

ARTICLE

Open Access

Does colectomy predispose to small intestinal bacterial (SIBO) and fungal overgrowth (SIFO)?

Satish S. C. Rao, MD, PhD¹, George Tan, MD¹, Hamza Abdulla, MD¹, Siegfried Yu, MD¹, Sebastian Larion, MD¹ and Pornchai Leelasinjaroen, MD¹

Abstract

Objectives: After subtotal colectomy, 40% of patients report chronic gastrointestinal symptoms and poor quality of life. Its etiology is unknown. We determined whether small intestinal bacterial overgrowth (SIBO) or small intestinal fungal overgrowth (SIFO) cause gastrointestinal symptoms after colectomy.

Methods: Consecutive patients with unexplained abdominal pain, gas, bloating and diarrhea (>1 year), and without colectomy (controls), and with colectomy were evaluated with symptom questionnaires, glucose breath test (GBT) and/or duodenal aspiration/culture. Baseline symptoms, prevalence of SIBO/SIFO, and response to treatment were compared between groups.

Results: Fifty patients with colectomy and 50 controls were evaluated. A significantly higher ($p = 0.005$) proportion of patients with colectomy, 31/50 (62%) had SIBO compared to controls 16/50 (32%). Patients with colectomy had significantly higher ($p = 0.017$) prevalence of mixed SIBO/SIFO 12/50 (24%) compared to controls 4/50 (8%). SIFO prevalence was higher in colectomy but not significant ($p = 0.08$). There was higher prevalence of aerobic organisms together with decreased anaerobic and mixed organisms in the colectomy group compared to controls ($p = 0.008$). Patients with colectomy reported significantly greater severity of diarrhea ($p = 0.029$), vomiting ($p < 0.001$), and abdominal pain ($p = 0.05$) compared to controls, at baseline. After antibiotics, 74% of patients with SIBO/SIFO in the colectomy and 69% in the control group improved ($p = 0.69$).

Conclusion: Patients with colectomy demonstrate significantly higher prevalence of SIBO/SIFO and greater severity of gastrointestinal symptoms. Colectomy is a risk factor for SIBO/SIFO.

Introduction

Colectomy is a common surgical procedure with an annual estimate of 235,000 procedures in the U.S.A¹. It is performed for a variety of indications and can be life-saving. However, up to 40% of patients undergoing subtotal colectomy report persistent gastrointestinal symptoms including gas, bloating, distension, pain and

diarrhea². A majority of these patients also report an impaired quality of life. The pathoetiology of these symptoms is unknown.

In a recent study, Singh et al., reported that 7/15 patients (47%) with severe slow-transit constipation and underlying neuropathy, and who underwent colectomy with ileorectal anastomosis, developed new onset of significant bloating, distension and flatulence³. Further testing revealed that all of these patients had SIBO and they responded to antibiotics. This observation suggested

Correspondence: Satish S. C. Rao (srao@augusta.edu)

¹Division of Gastroenterology and Hepatology, Department of Internal Medicine, Augusta University, Augusta, GA 30912, USA

© The Author(s) 2018



Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, and provide a link to the Creative Commons license. You do not have permission under this license to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

that colectomy may predispose patients to SIBO, but this concept has not been systematically assessed.

Small intestinal bacterial overgrowth (SIBO) or small intestinal fungal overgrowth (SIFO) is characterized by abdominal pain, distension, bloating and diarrhea, and the presence of an excessive amount of bacteria or fungus in the small bowel^{4–6}. SIBO can be identified with either breath hydrogen tests or culture of duodenal fluid^{6–8}, but quantitative culture of small bowel aspirate is the only method of identifying SIFO⁷.

Under normal physiological conditions several factors play a role in protecting the small intestine from bacterial colonization. These include a normal intestinal motility, especially the recurring cyclical migrating motor complex, gastric acid, mucous secretion, bile salts, and luminal immunoglobulins^{8–11}. The ileocecal valve also serves as an important anatomical barrier between the ileum and cecum, and not only regulates the flow of chyme but also prevents the reflux of colonic contents into the small bowel¹². In contrast, conditions that alter the normal gastric and small bowel function, such as opioids that inhibit motility, atrophic gastritis, Parkinson's disease, diabetes, pseudo-obstruction, scleroderma, blind loop syndrome and use of PPI's and others may each predispose to SIBO^{8,13,14}.

