

## Retrospective Study

# Predisposing factors for positive D-Xylose breath test for evaluation of small intestinal bacterial overgrowth: A retrospective study of 932 patients

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**Data sharing:** Because these data may be the subject of future research by our team, we will not be able to share these data at this time. However, readers and reviewers can request a copy of a de-identified data set and documented copies of the analytic programs from Dr. Baharak Moshiree at [bmoshiree@med.miami.edu](mailto:bmoshiree@med.miami.edu). Requests will be honored within 18 mo of

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## Abstract

**AIM:** To investigate, in the largest cohort to date, patient characteristics and associated risk factors for developing small intestinal bacterial overgrowth (SIBO) using the D-Xylose breath test (XBT).

**METHODS:** We performed a retrospective cross-sectional study to analyze patient characteristics who underwent the XBT for evaluation of SIBO. Diagnostic testing with the XBT was performed based on a clinical suspicion for SIBO in patients with symptoms of bloating, abdominal pain, abdominal distension, weight loss, diarrhea, and/or constipation. Consecutive electronic

medical records of 932 patients who completed the XBT at the University of Florida between 2005 and 2009 were reviewed. A two-way Analysis of Variance (ANOVA) was used to test for several associations including age, gender, and body mass index (BMI) with a +XBT. A two-way ANOVA was also performed to control for the differences and interaction with age and between genders. A similar analysis was repeated for BMI. Associations between medical conditions and prior surgical histories were conducted using the Mantel-Haenszel method for 2 by 2 contingency tables, stratified for gender. Reported odds ratio estimates reflect the odds of the prevalence of a condition within the +XBT group to that of the -XBT group. *P* values of less than 0.05 (two-sided) were considered statistically significant.

**RESULTS:** In the 932 consecutive eligible subjects studied, 513 had a positive XBT. A positive association was found between female gender and a positive XBT ( $P = 0.0025$ ), and females with a positive test were, on average, greater than 5 years older than those with a negative test ( $P = 0.024$ ). The mean BMI of positive XBT subjects was normal (24.5) and significantly lower than the subjects with a negative XBT (29.5) ( $P = 0.0050$ ). A positive XBT was associated with gastroesophageal reflux disease (GERD) (OR = 1.35; 95%CI: 1.02-1.80,  $P = 0.04$ ), peptic ulcer disease (PUD) (OR = 2.61; 95%CI: 1.48-4.59,  $P < 0.01$ ), gastroparesis (GP) (OR = 2.04; 95%CI: 1.21-3.41,  $P < 0.01$ ) and steroid use (OR = 1.35; 95%CI: 1.02-1.80,  $P = 0.01$ ). Irritable bowel syndrome, independent proton-pump inhibitor (PPI) usage, or previous abdominal surgery was not significantly associated with a positive XBT. No single subdivision by gender or PPI use was associated with a significant difference in the odds ratios between any of the subsets.

**CONCLUSION:** Female gender, lower BMI, steroid use, PUD, GERD (independent of PPI use), and GP were more prevalent in patients with SIBO, determined by a positive XBT. Increasing age was associated with SIBO in females, but not in males.

**Key words:** Intestine; Small; Irritable bowel syndrome; Xylose; Breath tests; Proton pump inhibitors; Gastroparesis; Bacteria

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**Core tip:** Our study represents the largest retrospective cohort to date of 932 patients evaluated for small intestinal bacterial overgrowth (SIBO) using the D-Xylose breath test (XBT). We found that a positive test for SIBO was seen more frequently in elderly females than males and that lower body mass index, reflux disease, ulcer disease, gastroparesis, and steroid use were more frequently seen in patients who tested positive with the XBT compared to those with a negative test. Our study did not show any association

between SIBO and irritable bowel syndrome or independent narcotic or proton-pump inhibitor usage as has previously been reported by some investigators.

