Intestinal methanogen overgrowth (IMO) is associated with delayed small bowel and colonic transit time (TT) on the wireless motility capsule (WMC)

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Abstract

Background

Methanogens are associated with gut dysmotility in animal models but have not been robustly studied in humans. The WMC assesses regional transit (TT) and pH in the GI tract.

Aims

To study the segmental TT and pH among patients with SIBO or IMO utilizing WMC.

Methods

We conducted a retrospective study of 207 patients who underwent a glucose or lactulose BT and WMC from 2010–2022. Diagnosis of SIBO and IMO were based on the 2017 North American consensus criteria. TT and pH were extracted from WMC recordings. We tested for differences in means of continuous variables and frequencies of categorical variables using two-sample t-tests, Chi-square, and Fisher exact tests. We used R version 3.3.1 (2016-06-21) for all statistical analyses.

Results

A total of 196 patients met criteria, mean age 47.4 years, 155 (79.1%) females. Of the 86 (43.9%) patients with SIBO, 42 (58.3%) had only IMO and 30 (34.9%) met both hydrogen and methane criteria for SIBO. Small bowel TT was longer in patients with IMO compared to negative patients (5h:49min vs 4hr:49min, p = 0.029). Colonic TT was longer in patients with SIBO compared to negative patients (48h:32min vs 39h:25min, p = 0.050). There were no significant differences in segmental pH compared to negative patients.

Conclusions

To our knowledge, this is the largest study of patients who have undergone BT and WMC. SIBO was associated with delayed CTT and IMO with delayed SBTT, but neither with pH. Future investigation is needed to elucidate whether changes in intestinal microbiota affect gut transit.

BACKGROUND

Small intestinal bacterial overgrowth (SIBO) refers to the clinical condition in which changes to the small intestine microbiota, namely an increase in number or change in composition of microorganisms, lead to gastrointestinal (GI) symptoms including bloating, diarrhea and abdominal discomfort[1–5]. There are

many well-established risk factors for SIBO, including anatomic changes, dysmotility and gastric hypochlorhydria[6–10]. The mainstay of treatment focuses on correction of the underlying cause and administration of antibiotics with the goal to restore a healthy and diverse microbiome, and thus alleviating symptoms[2,3,6,11].

More recently, intestinal methanogen overgrowth (IMO), grouped under SIBO, became its own entity as the microbiology, pathophysiology, symptoms, diagnosis and treatment differ from patients with SIBO. IMO refers to overgrowth of methanogens resulting in elevated levels of methane. The association between methanogens, methane and dysmotility has been well established as many prior studies have found that methanogen positivity on a breath test (BT) is positively correlated with constipation and prolonged transit time. This is a key difference between IMO and SIBO in that predominant symptoms for patients with IMO include constipation which is associated with prolonged colonic transit time (CTT) [12–17], both not seen in classic SIBO. Give these differences, treatment of IMO to address underlying causes, as well as methanogens, should differ significantly from SIBO treatment.

The wireless motility capsule (WMC) is an orally-ingested recording device that enables assessment of segmental GI transit through validated patterns in pressure, pH and temperature[18,19]. The WMC has been approved for evaluation of delayed gastric emptying, chronic idiopathic constipation, and diffuse dysmotility, allowing for one to study the association of intestinal dysmotility with SIBO and IMO. Most prior studies have assessed dysmotility based on markers of motility, such as alterations in the migrating motor complex, while few have truly assessed transit time[8–10,20,21].

In addition to dysmotility, gastric hypochlorhydria, frequently due to proton pump inhibitors, has been shown to be associated with SIBO[26–29]. One hypothesized mechanism is the loss of stomach acidity leading to unregulated growth of harmful, microorganisms that usually are unable to survive the caustic environment. This finding is well illustrated in the literature, however the relationship between SIBO or IMO and changes in small intestine or colonic pH has yet to be elucidated. The microbiota and pH have a bidirectional relationship: microbial metabolites affect intestinal pH which in turn influence microbiota diversity and fermentation production[30,31]. Not only is there a significant change in the number of bacteria, but rRNA gene sequencing has been shown that the bacterial composition significantly differs in patients with SIBO than those without SIBO[32,33]. Given this, it is quite plausible that intestinal pH could significantly alter the microbiota leading to SIBO or, alternatively, be affected by dysbiosis and microbial metabolites thus acting as another marker for SIBO.