The aim of this study was to assess the prevalence of SIBO and SIFO in a cohort of patients with chronic unexplained gastrointestinal symptoms following colectomy, and to compare this with a control group of patients with similar chronic symptoms but without previous colectomy. In addition, we assessed the prevalence of gastrointestinal symptoms in these patients at baseline and after treatment.

Methods

Patients

Consecutive adult patients who were referred to a specialist motility center over three years with unexplained chronic (>1 year) gastrointestinal symptoms such as gas, bloating, belching, diarrhea, and abdominal discomfort, and with a history of colectomy were evaluated. The control group consisted of patients with similar long-standing complaints of gas, bloating, pain and diarrhea but without colectomy, and any other gastrointestinal problems. Because of the overlapping nature of both upper and lower gastrointestinal symptoms and the presence of colectomy in one of our groups, they did not meet any of the Rome criteria for functional GI disorders. Patients were included if they had normal upper endoscopy, colonoscopy (except post-colectomy changes and intact anastomosis), computerized abdominal tomography scan, and normal hematology, biochemical profiles, tissue transglutaminase antibody, thyroid stimulating hormone, and normal right upper quadrant ultrasound

scan. Patients with upper gut or small bowel surgery and those who were hospitalized or with serious cardiac, pulmonary, or neurologic comorbidities or with known intestinal obstruction or motility disorders such as scleroderma or pseudo-obstruction were excluded. All patients underwent either glucose breath test and/or duodenal aspirate with culture. In addition, they filled out a validated symptom questionnaire¹⁵.

The Augusta University Medical Center Investigation Review Board approved the study, No. 659642-3 and the study was registered on clinical trials.gov—NCT03216239.

Glucose breath test

All patients were advised to consume a low carbohydrate diet for one day, avoid laxatives for one week and antibiotics for 6 weeks prior to the test. After an overnight fast, patients were asked to brush their teeth and rinse their mouth with an antiseptic mouthwash, at least 2 h before the test, to avoid false positive high basal levels from fermentation of substrate by oral bacteria. After obtaining a baseline breath sample, 75 grams of glucose dissolved in 250 ml of water was administered orally^{6,16}. Subsequently, breath samples were collected at 15-minute intervals for the next 2 h. The samples were collected in a bag (QuinTron Instrument Company, Inc., WI) and alveolar gas was analyzed for both H₂ and CH₄ levels by chromatography (QuinTron Micro Analyzer, QuinTron Instrument Company, Inc., WI). The patients were also asked to score the presence and severity of nine gastrointestinal symptoms on a visual analog scale(0–3), throughout the breath test.

Duodenal aspiration and quantitative culture

All patients were required to be free of antibiotic use for 6 weeks prior to testing. Aspiration of distal duodenal fluid was performed during an upper endoscopy. The procedure was performed under aseptic precautions to minimize contamination^{7,16}. A sterile 2 mm Liguory catheter (COOK Medical, Bloomington, IN, USA) was passed through the biopsy channel of the upper endoscope into the 3rd or 4th portions of the duodenum, followed by aspiration of 3–5 ml of duodenal fluid. Specimens were sent immediately to microbiology lab for standard aerobic, anaerobic and fungal cultures.

The duodenal aspirate specimens were plated for aerobic, anaerobic and fungal cultures. After vortexing the sample, the following agar plates were inoculated using a 0.001 calibrated loop: Blood, Chocolate, Maconkey, Columbia Naladixic Acid Agar (CAN) with blood, Anaerobe Blood, Phenyl Ethyl Alcohol (PEA), Anaerobic Remel which contains Paromycin and Vancomycin, Inhibitory Mold and Mycobiotic. They were then struck for colony count. The Blood and Chocolate agars were

held at 37° in CO₂ for 5 days. MacConkey and CNA plates were held in O₂ for 48 h before being discarded. Anaerobe media was incubated under anaerobic conditions for 5 days. Fungal plates were held for 4 weeks. Gram stains were reported.

Any bacterial growth $\geq 1,000$ CFU was identified and reported out using colony count numeration. All organisms were listed in the physician report, except in very rare cases multiple (typically >3) organisms were isolated and reported as multiple growth of aerobes or anaerobes.