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## INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is a common gastrointestinal (GI) motility disorder marked by an over-proliferation of enteric flora in the small bowel. The clinical manifestations of SIBO can include bloating, abdominal pain, diarrhea, constipation, abdominal distension and weight loss. Several clinical conditions which impair appropriate GI secretions (*i.e.*, gastric acid, pancreatic enzymes, and bile salts), gut peristalsis, mucosal and systemic immunity, and the structural integrity of the GI tract are thought to predispose to SIBO. Inflammatory conditions such as celiac disease, Crohn's disease (CD) and ulcerative colitis (UC) have all been associated with development of SIBO. Numerous studies illustrate the frequent co-existence of SIBO with irritable bowel syndrome (IBS), and there is likely a substantial overlap in symptoms as well as pathogenic mechanisms<sup>[1-6]</sup>.

Despite the prevalence of SIBO, the specific medical, pharmacological, and surgical risk factors associated with it continue to be debated. Several small studies have linked SIBO to factors such as chronic use of proton pump inhibitors (PPIs)<sup>[7-10]</sup>, previous abdominal surgeries<sup>[9,10]</sup>, gastroparesis (GP)<sup>[11]</sup>, and IBS<sup>[1-6]</sup>. The quality of the data is often limited by the lack of standardized and/or validated diagnostic testing<sup>[12]</sup>, and the results may be confounded by co-existing GI conditions.

While some studies have used jejunal aspirate and a bacterial count of  $> 10^5$  colony-forming units/milliliter as the most reliable diagnostic indicator<sup>[13]</sup>, most have focused on non-invasive breath tests. Most notable are the lactulose hydrogen (LHBT), glucose hydrogen (GHBT), and  $^{14}\text{C}$  D-Xylose (XBT) breath tests. These tests supply carbohydrates that colonic bacterial enzymes preferentially metabolize, allowing the identification of alterations in the small intestine<sup>[12,14]</sup>. Currently, the LHBT remains the most widely available and commonly used clinical test, despite evidence suggesting a low sensitivity and specificity in patients with rapid intestinal transit<sup>[15,16]</sup>. While the GHBT has performed better than the LHBT, concerns over this test's validity and sensitivity also remain, and its ability to detect distal overgrowth may be limited<sup>[9,15]</sup>.

Likewise, specific cut-off values for a “positive” breath test have not been standardized for either of these methods<sup>[9]</sup>. In our study, we use a comparable breath test, the XBT, which has the advantage of being absorbed over a longer segment of bowel, making it less likely to skip isolated portions of bacterial overgrowth, thus increasing the sensitivity<sup>[14,16]</sup>. Although even the XBT has diagnostic limitations, it benefits from a more specific ability of gram-negative bacteria to metabolize xylose, increasing the test’s specificity<sup>[14]</sup>.

Our study represents the largest cohort to date of patients evaluated for SIBO using the XBT. We aim to further elucidate clinical factors associated with SIBO.

## MATERIALS AND METHODS

### XBT

D-Xylose is a freely soluble, hydrophilic pentose sugar absorbed primarily in the proximal portion of the small intestine and partially absorbed and excreted in the urine. The XBT measures the intestinal catabolism of a very small dose of (10 uCi) <sup>14</sup>C D-Xylose (Amersham Biosciences, Arlington Heights, IL) to <sup>14</sup>CO<sub>2</sub> which is released in alveolar air. Under normal conditions, the proportion of the absorbed compound excreted in the air and urine remains fairly constant but depends upon gut transit and the bacterial population of the small intestine<sup>[17]</sup>. These properties allow the XBT to be useful in the evaluation and diagnosis of intestinal malabsorption and inappropriate translocation of colonic flora<sup>[18]</sup>. Aside from SIBO, it has been used in the evaluation of GI conditions such as celiac disease, tropical sprue, CD, immunoglobulin deficiencies, blind-loop syndrome, and radiation enteritis<sup>[12,17,18]</sup>.