Our study aims to assess the relationship of SIBO and IMO with data collected from WMC, namely pH and transit times, in different segments throughout the GI tract.

MATERIALS AND METHODS

Patient Population

This was a retrospective study of patients greater than 18 years of age who underwent both a glucose or lactulose BT and WMC at Stanford University Hospital from 2010–2022.

Patients were diagnosed with SIBO or IMO based on the hydrogen and methane criteria from The 2017 North American Consensus[34]. A rise in hydrogen of ≥ 20 p.p.m. from baseline by 90 min during either a glucose or lactulose BT was considered a positive test for hydrogen criteria. A methane level ≥ 10 p.p.m. during any part of the glucose or lactulose BT was considered a positive test for methane criteria.

Using these criteria, patients were divided into two different strata based on diagnostic criteria for hydrogen and methane. Patients in the SIBO group met hydrogen and or methane criteria. Whereas patients in the IMO only group met methane criteria only without hydrogen criteria. Patients who did not meet hydrogen or methane criteria were considered BT negative patients.

Data

We used the Stanford Research Repository (STARR), a clinical database that serves as a repository for all clinical data generated at Stanford for research purposes, to identify eligible participants. Demographic information including date of birth, age, gender, race and ethnicity as well as the dates and results from the BT and WMC were collected from STARR. Primary symptoms, comorbidities and medications were obtained by chart review in the electronic medical record (EMR) at Stanford University Hospital. These three variables were extracted from the clinic note written by the Gastroenterologist at the time that the first diagnostic test, either BT or WMC, was ordered.

WMC recordings were reanalyzed by one author to obtain more granular detail, including low, median and high pH values, mean pressure and motility index. All variables were collected in each of the following GI segments: stomach, antrum, duodenum, small bowel and colon. Gastric emptying time (GET), small bowel transit time (SBTT), colonic transit time (CTT), small and large bowel transit time (SLBTT) and whole gut transit time (WGTT) were also recollected to ensure accuracy of the times reported in the initial WMC results. This study was approved by the Institutional Review Board of Stanford University.

Statistical Analysis

We used R version 3.3.1 (2016-06-21) to perform all statistical analyses. For our two strata, BT positive or BT negative, we computed descriptive statistics of continuous variables and frequencies for categorical variables. We tested for differences across the groups using two-sample t-tests for continuous variables and Chi-square tests for categorical variables and proportions tests for dichotomous categorical variables. For categorical variables with less than five observations in a cell, we used the Fischer exact test.

For co-morbid diagnoses that have been previously identified as possible risk factors or predisposing conditions for SIBO, we created dummy variables that take the value 1 in the presence of the comorbid

condition and 0 otherwise. Proportion tests were used to test for differences in the frequency of these conditions across the two groups.

RESULTS

Clinical Characteristics

The study population consisted of 207 patients who underwent both a WMC study and either a glucose or lactulose BT. 11 patients had a high baseline hydrogen, thus they were excluded as the tests were uninterpretable. This resulted in a total of 196 patients included in our analysis.

Mean age of the study population was 47.4 years and 155 (79.1%) were females. Of the 196 patients, 120 (61.2%) patients underwent a glucose BT, 67 (34.2%) lactulose BT and 9 (4.6%) had both completed. There were 110 (56.1%) patients who had a negative BT, and 86 (43.9%) patients met either hydrogen or methane criteria and thus were considered positive for SIBO. Of those with positive tests, 42 (58.3%) had IMO only, meaning they met methane criteria only. Demographic results based on diagnosis, SIBO or IMO only, can be seen in Tables 1 and 2, respectively. Older age (> 65) and tobacco use were significantly more prevalent among patients with SIBO ($p = 0.013$ and $p = 0.011$, respectively) and IMO ($p = 0.038$ and $p = 0.048$), respectively, when compared to negative patients. The distribution of primary gastrointestinal symptoms was significantly different in patients with IMO compared to negative patients ($p = 0.036$), constipation and bloating being more prevalent.