Identification of organisms including yeast were generally by mass spectrophotometry (Maldi-Time of Flight). Some organisms (i.e., *Neisseria* sp, Gram-positive bacilli resembling Diphtheroids/*Coryneforms*, *Lactobacillus* species, *Streptococcus viridans* group, *Staphylococcus coagulase negative*, *Rothia* sp.) were identified based on gram stain, colonial morphology, or spot tests. Wherever appropriate antibiotic susceptibility panels were performed and reported. Culture plates were held for 10 days.

Symptom questionnaire

All patients completed a validated Likert-like bowel symptom questionnaire at their initial clinic visit that assessed nine symptoms: abdominal pain, belching, bloating, fullness, indigestion, nausea, diarrhea, vomiting and gas^{15,17}. Patients were asked to rate the frequency, intensity and duration of each symptom on a 0–3 scale. Intensity: 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe symptoms. Frequency: 0 = None; 1 = Less than 1 episode/week, 2 = 1 episode/week, 3 = More than 1 episode/week. Duration: 0 = None, 1 = Less than 10 min, 2 = 10–30 min, 3 = Greater than 30 min. The total score for each symptom ranged from 0 to 9.

After establishing a diagnosis of SIBO with either GBT and/or duodenal cultures, patients were treated with appropriate antibiotics based on culture and antibiotic sensitivity, patient's allergy profile and previous antibiotic use. Patients with SIFO were treated with antifungals and those with mixed SIBO/SIFO were treated with antibiotics and antifungals. Three months later, they either attended a follow up clinic visit or were contacted over the phone and asked to complete the aforementioned symptom questionnaire, and rate their overall gastrointestinal symptoms on a VAS scale (0 = very dissatisfied, 100 = completely satisfied.)

Data analyses

Patients were adjudicated as having SIBO if the culture showed bacterial concentration of $\geq 10^3$ CFU/mL for aerobic or anaerobic organisms^{6,8,16,18}. Glucose breath test was considered positive for SIBO if the following criteria were met: ≥ 20 PPM increase above baseline for H₂, or ≥ 15 PPM increase above baseline for CH₄, or ≥ 15 PPM increase above baseline for combined H₂ and

CH₄ values^{7,16}. The diagnosis of SIFO was made if the duodenal culture yielded a growth of fungal organisms at a concentration of $\geq 10^3$ CFU/ml^{7,19}.

Statistical analysis

Data are presented as mean \pm SD unless otherwise stated. Continuous variables were compared using Student's *t*-test for parametric data or Mann-Whitney *U*-test for non-parametric data. Categorical variables including prevalence in subgroups were compared using chi-square with Yate's correction factor or Fisher's exact test, as appropriate. Statistics were performed using Sigmaplot v12.2 (San Jose, CA) that checks for normal distribution. A *p* < 0.05 was considered statistically significant.

Results

Demographics

The colectomy group comprised of 50 patients (F/M = 41/9), mean age 52.3 years (range: 20–85), and with a mean duration of symptoms of 79.9 months. The indication for colectomy was colon inertia/slow-transit constipation (40%), colorectal carcinoma/polyps (14%), diverticular disease (14%), bowel obstruction (14%), Crohn's disease (6%), and others (12%). Regarding the type of surgery, 28/50 (56%) had partial colectomy, 11/50 (22%) had subtotal colectomy and 11/50 (22%) had total colectomy. Three additional patients with colectomy were excluded because of recurrent hospitalization, small bowel surgeries and pseudo-obstruction syndromes. The control group comprised of 50 patients (F/M = 38/12) with a mean age of 49.9 years (range 18–88), and with a mean duration of symptoms of 77.6 months, and no history of bowel surgery. Two additional patients in the control group were excluded because of scleroderma, and bariatric surgery with blind loop syndrome. There were no differences in the demographic features between the two groups.

Symptom patterns

Patients with colectomy reported significantly higher severity of diarrhea (4.63 vs 2.98; *p* = 0.029), vomiting (2.54 vs 0.30; *p* < 0.001) and abdominal pain (7.25 vs 6.18; *p* = 0.05) compared to those without colectomy at baseline. Other gastrointestinal symptoms were not significantly different between the two groups, although their severity was generally higher in the colectomy group (Table 1).