Multiple studies have evaluated the sensitivity and specificity of the XBT and have compared it to the gold standard of duodenal aspirate<sup>[14,19-21]</sup>. Compared to the more frequently performed breath tests in the United States (*i.e.*, lactulose and glucose hydrogen breath tests), the XBT has generally shown a higher sensitivity and specificity<sup>[22]</sup> and some have recommended it as the first-line breath test in testing for SIBO<sup>[23]</sup>. The initial validating studies were performed by King *et al.*<sup>[14,24]</sup> who demonstrated a sensitivity and specificity between 90%-100%. In subsequent follow-up studies, Lewis *et al.*<sup>[19]</sup> found a sensitivity of 71% and specificity of 85% and Chang *et al.*<sup>[20]</sup> 60% and 90%, respectively. One disadvantage of the XBT is the trivial radiation exposure with the release of the radioactive isotope of <sup>14</sup>CO<sub>2</sub> which, after absorption, is detectable in breath samples. For this reason, pregnant females are excluded from evaluation with the XBT.

Interpretation of the results for intestinal absorption requires meticulous attention to technical details and that false positives can occur in the presence of vomiting, dehydration, hypothyroidism, renal insufficiency, previous resection of the small intestine,

and rapid gut transit<sup>[19,25,26]</sup>. The test is performed for a total of 3 h to more reliably evaluate patients that may have delayed gastric emptying.

### Study design and subjects

We performed a retrospective cross-sectional study which analyzed data from all patients at the University of Florida motility laboratory who underwent the XBT for evaluation of SIBO. After an expedited Institutional Review Board (IRB) acceptance, consecutive electronic medical records of patients who completed the XBT between 2005 and 2009 were reviewed. Diagnostic testing with the XBT was performed based on a clinical suspicion for SIBO in patients with symptoms of bloating, chronic abdominal pain, abdominal distension, weight loss, diarrhea, and/or constipation without an established diagnosis. Each patient was thoroughly evaluated by a faculty specialist with physical examination, laboratory data, and endoscopies as indicated. *Helicobacter pylori* (*H. pylori*) was ruled out in patients with upper GI symptoms by either endoscopic biopsy or stool antigen testing prior to undergoing the XBT. All patients had prokinetic and/or PPI therapy discontinued two weeks prior to the XBT, and all antibiotics were discontinued four weeks prior to testing. The diagnosis of gastroparesis was established quantitatively based on gastric emptying time with radiolabeled egg meal in accordance with national consensus recommendations for gastric emptying scintigraphy initiated in 2008<sup>[27]</sup>. The diagnosis of gastroesophageal reflux disease (GERD) was based on clinical symptoms, endoscopic findings, or pH testing. A history of IBS or IBD was also documented.

The analysis was performed for the purpose of describing which predisposing factors are associated with a positive (+XBT) vs a negative (-XBT) in patients with symptoms suggesting SIBO. Given that our study is retrospective, we acknowledge confounding variables inherent in such a study, and our aim was to describe conditions associated with SIBO and not to imply causality.

### Data collection

An IRB-approved waiver of informed consent was obtained to perform this retrospective chart review. A total of 932 consecutive subjects were reviewed to obtain the following available information: age, gender, body mass index (BMI), XBT results, comprehensive past medical and surgical histories (including endoscopy reports and all relevant GI-laboratory data), and concomitant medications.

The XBT was performed according to the Institutional Standard Operating Procedure. A positive XBT is denoted as “+XBT” and is defined as a greater than two standard deviation rise in CO<sub>2</sub> (<sup>14</sup>C) value above the normal range at any one or more of the following time points: 30 min ( $\geq 0.0014$ ), 60 min ( $\geq 0.0029$ ),