Table 1
Comparison of baseline demographics and clinical characteristics of patients with SIBO, defined by those meeting H2 criteria and/or CH4 criteria, to those without.

Characteristics	Total (N = 196)	SIBO (N = 86)	BT negative (N = 110)	P value (comparison of SIBO vs BT negative)
Age > 65	38 (19.4%)	24 (27.9%)	14 (12.7%)	0.013*
Female	155 (79.5%)	66 (76.7%)	89 (81.7%)	0.507
Tobacco Use	28 (14.3%)	19 (22.1%)	9 (8.2%)	0.011*
Marijuana Use	23 (11.7%)	11 (12.8%)	12 (10.9%)	0.855
PPI Use	77 (39.3%)	29 (33.7%)	48 (43.6%)	0.207
Prior abdominal surgery	79 (40.3%)	39 (45.3%)	40 (36.4%)	0.260
Comorbidities:	13 (6.6%)	4 (4.7%)	9 (8.2%)	0.395
Gastroparesis	5 (2.6%)	2 (2.3%)	3 (2.7%)	1.000
Pancreatitis	3 (1.5%)	2 (2.3%)	1 (0.9%)	0.583
Crohn’s	8 (4.1%)	6 (7.0%)	2 (1.8%)	0.141
Hiatal Hernia	4 (2.0%)	1 (1.2%)	3 (2.7%)	0.633
Gastritis	12 (6.1%)	6 (7.0%)	6 (5.5%)	0.888
Diabetes	16 (8.2%)	4 (4.7%)	12 (10.9%)	0.125
Ehlers's Danlos	26 (13.3%)	12 (14.0%)	14 (12.7%)	0.969
Hypothyroidism				

BT denotes breath test, PPI proton pump inhibitor. All values are written as the following: number of patients (percent of patients).

Table 2
Comparison of baseline demographics and clinical characteristics of patients with IMO only, defined by those meeting CH4 criteria only, to those without.

Characteristics	Total (N = 196)	IMO only (N = 42)	BT negative (N = 110)	P value (comparison of IMO only vs BT negative)
Age > 65	38 (19.4%)	12 (28.6%)	14 (12.7%)	0.038*
Female	155 (79.5%)	30 (71.4%)	89 (81.7%)	0.248
Tobacco Use	28 (14.3%)	9 (21.4%)	9 (8.2%)	0.048*
Marijuana Use	23 (11.7%)	6 (14.3%)	12 (10.9%)	0.768
PPI Use	77 (39.3%)	15 (35.7%)	48 (43.6%)	0.482
Prior abdominal surgery	79 (40.3%)	18 (42.9%)	40 (36.4%)	0.582
Comorbidities:	13 (6.6%)	0 (0.0%)	9 (8.2%)	0.063
Gastroparesis	5 (2.6%)	2 (4.8%)	3 (2.7%)	0.617
Pancreatitis	3 (1.5%)	0 (0.0%)	1 (0.9%)	1.000
Crohn’s	8 (4.1%)	1 (2.4%)	2 (1.8%)	1.000
Hiatal Hernia	4 (2.0%)	1 (1.4%)	3 (2.7%)	1.000
Gastritis	12 (6.1%)	2 (4.8%)	6 (5.5%)	1.000
Diabetes	16 (8.2%)	2 (4.8%)	12 (10.9%)	0.352
Ehlers's Danlos	26 (13.3%)	4 (9.5%)	14 (12.7%)	0.781
Hypothyroidism				

BT denotes breath test, PPI proton pump inhibitor. All values are written as the following: number of patients (percent of patients).

Transit Time Results

CTT was significantly longer in patients with SIBO relative to negative patients (48h:32min vs 39h:25min, p = 0.050, Fig. 1). There was no statistically significant difference in CTT in patients with IMO only compared to BT negative patients. However, in a subgroup analysis looking at all patients with IMO, thus including patients that met CH4 criteria with or without H2 criteria, CTT was significantly longer compared to BT negative patients (n = 72; 49h:37min vs 39h:25min, p = 0.038). SBTT was significantly longer in patients with IMO only compared to negative patients (5h:49min vs 4hr:49min, p = 0.029,

Fig. 2). There was no statistically significant difference in SBTT in patients with SIBO compared to BT negative patients. GET, SLBTT and WGTT were not significantly different in SIBO or IMO only compared to BT negative patients.

pH Results

In assessing for differences in segmental pH between BT positive and BT negative patients, no significant differences were found in the stomach, antrum, duodenum, small intestine or colon (Fig. 3).