Glucose breath test

In the colectomy group, 48/50 patients underwent glucose breath testing and the remaining 2 subjects had duodenal aspiration alone. Of these, 21/48 (43.8%) tested positive for SIBO. Likewise, in the control group, 48/50 patients underwent glucose breath testing, and 2 had

Table 1 Baseline gastrointestinal symptom scores in patients with and without colectomy

Gastrointestinal symptom	Colectomy (N = 50)	Controls (N = 50)	p-value
Abdominal pain	7.25 (2.1)	6.18 (3.2)	0.05
Belching	4.08 (3.1)	3.42 (3.4)	0.322
Bloating	6.21 (3.3)	6.64 (3.3)	0.515
Fullness	6.58 (3.3)	6.02 (3.4)	0.408
Indigestion	4.83 (3.2)	4.20 (3.9)	0.379
Nausea	5.64 (3.5)	4.94 (3.7)	0.334
Diarrhea	4.63 (3.8)	2.98 (3.5)	0.029
Vomiting	2.54 (3.6)	0.30 (1.3)	<0.001
Gas	5.52 (3.6)	5.50 (3.4)	0.976

Data shown as mean (SD).

duodenal aspiration alone. Of these, 5/48 (10.4%) patients without colectomy tested positive for SIBO.

Duodenal aspirate/culture

In the colectomy group, 35 patients had duodenal aspirates performed, of whom 20/35 (57.1%) had SIBO. In the control group, 32 patients had duodenal aspirates of whom 12/32 (37.5%) had SIBO. In the colectomy group, 14/20 (70%) patients had >10³ CFU/mL and 6/20 (30%) patients had >10⁵ CFU/mL. In the control group, 10/12 (83%) patients had >10³ CFU/mL and 2/12 (17%) patients had >10⁵ CFU/mL. There was no difference (p = 0.8) between groups. Duodenal cultures grew a variety of organisms that are summarized in Table 2. There was significantly greater (p = 0.008) prevalence of aerobic organisms (45% vs 17%) including primarily *Streptococcus species*, *Escherichia coli*, *Klebsiella pneumoniae* in patients with colectomy compared to controls. With regards to the anaerobic organisms, the prevalence was 40% vs 58%, and with regards to mixed aerobic and anaerobic organisms, the prevalence was lower in the colectomy group at 15% vs 25%, when compared to the control group, (p = 0.008; Fig. 1).

Prevalence of SIBO/SIFO

The overall prevalence of SIBO (positive GBT or positive duodenal aspirate) was significantly higher (p = 0.005) in the colectomy group when compared to controls (62% vs 32%; Fig. 2). Table 3 summarizes our data on the prevalence of SIBO based on GBT, duodenal cultures or both. In addition, in the colectomy group 12/50 (24%) had SIBO and SIFO compared to 4/50 (8%) in those without colectomy (p = 0.017). The overall prevalence of SIFO was also higher in the colectomy group compared to controls but this finding was not significant (28% vs 12%;

Table 2 Duodenal culture results in colectomy patients versus controls

	Colectomy	Controls
Culture results (≥10 ³ CFU/mL)	N = 35 (%)	N = 19 (%)
Streptococcus species	8 (23)	5 (26)
Escherichia coli	4 (11)	1 (5)
Klebsiella pneumoniae	4 (11)	2 (11)
Staphylococcus aureus	2 (6)	0 (0)
Lactobacilli	3 (9)	1 (5)
Citrobacter	1 (3)	0 (0)
Neisseria	1 (3)	1 (5)
Rothia species	1 (3)	0 (0)
Coryneform	1 (3)	0 (0)
Bacteroides	2 (6)	0 (0)
Peptostreptococcus	1 (3)	0 (0)
Anaerobic Gram-positive cocci	2 (6)	0 (0)
Anaerobic Gram-negative bacilli	1 (3)	0 (0)
Veillonella	1 (3)	3 (16)
Diphtheroids	0 (0)	1 (5)
Microaerophilic streptococci	0 (0)	1 (5)
Stenotrophomonas maltophilia	0 (0)	1 (5)
Haemophilus influenzae	0 (0)	1 (5)
Coagulase-negative staphylococci	0 (0)	1 (5)
Serratia marcescens	0 (0)	1 (5)
Others ^a	3 (9)	0 (0)