**Table 1 Patient demographics**

	+XBT			-XBT			<i>P</i> value
	<i>n</i>	mean	SD	<i>n</i>	mean	SD	
Age contrasts (yr) ( <i>n</i> = 932)	513	58.7	14.8	419	55.9	15.9	<i>P</i> = 0.10 (XBT)
Male:	56	59.6	15.9	148	60.3	16.3	<i>P</i> = 0.0025 (Gender)
Female:	457	58.6	14.7	271	53.4	15.2	<i>P</i> = 0.024 (Interact)
Overall mean: 57.4 overall SD: 15.4							
BMI contrasts ( <i>n</i> = 451)	244	24.1	5.90	207	29.5	7.33	<i>P</i> = 0.0050 (XBT)
Male: ( <i>n</i> = 91)	23	24.3	5.65	68	28.8	6.96	<i>P</i> = 0.26 (Gender)
Female: ( <i>n</i> = 360)	221	24.0	5.94	139	29.9	7.52	<i>P</i> = 0.42 (Interact)
Overall mean: 26.6 overall SD: 7.1							
Gender contrast ( <i>n</i> = 932)							
Male, <i>n</i> (%)		56 (11)			148 (35)		<i>P</i> < 0.0001
Female, <i>n</i> (%)		457 (89)			271 (65)		

XBT: D-Xylose breath test; BMI: Body mass index.

and/or 180 min ( $\geq 0.0043$ ).

### Statistical analysis

This observational study used a two-way Analysis of Variance (ANOVA) to test for several associations including age, gender, and BMI with a +XBT. We used a two-way ANOVA to test for differences in age in terms of a -XBT and +XBT (main effect) and between gender (main effect), as well as the interaction between XBT and gender (Table 1). Interaction assessed the mean difference in age between -XBT and +XBT according to differences by gender (see "Interact," Table 1). This analysis was also repeated for BMI, which was available in about half the subjects. Apart from BMI, the data were complete on all subjects. We presumed the BMI data were missing at random.

Associations between medical conditions (Table 2), stratified for gender, and prior surgical histories (Table 3) were conducted using the Mantel-Haenszel methods for 2 by 2 contingency tables. Reported odds ratio estimates reflect the odds of the prevalence of a condition within the +XBT group to that of the -XBT group. Gender vs XBT (Table 1) used the Mantel-Haenszel method, but was not stratified. *P*-values of less than 0.05 (two-sided) were considered statistically significant.

The primary purpose of this analysis was to determine whether age, BMI, and gender are associated with a +XBT or -XBT. Secondly, we investigated the relationship of a positive test with other common GI and systemic conditions, prior abdominal surgeries, and certain medications that have been previously associated with SIBO. Because there are a large number of factors investigated, any significant findings in these secondary analyses should be confirmed in independent studies before considering them as definitive. 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.

The statistical review of the study was performed

by Dr. Jonathan Shuster, Director, Research Design and Analysis Program, University of Florida Clinical and Translational Science Institute. He performed the analysis and did extensive quality control review of the data. He has co-authored over 350 peer reviewed articles, including over 50 articles in biostatistical methodology.

## RESULTS

### Baseline and demographic characteristics

Of the 932 patients reviewed, 513 had a +XBT, with demographics for gender, age, and BMI included in Table 1. BMI data were only available for patients with a recorded height. Across the cohort, patient age did not show significant correlation with the likelihood of a +XBT (*P* = 0.10). However, female patients with a +XBT were, on average, > 5 years older than females with a -XBT (*P* = 0.024). Moreover, women were disproportionately more likely to have a +XBT than men (*P* < 0.0001). Also significant were associations between a lower BMI (24.1) and a +XBT, compared with a higher BMI (29.5) in patients with a -XBT (*P* = 0.0050).

### Medical conditions and medications and XBT positivity

A multivariate logistic regression specifically analyzed the association of existing medical conditions and a +XBT (Table 2). A separate analysis evaluated the use of PPIs, narcotics, steroids, and anticholinergic medications and their association with a +XBT (Table 2). The odds of a +XBT was significantly associated with gastroesophageal reflux disease (GERD) (OR = 1.35; 95%CI: 1.02-1.80, *P* = 0.04), peptic ulcer disease (PUD) (OR = 2.61; 95%CI: 1.48-4.59, *P* < 0.01), GP (OR = 2.04; 95%CI: 1.21-3.41, *P* < 0.01) and steroid use (OR = 1.35; 95%CI: 1.02-1.80, *P* = 0.01). Interestingly, IBS, PPI usage, and the use of narcotics were not associated with a +XBT. Sub-analyses were performed on all elements in Table 2 with a set *P* value < 0.05 to control for possible gender and PPI confounding. No single subdivision by gender