DISCUSSION

Dysmotility, as measured by alterations in markers of motility such as the migrating motor complex, is frequently reported as a risk factor for the development of SIBO and IMO, however, few studies have assessed the direct association with transit time[9,21,35]. The current study found significantly longer SBTT in patients with IMO only compared to those without, as well as significantly longer CTT in the subgroup analysis of any patient with IMO. To our knowledge, this is the first study to find prolonged SBTT and CTT in patients with IMO using the WMC and is one of few studies where SIBO is subdivided into hydrogen and methane criteria. The association between dysmotility and methanogens has been well established. Many previous studies have found a positive correlation between methanogen positivity on a BT, prolonged transit time and symptoms of constipation[12–17]. For example, a recent retrospective study of 78 patients who underwent both a lactulose BT and whole gut transit scintigraphy found a significant delay in SBTT and CTT in patients meeting methane criteria compared to patients meeting hydrogen criteria (mean accumulated tracer 71.5% vs 44.1%, $p < 0.05$; mean geometric center 4.4 vs 3.1, $p < 0.01$, respectively)[17] consistent with our results. The difference in prolonged TT between the IMO only group and the subgroup including all patients meeting CH4 criteria is likely due to small sample size and limited power in the IMO group (42 vs 72, respectively). There is some data in both animals and humans to support methane directly disturbing intestinal motility, possibly by acting as a neurotransmitter[36,37]. Given these findings of both delayed SBTT and CTT in patients with IMO, as well as the proposed mechanisms for dysmotility, additional treatments including prokinetics and pelvic floor therapy aimed at addressing constipation could improve symptoms in patients with IMO compared to or instead of antibiotics alone. WMC could aid in identifying patients who indeed have prolonged TT and thus could respond to additional therapy besides antibiotics. Further, prospective studies are needed to see if patients diagnosed with IMO benefit from non-antibiotic treatments.

The current study found an association between SIBO and prolonged CTT but not SBTT on WMC. Prolonged CTT in SIBO is a new finding but likely reflects the current study population in which 83.7% of patients with SIBO met methane criteria and thus likely had underlying physiology similar to patients with IMO only. The lack of association between SIBO and prolonged SBTT has previously been found. A recent retrospective study of 78 patients found no difference in SBTT between BT positive patients and BT negative patients using whole gut transit scintigraphy (62.1% vs 58.6%, $p = 0.63$)[17]. Similarly, another retrospective study of patients with Parkinson's found no relationship between SBTT and SIBO ($p =$

0.5)[25]. However, these findings differ from the three studies by Roland et al. illustrating prolonged SBTT in patients with SIBO. They conducted two retrospective cohort studies of patients who underwent both a WMC and LBT. SBTT was significantly longer in patients with SIBO than patients without (n = 23; 5.82h vs 3.81h, p = 0.05[22] and n = 34; 6.6h vs 4.2h, p = 0.04[23]). These were followed by a prospective study where 30 patients with suspected SIBO underwent a lactulose BT, small bowel aspirate and WMC study. Again, SBTT was significantly longer in SIBO vs non-SIBO patients (10h vs 1.1h, p = 0.027)[24]. These conflicting results could be due to a few differences between the studies. The current sample size was much larger than prior studies and the sample size included more female and older aged patients. In addition, different cutoffs were used when interpreting BTs. Prior studies considered baseline H2 > 10 p.p.m., baseline CH4 > 7 p.p.m. or an increase of CH4 ≥ 12 p.p.m. by 90 minutes as positive tests. Further, the reasons for ordering the tests and the time interval between completion of both tests was extremely variable. Thus, changes in treatment or disease state after one test could impact the results of the other test. At this time, further, prospective studies are needed to determine if there is truly transit time alterations in patients with SIBO which could affect treatment decisions.