^a Reported as multiple anaerobic gram-positive and gram-negative organisms

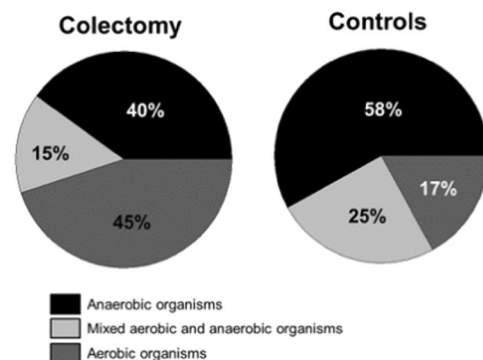


Fig. 1 The prevalence of aerobic and/or anaerobic organisms in patients with colectomy compared to controls

p = 0.08; Fig. 2). Moreover, two patients in each group had SIFO alone. Most (61%) grew *Candida albicans* and a smaller percentage (39%) grew *Candida glabrata*.

Furthermore, we found that the prevalence of SIBO/SIFO was not influenced by those with or without a history of slow-transit constipation ($p = 0.94$), and the presence/absence of IC valve ($p = 0.26$).

Effects of antibiotic/antifungal treatment on gastrointestinal symptoms

Patients who received antibiotics reported significant improvement in the prevalence and severity of gastrointestinal symptoms when compared to their baseline symptoms, both in the colectomy group (Table 4a), and in the control group (Table 4b). The following antibiotics were prescribed for SIBO based on the microbial sensitivity and the patients’ allergy profile: Rifaximin, Amoxicillin, Amoxicillin-Clavulanate, Cotrimoxazole, Cephalosporin, Metronidazole, Tinidazole, Ciprofloxacin, Levofloxacin and Tetracycline. Oral Fluconazole and very rarely Itraconazole was given for treatment of SIFO. In the colectomy group, of the 2 patients with SIFO only, one reported 70% improvement and the other no improvement. Likewise, in the control group, of the 2 patients with SIFO only, one reported 33% improvement and the

other 50% improvement. During follow up, overall 74% and 69% of patients with SIBO/SIFO in the colectomy and control groups respectively ($p = 0.69$), reported improvement in symptoms, and on a VAS scale, overall gastrointestinal symptom satisfaction after treatment averaged a rating of 61% for the colectomy group and 42% for controls (0 = very dissatisfied, 100 = completely satisfied).

Discussion

Over a 3-year period, we investigated a consecutive series of patients referred to our tertiary care center with refractory gastrointestinal symptoms including abdominal pain, gas, bloating, distension and diarrhea, following colectomy. In this colectomy group, we found a significant and two-fold higher prevalence of SIBO (62%) when compared to a control group of patients with similar chronic gastrointestinal complaints but without colectomy (32%). We also found significant differences in the type of bacterial flora, with a predominance of aerobic bacterial organisms and fewer anaerobic organisms in post-colectomy SIBO patients when compared to the controls. The duodenal cultures grew a variety of organisms including primarily *Streptococcus species*, *Escherichia coli*, *Klebsiella pneumoniae* and *Lactobacilli*.

In addition, we found a higher prevalence of small intestinal fungal overgrowth (SIFO) in patients with colectomy when compared to the control patients. The most common fungus that was cultured was candida species. This finding reaffirms recent studies that SIFO is another important component of the small intestinal overgrowth syndromes¹⁹. A recent article showed that fungus may co-exist and interact with bacteria in the gut and form fungal–bacterial biofilms in the GI tract²⁰. Further studies are required to explore the role of fungus in overgrowth syndromes, and in particular whether they are co-pathogens and cause greater morbidity as opposed to either SIBO or SIFO alone.

The glucose breath test is a simple, widely available and non-invasive method of diagnosis of SIBO, and it

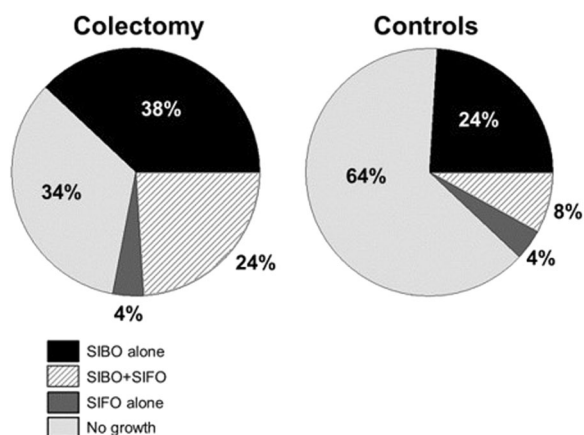


Fig. 2 The prevalence of SIBO and/or SIFO in patients with colectomy and controls without colectomy