**Table 2 Association of medical conditions and medications and small intestinal bacterial overgrowth *n* (%)**

+XBT: 513	+XBT	-XBT	<i>P</i> value	OR (95%CI)
-XBT: 419	M: 56 F: 457	M: 148 F: 271		F:M 4.46 (3.17-6.28)
	+PPI: 200 -PPI: 313	+PPI: 194 -PPI: 225		
GERD	171 (33) M: 22 F: 149	113 (27) M: 39 F: 74	0.04	1.35 (1.02-1.80)
	+PPI = 112 -PPI = 59	+PPI = 91 -PPI = 22		
Irritable bowel syndrome	77 (15) M: 3 F: 74	47 (11) M: 8 F: 39	0.09	1.40 (0.95-2.06)
	+PPI: 32 -PPI: 45	+PPI: 29 -PPI: 18		
PUD	51 (10) M: 6 F: 45	17 (4) M: 7 F: 10	< 0.01	2.61 (1.48-4.59)
	+PPI: 23 -PPI: 28	+PPI: 13 -PPI: 4		
Inflammatory bowel disease	20 (4) M: 2 F: 18	12 (3) M: 7 F: 5	0.39	1.38 (0.66-2.84)
Gastroparesis	52 (10) M: 5 F: 47	22 (5) M: 3 F: 19	< 0.01	2.04 (1.21-3.41)
Hypothyroidism	83 (16) M: 5 F: 78	53 (13) M: 8 F: 45	0.13	1.33 (0.91-1.93)
Diabetes mellitus	57 (11) M: 7 F: 50	88 (21) M: 33 F: 55	< 0.01	0.47 (0.33-0.68)
PPI	200 (39) M: 19 F: 181	194 (46) M: 69 F: 125	0.02	0.74 (0.57-0.96)
Narcotics	84 (16) M: 5 F: 79	64 (15) M: 23 F: 41	0.65	1.09 (0.76-1.55)
	+XBT: 45 -XBT: 39	+XBT: 36 -XBT: 28		
Steroids	36 (7) M: 7 F: 29	14 (3) M: 9 F: 5	0.01	2.18 (1.16-4.11)
	+PPI: 20 -PPI: 16	+PPI: 8 -PPI: 6		
Anticholinergic drugs	52 (10) M: 1 F: 51	38 (9) M: 7 F: 31	0.58	1.13 (0.73-1.76)

Sub-analyses for gender and PPI were performed on those elements in Table 2 where the *P* value was below 0.05. Not a single subdivision by either gender or med PPI was associated with a significant difference in odds ratios between subsets. GERD: Gastroesophageal reflux disease; PUD: Peptic ulcer disease; PPI: Proton pump inhibitor; XBT: D-Xylose breath test.

or PPI use was associated with a significant difference in the odds ratios between any of the subsets.

### Previous abdominal surgeries and XBT positivity

Our study also analyzed the association between a +XBT and certain abdominal surgeries including gastric bypass, hernia repair, appendectomy, hysterectomy, cholecystectomy, Nissen Fundoplication, and Billroths I and

**Table 3 Association of previous abdominal surgical procedures (yes/no) with small intestinal bacterial overgrowth *n* (%)**

Procedure	+XBT	-XBT	<i>P</i> value	OR (95%CI)
Gastric bypass	15 (3)	8 (2)	0.32	1.54 (0.65-3.69)
Hernia repair	14 (3)	25 (6)	0.01	0.44 (0.23-0.86)
Cholecystectomy	142 (28)	139 (33)	0.07	0.77 (0.58-1.02)
Appendectomy	106 (21)	67 (16)	0.07	1.37 (0.98-1.92)
Hysterectomy (females)	183 (40)	90 (33)	0.07	1.34 (0.98-1.84)

Limited patient numbers for Nissen Fundoplication (*n* = 17), Billroth I (*n* = 1) and Billroth II (*n* = 4) procedures. Subanalyses for gender performed on all elements of Table 3. Gender did not significantly alter the *P* value or odds ratio between subsets. XBT: D-Xylose breath test.