Many studies have assessed the relationship between gastric pH and SIBO, however, few have assessed intestinal pH. In the studies completed by Roland et al. discussed above, results regarding small intestinal pH varied depending on the study. In one of the retrospective studies, mean small bowel pH was not significantly different in patients with SIBO when compared to those without[22]. Whereas there was a significant difference in mean small bowel pH in the prospective study (7.01 for SIBO vs 6.49 non-SIBO, p = 0.002)[24]. The current study revealed no significant differences in intestinal pH between patients with SIBO or IMO than those without. Negative results are unsurprising as pH is driven by several factors including hormones, diet, medications and microbial metabolites, to name a few. Despite the challenges in identifying pathogenic changes in intestinal pH, it remains an essential property of the environment imposing selective pressures on microbial communities, which in turn, influences host physiology and health[38]. Given the paucity of data, future research is needed to determine if there are indeed intestinal pH differences in patients with SIBO so future therapeutics can be developed to restore the normal pH and healthy microbiome.

In the current study, history of tobacco use and age were significantly associated with SIBO and IMO only. Tobacco use is a known risk factor for many GI diseases; however, prior studies have had varied results regarding the association between tobacco and SIBO[39–41]. Some mechanisms by which cigarette smoke influences microbiota composition include direct antimicrobial effects, alteration of immune homeostasis and mucin production, changes in duodenal pH and prolonged GET to name a few[42–45]. A recent prospective study assessed the impact of smoking on mucosa-associated microbiota in patients undergoing upper GI endoscopy. Both current and previous smoking was associated with reduced diversity, however, total density of bacteria present was unchanged[46]. With the positive association between tobacco use and SIBO found in this study, combined with the known effects of cigarettes on the microbiome, it is likely that tobacco use is indeed associated with SIBO and could have more of a causative relationship.

Consistent with prior studies, the current study shows that age > 65 years is associated with SIBO and IMO only. Age has been well described as a risk factor for SIBO, likely through several mechanisms including changes in intestinal motility and acid secretion as well as increasing comorbidities and polypharmacy in older age. Though there are some negative studies, the overwhelming majority do show an association between age and SIBO[6,41,47].

Given the retrospective nature of our study, there are a few limitations. The cohort of patients came from a single, tertiary center with a specific motility clinic and was a relatively small sample size, thus making the results potentially less generalizable to the average patient. However, in comparison to prior studies, the current study included 196 patients which is significantly more than prior sample sizes (n = 30, 34, 64) evaluating transit time and intestinal pH with a WMC in patients with SIBO[22–24]. In addition, our data was collected through chart review, and so we are unable to determine if the patients properly prepared for the BT and WMC based on the recommended standards. For example, prior to the BTs, patients should avoid antibiotics within 4 weeks, promotility agents within 1 week and fermentable foods the day before the test[2,34]. Furthermore, patients had variable timing between WMC and BT studies, and some patients underwent different treatments between the two tests. This could be better regulated in a prospective study. Lastly, there are many imperfections with BTs, although this is currently the most accepted and used diagnostic test for SIBO.

CONCLUSIONS

To our knowledge, this is the largest study of patients who have undergone a BT and WMC study. IMO was associated with both delayed SBTT and CTT, but not changes in pH. SIBO was associated with delayed CTT, but not SBTT or changes in pH. These findings show the importance of differentiating between SIBO and IMO, as these clinical entities have different microbiota changes and effects on the gastrointestinal system, and thus patients could benefit from different treatments. It is unclear whether alterations in intestinal microbiota affect gut transit, or rather changes in transit influence the microbiota present. Further investigation is needed to elucidate the cause and effect of this relationship to help drive further therapeutics for SIBO and IMO.

Declarations

Author contributions: All authors contributed to the study conception and design. Material preparation and data collection were performed by Sarah Talamantes and Irene Sonu. Analysis was performed by Faye Steiner. The first draft of the manuscript was written by Sarah Talamantes and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Ethics approval:

- The retrospective chart review study involving human participants was in accordance with the ethical standards of the institution and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standard. The Human Investigation Committee (IRB) of Stanford University approved this study.
- Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

Data availability: The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in a controlled access data storage.

