td>
<td>15/112 (13)</td>
<td>0,039</td>
</tr>
<tr>
<td>Weightgain, n (%)</td>
<td>7/112 (6)</td>
<td>7/112 (6)</td>
<td>ns</td>
</tr>
<tr>
<td>Diarrhea, n (%)</td>
<td>49/112 (44)</td>
<td>57/112 (51)</td>
<td>ns</td>
</tr>
<tr>
<td>Constipation, n (%)</td>
<td>61/112 (55)</td>
<td>54/112 (48)</td>
<td>ns</td>
</tr>
<tr>
<td>Bloating, n (%)</td>
<td>91/112 (81)</td>
<td>88/112 (79)</td>
<td>ns</td>
</tr>
<tr>
<td>Abdominal pain, n (%)</td>
<td>59/112 (53)</td>
<td>68/112 (61)</td>
<td>ns</td>
</tr>
<tr>
<td>Gases, n (%)</td>
<td>52/112 (46)</td>
<td>54/112 (48)</td>
<td>ns</td>
</tr>
</tbody>
</table>

3.4 Gender and ages

Of the women who did the breath test 46% (105/230) had a positive test and among the men there was 48% (39/81) that had a positive breath test ($p=0,698$).

The mean age for a positive breath test was 49 years and the mean age for a negative breath test was 45 years ($p=0,104$). The mean age for females was 48 years and the mean age for males was 44 years ($p=0,103$). The mean age among men who had a positive test was 47 years compared to those who had a negative test where the mean age was 42 years ($p=0,208$). The mean age among women who had a positive test was 49 years compared to those who had a negative test where the mean age was 47 years ($p=0,238$).

The mean age for the study participants who experienced abdominal pain was lower. Here the mean age was 45 years compared to the study participants that did not had abdominal pain where the mean age was 50 years ($p=0,006$). The mean age for the study participants who experienced nausea was also lower, the mean age was 44 years compared to the study participants that did not had nausea where the mean age was 49 years ($p=0,029$).
4 Discussion

4.1 Glucose breath test and lactulose breath test

At Columbia University the lactulose breath test was more commonly used. Thus, in this study 224 patients performed the lactulose breath test, compared to 87 patients who did the glucose breath test. The reason for this was simply that the physicians at Columbia University were more likely to choose the lactulose breath test for the patients. The decision the physicians made about which sugar solution (glucose or lactulose) the patient should get was not based on any guidelines, except for the physicians’ own experience and opinions of the different methods.

In total, 46 % (144/311) had a positive breath test in this study. The results showed that 50 % of the patients had a positive lactulose breath test and 37 % had a positive glucose breath test ($p=0.036$). This finding is consistent with other studies that also found that glucose breath test may underdiagnose SIBO since the method fails to diagnose SIBO in the distal part of the small intestine [27,28,33]. The lactulose breath test on the other hand may overdiagnose SIBO if the patients have a rapid orocecal transit time [26,27,30]. Since the lactulose breath test seems to be more positive compared to glucose breath test, one suggestion for further studies could be to compare these breath tests more and then create guidelines about which test that should be used for which patients. One improvement in this study would be if all the study participants did both the lactulose and the glucose breath test, then it would have been easier to compare these tests. Furthermore, it would have been interesting to compare the breath tests with direct aspiration and culture of jejunal fluid, which is considered to be the gold standard for diagnosis of SIBO [1,5,8,10,11].

4.2 Hydrogen and methane

In total, it was more common that the patients were positive for $H_2$ (87/311=28 %) than for $CH_4$ (68/311=22 %) ($p=0.014$). This is expected since the bacterial fermentation of glucose or lactulose in the small intestine produces hydrogen [5,7,27-29], however, not everyone produces methane. Approximately 15-30 % of the population are colonized with Methanobrevibacter smithii, which make them capable to convert hydrogen to methane [30].
4.3 Symptoms

As already mentioned, the most commonly perceived symptom in both lactulose and glucose breath test group was bloating. Bloating was also the most common symptom among those patients with a positive breath test result, but it was no significant difference compared to those patients with a negative breath test result.

Table 3 shows that patients with a positive glucose breath test is more likely to experience gases than the patients with a negative test ($p=0.028$). In table 4 there was a significant difference regarding weightloss, as patients with a negative lactulose breath test result more often experienced weightloss than the patients with a positive test ($p=0.039$).

4.4 Gender and ages

According to other studies, it seems more likely that women are suffering from SIBO compared to men [20,34], but this study could not confirm that. In this study, 46% of the women and 48% of the men had a positive breath test, thus there was no significant association between gender and a positive breath test result ($p=0.698$).

Previous studies have demonstrated that SIBO is associated with increasing age, probably because older people have reduced intestinal motility [20,34]. This study do not support this finding since the mean age for a positive breath test was 49 years and the mean age for a negative breath test was 45, thus there was no statistical significant difference concerning age ($p=0.104$).