II (Table 3). Only hysterectomy (OR = 1.34; 95%CI: 0.98-1.84, *P* = 0.07) and appendectomy (OR = 1.37; 95%CI: 0.98-1.92, *P* = 0.07) showed a trend toward a significant positive association with SIBO.

## DISCUSSION

Patients with a +XBT were considered to have SIBO and then treated with antibiotics. Our study found several significant associations between a +XBT and female age, gender, BMI, and clinical conditions including GERD, PUD, and GP. However, contrary to a prior smaller studies<sup>[28]</sup>, no significant positive association was found between a +XBT and PPI use independent of GERD and PUD history.

### Associations of GERD, PUD, and PPI use

Our large-scale retrospective analysis suggests a significant association between a +XBT and both GERD and PUD. The finding that PPI use, independent of those two clinical conditions, was not positively associated with SIBO is compelling, given recent studies suggesting PPI use predisposed patients to developing SIBO by creating an environment more suitable for bacterial colonization and growth<sup>[28,29]</sup>. This presumed association may also stem from their widespread initiation and continued use off PPI therapy amongst hospitalized and clinic patients<sup>[8]</sup>. Similar to our study, several larger analyses also suggest a lack of independent association between PPI usage and SIBO<sup>[30,31]</sup>. These studies suggest earlier associations between PPIs and SIBO may stem from small sample sizes and/or the use of the less-accurate LHBT to diagnose SIBO. On the other hand, the absence of a positive association may reflect incomplete acid suppression, intermittent usage of PPIs, or transient gastric pH levels of < 4<sup>[29]</sup>.

Somewhat surprisingly, given no positive independent association between PPI usage and a +XBT, we found a significant correlation between a documented history of GERD (*P* = 0.04) or PUD (*P* ≤ 0.01) and a +XBT. Many of these patients are placed on lifelong acid suppression therapy, often using high-potency

pharmacotherapies. A less acidic gastric milieu could create an environment more conducive to SIBO. The positive association with PUD may also specifically be related to changes to intestinal microbiota that occur in the presence of PUD. This condition is commonly associated with *H. pylori*, which is treated with antibiotics combined with high-dose PPIs. Studies have demonstrated changes to gut microflora with use of antibiotics causing eradication or suppression of some microbiota, while enabling others to flourish<sup>[28]</sup>. While our study was unable to account for which patients with PUD had previously been treated for *H. pylori*, a future study would certainly be warranted to adequately address the pathophysiologic basis of the association between PUD and SIBO.

#### **Associations of age, gender, and BMI with SIBO**

Our analyses found female gender to be highly associated with a +XBT, consistent with results from other studies<sup>[6,32]</sup>. Although one of these prior studies<sup>[6]</sup> attributed the increased prevalence of SIBO among women to the higher prevalence of IBS in females, we did not find a significant association between IBS and a +XBT. However, our study was able to establish a significant association between GP and SIBO, a condition also more common in the female population<sup>[29]</sup>.

Increasing female (but not male) age was also associated with the presence of SIBO. This association may result from the prevalence of small intestinal dysmotility, GP, immunosuppression, and previous abdominal surgery in an aging population, all of which were analyzed in this study. We do not have an explanation for a lack of association between increasing age in males and SIBO. Nevertheless, our study provides a preliminary indication that changes in gut microbiota may occur with advanced age and lead to GI complaints which can be differentiated as SIBO rather than other benign, age-associated conditions<sup>[33-35]</sup>.

Our analysis also uncovered an inverse association between BMI and the presence of SIBO. One potential explanation for this association could be that SIBO can cause malabsorption and weight loss<sup>[36,37]</sup>. However, multiple studies suggest that alterations in enteric flora can impact BMI<sup>[38-41]</sup>, suggesting the possibility that this relationship may be much more complex. This association warrants further review.