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Figures

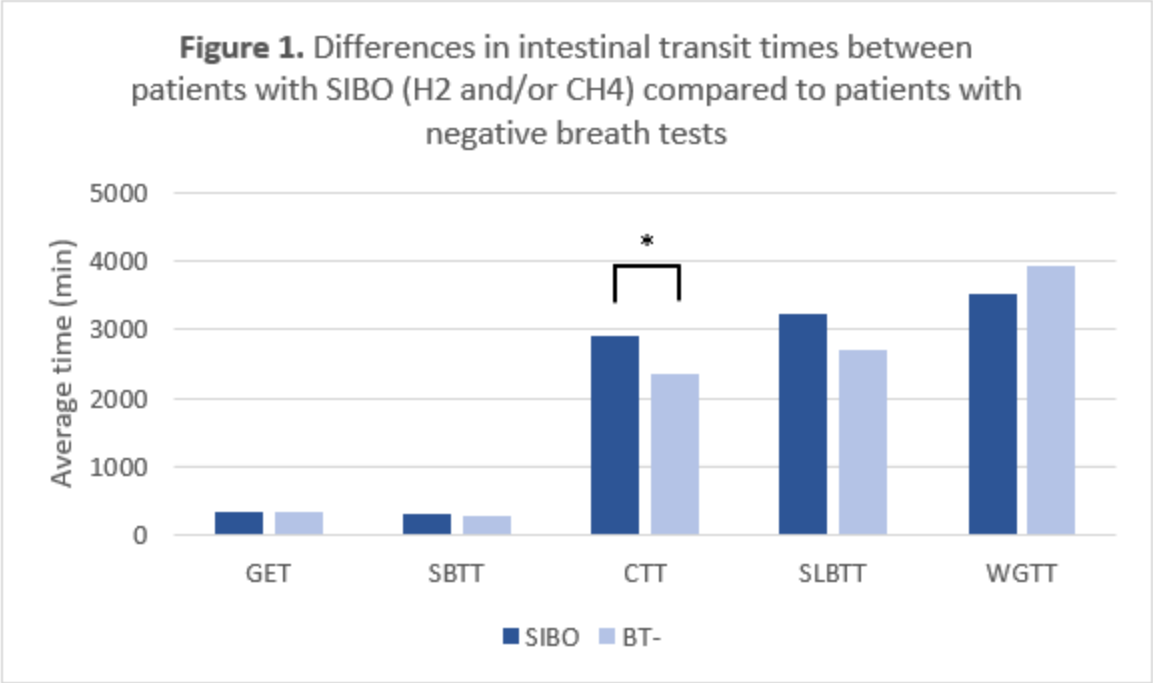

Figure 1

Differences in intestinal transit times between patients with SIBO (H2 and/or CH4) compared to patients with negative breath tests