Table 3 Diagnostic yield of Glucose Breath Test (GBT) and Duodenal Aspirate/Culture (DA) in patients with colectomy and controls

	GBT only	DA only	GBT+/DA+	GBT+/DA-	GBT-/DA+	GBT-/DA-
<i>Colectomy, N = 50</i>						
SIBO+, N = 31	8	2	10	3	8	0
SIBO-, N = 19	12	0	0	0	0	7
<i>Controls, N = 50</i>						
SIBO+, N = 16	2	1	1	2	10	0
SIBO-, N = 34	16	1	0	0	0	17

DA duodenal aspirate and culture, GBT glucose breath test, SIBO small intestinal bacterial overgrowth, + positive test, - negative test

Table 4a Symptom prevalence and severity score before and after treatment in the colectomy group

SIBO (N = 19)				SIBO/SIFO (N = 12)		
Symptoms	Prevalence	Severity	Improvement	Prevalence	Severity	Improvement
Abdominal pain	100%	7.7	53%	92%	6.8	40%
Belching	61%	3.6	33%	83%	4.2	48%
Bloating	94%	6.4	44%	100%	7.5	47%
Fullness	83%	6.1	41%	92%	7.5	48%
Indigestion	67%	4.0	45%	92%	6.7	49%
Nausea	78%	5.6	41%	92%	7.8	53%
Diarrhea	78%	5.8	26%	83%	5.7	34%
Vomiting	28%	1.6	56%	42%	3.0	67%
Gas	83%	6.0	45%	100%	6.3	41%

Table 4b Symptom prevalence and severity score before and after treatment in the control group

SIBO (N = 12)				SIBO/SIFO (N = 4)		
Symptoms	Prevalence	Severity	Improvement	Prevalence	Severity	Improvement
Abdominal pain	100%	7.1	31%	100%	8.3	44%
Belching	64%	4.5	46%	75%	3.7	45%
Bloating	91%	7.1	31%	100%	8.7	54%
Fullness	100%	6.5	21%	100%	8.7	58%
Indigestion	73%	4.9	30%	75%	5.7	47%
Nausea	91%	5.4	26%	100%	7.7	48%
Diarrhea	45%	3.2	34%	100%	7.3	59%
Vomiting	0%	0.0	NA	0%	0.0	NA
Gas	40%	6.4	30%	75%	5.3	43%

was positive in 44% of patients with colectomy and 11% of patients without colectomy. Although specific, GBT has low sensitivity for diagnosis of SIBO^{6,8,16}. Consequently, if the GBT is negative, and there is a high index of clinical suspicion for SIBO, such as in the post-colectomy population, further testing with duodenal aspiration and quantitative culture should be considered. This study further confirms previous observations that duodenal culture has a higher yield for diagnosis of SIBO/SIFO than GBT^{8,16}. All patients diagnosed with SIBO and/or SIFO should be treated with antibiotics and/or antifungals and are likely to benefit symptomatically as observed in our study. Also, the improvement in symptoms of SIBO observed here is similar to those reported in other studies of SIBO treatment with antibiotics such as norfloxacin and rifaximin^{21–23}.

Colectomy combined with ileocolonic anastomosis has become the procedure of choice in the surgical management of colon cancer, refractory constipation, ulcerative colitis, familial polyposis and others^{24–28}. Morphological studies have shown that the adaptation of the terminal ileum to its neorectum function is accompanied by a progressive transformation to a colonic type mucosa²⁹. Typically, the bacterial fermentation of both the endogenous mucus and the undigested carbohydrates normally occurs in the large intestine resulting in short chain fatty acids (SCFAs), carbon dioxide, hydrogen, and methane³⁰. However, in patients with SIBO, this process occurs prematurely in the small bowel causing gas, bloating, distention and diarrhea, symptoms that are often mislabeled as IBS³¹.