#### **Association of gastroparesis and SIBO**

Our study found a significant association between a +XBT and a prior diagnosis of GP ( $P = 0.01$ ). SIBO in patients with GP may stem from impaired phase III migrating motor complexes, resulting from malfunctioning interstitial cells of Cajal leading to intestinal stasis<sup>[42,43]</sup>. Given the significant overlap in upper GI symptoms with SIBO and GP, clinicians should have a high suspicion for SIBO in patients

diagnosed with GP. The significant association between SIBO and GP is especially striking, given that our study failed to reveal a similarly significant association between SIBO and other conditions that alter gut motility and are co-morbid with GP, including diabetes, hypothyroidism, connective tissue diseases, and use of narcotics or anticholinergic medications<sup>[44]</sup>.

#### **Association of IBS and SIBO**

Our analyses did not establish an independent association between a +XBT and IBS. One well-known study has suggested that since patients with IBS are more likely than controls to receive PPIs, failing to account for their influence may have contributed to a lack of significant association between IBS and SIBO<sup>[28]</sup>. However, while many IBS patients in our study were prescribed PPIs (49%), no significant difference distinguished patients taking a PPI with a +XBT from those with a -XBT, suggesting this lack of association may be unrelated to concurrent PPI usage. This finding is consistent with another recently published study which also analyzed a large population of patients presenting with SIBO symptoms and controlled for PPI usage<sup>[31]</sup>.

The role of SIBO in the development of IBS and its subsequent treatment continues to be highly contentious. Considerable overlap in patient demographics and symptomatology of both diseases has fueled this controversy, with one prominent study suggesting up to 80% of patients with IBS have SIBO<sup>[45]</sup>. However, most studies associating SIBO with IBS have also relied on limited specificity of diagnostic tests<sup>[12,16,33]</sup>. In fact, the LHBT results used in these studies may reflect more rapid orocecal transit times, rather than IBS, especially in patients presenting with diarrhea-predominant symptoms<sup>[46]</sup>.

#### **Association of steroid use and SIBO**

Steroid use and SIBO may be associated as our study suggested a strong association between steroid use and a +XBT (7% in + XBT vs 3% in -XBT,  $P = 0.01$ ). In an already predisposed individual, steroid-induced immune dysregulation may impair gut mucosal immunity through bacterial adherence to intestinal mucosa and decreased serum Immunoglobulin A<sup>[47,48]</sup>, leading to overgrowth of undesirable bacteria. The widespread usage of glucocorticoids warrants a future well-designed study specifically focusing on their impact on gut microflora.

Steroids have also been shown to be a risk factor for PUD which was positively associated with SIBO. It is also possible that the use of steroids may contribute to the hypothesized increased prevalence of SIBO in patients with inflammatory conditions including connective tissue diseases, CD<sup>[49]</sup>, and UC<sup>[50]</sup>, although this was not directly observed in our study. Nevertheless, it is difficult to determine the extent to which steroids play a role as inflammatory bowel disease can intrinsically

disrupt normal intestinal physiology and flora. Higher rates of intestinal surgeries in these patients may promote gut dysmotility and stasis, while ileocecal (IC) valve resection in patients with extensive ileal or right sided colonic involvement can result in the pathological translocation of colonic flora.

### **Association of abdominal surgeries and SIBO**

Some abdominal surgeries have been thought to predispose patients to SIBO, largely secondary to adhesions, anatomical stasis, or IC valve incompetence. However, we were unable to confirm any significant association in our cohort. This outcome may stem from the limited number of patients in the study population with a history of Billroth procedures, Nissen fundoplication, or gastric bypass surgery. However, the association between hysterectomy and +XBT approached statistical significance ( $P = 0.07$ ). This finding may be confounded by the fact that hysterectomies tend to be most commonly performed in older, postmenopausal females with abdominal pain and vaginal bleeding.