Regarding the association between ages of the patients and reported symptoms, there was no statistical significant difference except for two symptoms. The mean age for the study participants who experienced abdominal pain ($p=0.006$) and nausea ($p=0.029$) were lower than for those who did not report these two symptoms. It is difficult to explain the reason for this difference apart from the fact that the abdominal pain and nausea the younger patients experienced could have other reasons than SIBO.

4.5 Strengths and limitations of the study

The strength of this study was its sample size and the fact that we had access to the analytical records of all 311 patients. Unfortunately, the analytical record did not include any demographic information about the patients, except for age and gender. In further studies, it would be useful to include more data about the patients’ previous diseases, medical treatment and other factors that may predispose to SIBO.
A limitation of the study was that the patients’ reported symptoms on the analytical records were subjective and not specified. The only thing that was specified was unexplained weightloss or weightgain during the last six months, and other gastrointestinal symptoms during the last month. For further research, we would like to suggest using more standardized questionnaires.

Another suggestion for further studies is to study the outcome of treatment of SIBO, which in this study has not been discussed.

5 Conclusion

In total, 46 % (144/311) of the referred patients had a positive breath test. The most commonly perceived symptom among all participants was bloating. The only statistical significant symptom with glucose breath test positivity was gases ($p=0.028$). The mean age for the study participants who experienced abdominal pain and nausea was lower ($p=0.006$ and $p=0.029$).

This study indicated that the lactulose breath test results more often are positive compare to the glucose breath test. Also, it was more common that the study participants were positive for $H_2$ than for $CH_4$. Furthermore, the results showed that there was no significant association between a positive breath test result and gender or age.

Acknowledgement

The author would like to acknowledge the staff of the Celiac Disease Center at Columbia University. Special thanks to the clinical research coordinators Maria Terese Minaya and Milka Monegro. The author also wishes to express special appreciation to her supervisor Reidun Stenberg who helped and supported her during this study.
References


Dear Editor-in-chief,

Attached is our manuscript titled *Outcome of breath test in adult patients with suspected small intestinal bacterial overgrowth* for consideration for publication in your journal.

Small intestinal bacterial overgrowth (SIBO) is a syndrome characterised by an increased number of bacteria in the small intestine. A patient with SIBO may suffer from different kinds of gastrointestinal problems, e.g. abdominal pain, bloating, nausea, constipation and diarrhea. The prevalence of SIBO is unknown, but in general, SIBO is underdiagnosed. This study was a retrospective cross sectional study of 311 patients that performed the breath test for diagnosis of SIBO at Celiac Disease Center of Columbia University in New York.

This study indicated that the lactulose breath test more often show a positive result than the glucose breath test. Also, it was more common that the study participants were positive for $\text{H}_2$ than for $\text{CH}_4$. Furthermore, the results showed that there was no significant association between a positive breath test result and gender or age. The results showed that the most commonly perceived symptom among all participants was bloating.

This paper is original and none of its content has been published elsewhere.

We look forward to your review.

Yours sincerely,

Johanna Mattsson
Appendix 2: Press release

Bakteriell överväxt på tunntarmen är ett syndrom som kännetecknas av att man har för många bakterier i tunntarmen. Om man lider av denna sjukdom så kan man uppleva symtomen som t.ex. buksmärta, uppblåsthetskänsla i buken, illamående, förstoppning och diarré. Ett sätt att diagnostisera bakteriell överväxt på tunntarmen är med hjälp av ett utandningstest som mäter nivåerna av vätgas och metan i utandningsluften. I en nyligen publicerad studie som utfördes på Celiac Disease Center på Columbia University i New York genomförde 311 personer utandningstestet.

Det finns olika typer av utandningstest och studiedeltagarna i denna studie genomfördes utandningstestet genom att dricka två olika sockerarter, antingen glukos eller laktulos.
Resultaten visade att utandningstestet med laktulos tenderar att vara oftare positivt än glukos. I studien framkom också att det är vanligare att ha höga nivåer av vätgas jämfört med metan. Det vanligaste symtomen som framkom hos studiedeltagarna var uppblåsthetskänsla i buken och det vanligaste symptomet som visade en statistisk säkerställd signifikans med ett positivt glukos-test var gaser från tarmen.
Appendix 3: Ethical considerations

The breath test is non-invasive and there are no known risks with the test. The patients have some restriction in their daily life, for example, 24 hours before the test no meals with fiber, fast for 12 hours before they started the breath test, no smoking and no sleeping for at least 1 hour before the procedure, and not exercise for at least 1 hour before. The patients receive the information about the restrictions from their physician a couple of weeks before the breath test so they are well prepared.

Patients with diabetes were not allowed to do the glucose breath test since glucose can affect the blood glucose levels. They were only allowed to have lactulose breath test after monitoring they controlled their blood glucose levels with blood samples prior and during the breath test.

One important aspect is to respect the confidentiality of the patients’ information. The medical records, or in this study the analytical records, need to be inaccessible to others than the researchers that do the study and therefore they have to be stored in a safe place. For example in this study, the analytical records were kept in a locked cabinet in a locked room. It is important that no sensitive personal data is disseminated. The sensitive personal data must be handled in such a way that none of the study participants can be identified, for example by encoding the study participants.