The ileocecal valve serves as an important barrier and gatekeeper that prevents reflux of colonic contents into

the small bowel. In contrast, conditions that favor low ileocecal valve pressure or loss of the ileocecal barrier, such as following colectomy and construction of an ileocolonic anastomosis, may allow transmigration of bacteria from the colon and predispose patients to the development of SIBO^{32,33}.

Can symptoms alone help with a diagnosis of SIBO? Our detailed analyses revealed that no single symptom or clusters of symptoms at baseline could identify patients who have SIBO. Interestingly, patients with SIFO also share a similar set of symptoms as those with SIBO. Furthermore, symptoms alone could not differentiate between patients with or without colectomy at baseline, or between those with positive and negative SIBO/SIFO. Thus, the two groups were well matched for symptom presentation, but symptoms alone were poor predictors for the presence of bacterial and/or fungal overgrowth, irrespective of the underlying predisposing mechanism.

The limitations of our study include the secondary analysis of prospectively collected data and potential referral bias, since all of these patients were evaluated at a tertiary care gastrointestinal motility center. Consequently, our observations may not reflect the prevalence of this condition in the general population. Also, there is no gold standard for the diagnosis of SIBO/SIFO, and our method of aspiration and quantitative culture cannot definitively exclude the risk of contamination of aspirates. However, we have tried to minimize this by using standard sterile techniques, and the procedure was performed by a single experienced operator. Also, we did not repeat the breath test or aspirate after treatment as the study was not designed for this purpose. The treatment with appropriate antibiotics and/or antifungals was based on breath test results, culture positivity, patients' drug allergy profile, and insurance coverage and previous antibiotic use, and not with a single drug, as this was a non-randomized treatment study. The significant improvement in symptoms however, after antibiotics and antifungals, support the likely causal association with SIBO/SIFO.

In conclusion, our study demonstrates a significantly higher prevalence of SIBO/SIFO in a cohort of patients with colectomy and chronic unexplained gastrointestinal symptoms. This finding implies that colectomy is a significant risk factor for the development of SIBO/SIFO. Although patients with colectomy had greater baseline severity of symptoms, by themselves they were poor predictors of SIBO/SIFO. Therefore, the use of breath tests and/or duodenal aspirate/culture is essential for confirming a diagnosis of SIBO/SIFO. Treatment with antibiotics and/or antifungals led to significant improvement of symptoms in these patients.

Study Highlights

What Is Current Knowledge

- Colectomy is a common surgical procedure. About 40% of patients undergoing subtotal colectomy report persistent gastrointestinal symptoms and an impaired quality of life.
- The underlying cause for these symptoms is unclear.

What Is New Here

- The prevalence of SIBO/SIFO is significantly higher in patients with unexplained gastrointestinal symptoms following colectomy when compared to controls.
- Colectomy with ileocolonic anastomosis is a significant risk factor for the development of SIBO/SIFO.
- Symptoms alone are poor predictors of SIBO/SIFO, and breath tests and/or duodenal aspirate/culture is key for establishing this diagnosis.
- Treatment with antibiotics and/or antifungals results in significant improvement of symptoms.

Acknowledgements

We sincerely thank H. Smith for superb secretarial assistance and Collier Badger and Arie Mack for assistance with breath tests and Nicole Martinez De Andino with patient assessment.

Conflict of interest

Guarantor of the article: Satish S.C. Rao, MD., Ph.D., FRCP (LON).

Specific author contributions: Satish SC Rao—Study concept and design, performing duodenal aspiration, breath test interpretations, data acquisition, data collection, study recruitment, data analysis and interpretation, manuscript preparation, critical revision, and important intellectual content and final approval. G. Tan, MD: Data collection and analysis of controls, manuscript preparation. H. Abdulla, MD: Data collection, data analysis and interpretation, manuscript preparation. S. Yu, MD: Study recruitment, Interpretation breath tests, IRB, Data analysis and interpretation, manuscript preparation. P. Leelasinjaroen, MD: Data collection and analysis, manuscript preparation. S. Larion, MD: Data analysis and statistics, manuscript preparation. All authors are affiliated and located at Augusta University and all authors have approved the final draft submitted.

Financial support: none.

Potential competing interest: none.

Received: 28 September 2017 Revised: 26 January 2018 Accepted: 6 February 2018

Published online: 25 April 2018

References

1. Agency for Healthcare Research and Quality (AHRQ): HCUPnet: healthcare cost and utilization project. Rockville, MD: AHRQ, <http://hcupnet.ahrq.gov/>. Accessed 2 August 2017.
2. Knowles, C. H., Scott, M. & Lunniss, P. J. Outcome of colectomy for slow transit constipation. *Ann. Surg.* **230**, 627–638 (1999).