While other abdominal surgeries were not significantly associated with SIBO, substantial numbers of patients with both +XBT (18.5%) and -XBT (30.1%) who reported symptoms consistent with SIBO had previously undergone appendectomy or cholecystectomy. Unfortunately, our analyses were unable to account for patients who had previously undergone right-sided hemicolectomy. As alluded to earlier, this may potentiate the translocation of colonic flora to the small intestine by eliminating the ileocecal valve, specifically increasing the concentration of gram-negative and anaerobic species<sup>[51]</sup>. This, in light of another new study demonstrating the association of low ileocecal valve pressure with SIBO, highlights the need to specifically address ileocecal resection itself as a possible risk factor for SIBO, particularly in the setting of inflammatory bowel disease<sup>[52]</sup>.

Although we did our best to limit bias by studying a series of consecutive patients, we acknowledge several study limitations given its retrospective design. This may present a selection or referral bias as all subjects in the study were potentially referred to the motility laboratory by different GI specialists with clinical symptoms of SIBO. For example, this cohort may present more severely on average than those seen in the community. In addition to sampling biases, there may be a lack of statistical power for each specific factor in relation to a positive XBT. For instance, not observing significance in the male population might be due to the small sample size for male gender in this study. The retrospective nature of the study also limited the analysis of associations across all patients with SIBO and IBS, SIBO and PPI or narcotic use, as well as data indicative of patients' potential vitamin deficiencies or loss of muscle mass. Furthermore, these findings, similar to many studies relying on breath testing for diagnosing SIBO, should

be interpreted in light of the fact that the XBT positivity cannot 100% confirm SIBO.

In conclusion, this study uses the largest cohort to date of 932 subjects reporting symptoms consistent with SIBO, and analyzes the patient characteristics and their associations with risk factors for developing SIBO. Our study found the female gender to be the single most highly associated variable with SIBO, and females with a positive test were also significantly older than those with a negative test. Other associated conditions were a lower BMI, GERD, PUD, GP, and steroid use. In contrast, our analysis failed to uncover associations between SIBO and a history of IBS or narcotic or PPI usage.

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## **COMMENTS**

### **Background**

Small intestinal bacterial overgrowth (SIBO) is a debilitating gastrointestinal (GI) motility disorder with several possible predisposing factors for its development including irritable bowel syndrome, inflammatory bowel disease, use of proton pump inhibitors, GI surgeries and systemic conditions such as hypothyroidism and diabetes. Given the overlap of symptoms of SIBO with other common GI conditions, it is important to consider these predisposing conditions and consider SIBO as an explanation for ongoing symptoms of bloating, abdominal pain, diarrhea, constipation and weight loss.

### **Research frontiers**

These large retrospective cohort of 932 patients from the motility laboratory uses the D-Xylose breath test (XBT) database to identify specific conditions found to be more associated with SIBO. The XBT is a validated method for testing for the presence of SIBO with good specificity and sensitivity when compared to the gold standard small bowel aspirate.

### **Innovations and breakthroughs**

This large database addresses the clinical importance of discovering variables more commonly associated with SIBO to help clinicians determine which patient population is more vulnerable to development of overgrowth, which to then test for this condition, and perhaps which to avoid using steroids or narcotics unless absolutely necessary. The population most at risk for SIBO is the elderly female with a normal to low body mass index. Moreover, patients with gastroparesis, peptic ulcer disease, and gastroesophageal reflux disease more commonly had SIBO independent of proton-pump inhibitor (PPI) therapy. Interestingly, PPI use and IBS were not associated with SIBO.

### **Applications**

All findings stress the importance of testing for SIBO in the at risk population and identifies specific medical conditions and medications which predispose to SIBO.

### **Terminology**

D-Xylose is a freely soluble, hydrophilic pentose sugar absorbed in the proximal small intestine and partially absorbed and excreted in the urine. Intestinal catabolism of D-Xylose to  $^{14}\text{CO}_2$  depends upon gut transit and the bacterial population of the small intestine. These properties allow the XBT to be useful in the evaluation and diagnosis of intestinal malabsorption and inappropriate translocation of intestinal flora.

### **Peer-review**

This paper is interesting. Although these data were gathered in a retrospective manner via an electronic records search, the sample size is impressive nonetheless. The paper is well-written and the statistical methods are appropriate.

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