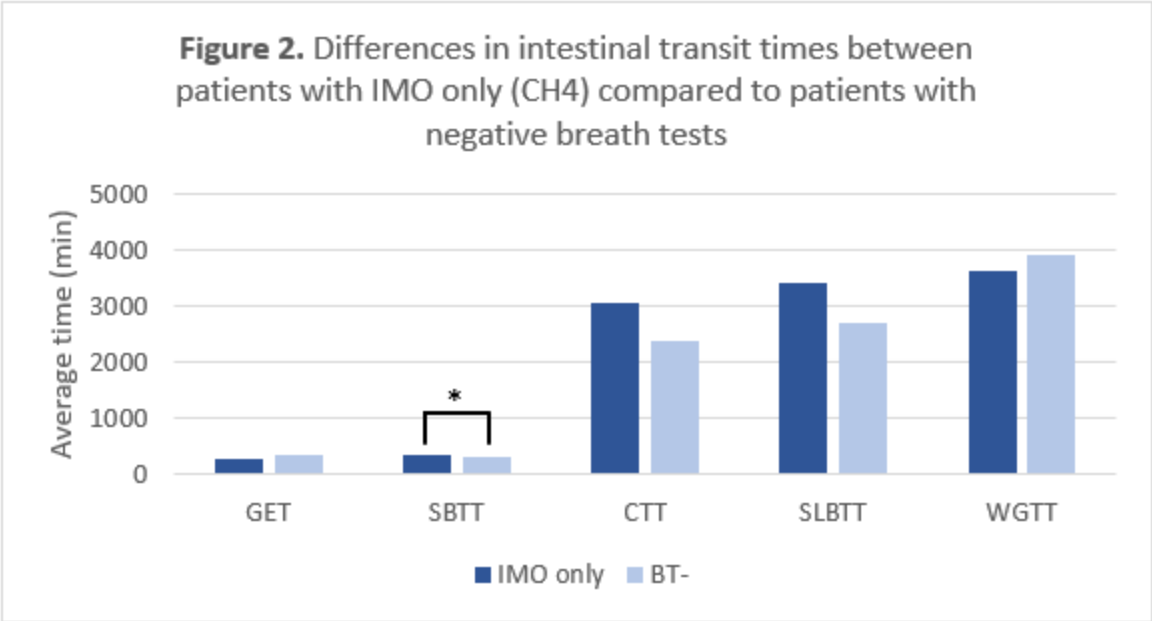

Figure 2

Differences in intestinal transit times between patients with IMO only (CH4) compared to patients with negative breath tests

GET: gastric emptying time, SBTT: small bowel transit time, CTT colonic, SLBTT small/large bowel transit time, WGTT whole gut transit time

* Indicates a statistically significant difference

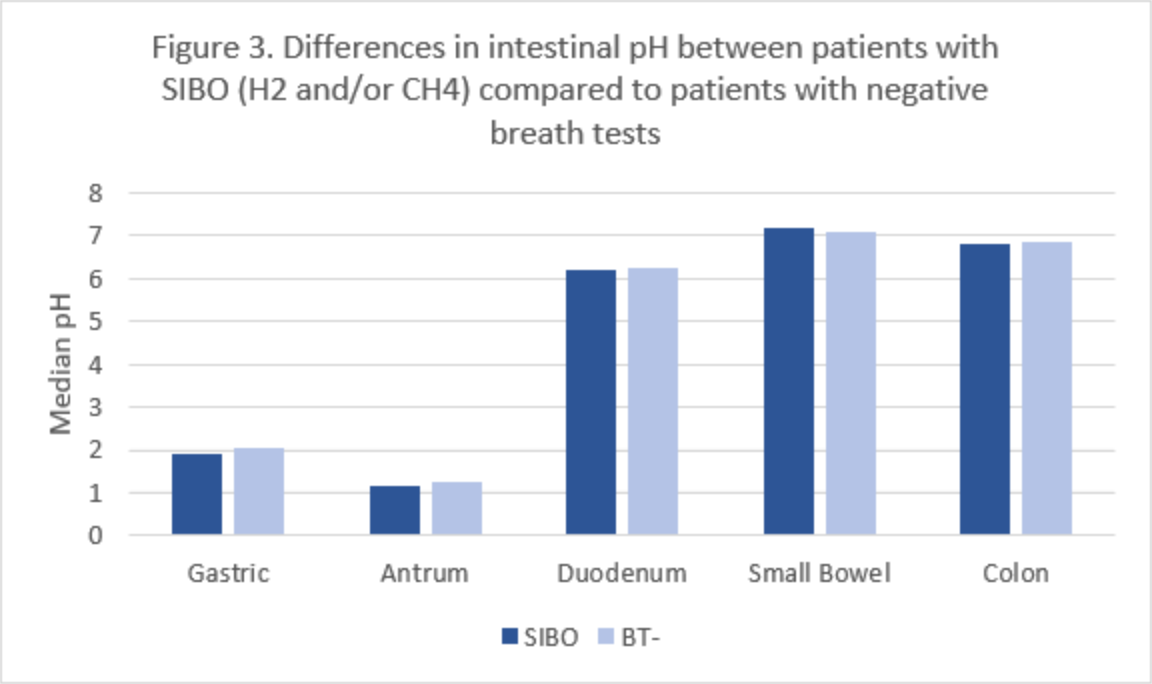

Figure 3

Differences in intestinal pH between patients with SIBO (H2 and/or CH4) compared to patients with negative breath tests