3. Singh, S., Heady, S., Coss-Adame, E. & Rao, S. S. C. Clinical utility of colonic manometry in slow transit constipation. *Neurogastro Motil.* **25**, 487–495 (2013).
4. Grace, E., Shaw, C., Whelan, K. & Andreyev, H. J. N. Review article: small intestinal bacterial overgrowth – prevalence, clinical features, current and developing diagnostic tests and treatment. *Aliment. Pharmacol. Ther.* **38**, 674–688 (2013).
5. Khoshini, R., Dai, S. D., Lezcano, S. & Pimental, M. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. *Dig. Dis. Sci.* **53**, 1443–1454 (2008).
6. Rezaei, A. et al. Hydrogen and methane-based breath testing in gastrointestinal disorders: the north american consensus. *Am. J. Gastroenterol.* **112**, 775–784 (2017).
7. Erdogan, A., Lee, Y., Sifuentes, H. & Rao, S. S. Small intestinal fungal overgrowth (SIFO): a cause of gastrointestinal symptoms. *Gastroenterology* **146**, S358 (2014).
8. Jacobs, C., Coss Adame, E., Attaluri, A. & Rao, S. S. C. Dysmotility and proton pump inhibitor use are independent risk factors for small intestinal bacterial and/or fungal overgrowth. *Alim Pharmacol. Ther.* **37**, 1103–1111 (2013).
9. Justus, P. G. et al. Altered myoelectric activity in the experimental blind loop syndrome. *J. Clin. Invest.* **72**, 1064–1071 (1983).
10. Dawson, A. M. & Isselbacher, K. J. Studies on lipid metabolism in the small intestine with observations on the role of bile salts. *J. Clin. Invest.* **39**, 730–740 (1960).
11. Brown, W. R. Relationships between immunoglobulins and the intestinal epithelium. *Gastroenterology* **75**, 129–138 (1978).
12. Phillips, S. F., Quigley, E. M., Kumar, D. & Kamath, P. S. Motility of the ileocolonic junction. *Gut* **29**, 390–406 (1988).
13. Sachdev, A. H. & Pimentel, M. Gastrointestinal bacterial overgrowth: pathogenesis and clinical significance. *Ther. Adv. Chronic Dis.* **4**, 223–231 (2013).
14. Tan, A. H. et al. Small intestinal bacterial overgrowth in Parkinson's disease. *Parkinsonism Relat. Disord.* **20**, 535–540 (2014).
15. Choi, Y., Kraft, N., Zimmerman, B., Jackson, M. & Rao, S. Fructose intolerance in IBS and utility of fructose-restricted diet. *J. Clin. Gastroenterol.* **42**, 233–238 (2008).
16. Erdogan, A. et al. Small intestinal bacterial overgrowth: duodenal aspiration vs glucose breath test. *Neurogastroenterol. Motil.* **27**, 481–489 (2015).
17. Erdogan, A. et al. What is the optimal threshold for an increase in hydrogen and methane levels with glucose breath test (GBT) for detection of small intestinal bacterial overgrowth (SIBO)? *Gastroenterology* **146**, S532 (2014).
18. Rezaei, A., Pimental, M. & Rao, S. How to test and treat small intestinal bacterial overgrowth: an evidence-based approach. *Curr. Gastroenterol. Rep.* **18**, 81–11 (2016).
19. Erdogan, A. & Rao, S. S. Small intestinal fungal overgrowth. *Curr. Gastroenterol. Rep.* **17**, 16.1–7 (2015).
20. Sam, Q. H., Chang, M. W. & Chai, L. Y. A. The fungal microbiome and its interaction with gut bacteria in the host. *Int. J. Mol. Sci.* **18**, 330–341 (2017).
21. Ghoshal, U. C., Baba, C. S. & Ghoshal, U. Low-grade small intestinal bacterial overgrowth is common in patients with non-alcoholic steatohepatitis on quantitative jejunal aspirate culture. *Indian J. Gastroenterol.* **36**, 390–399 (2017).
22. Ghoshal, U. C., Mittal, B. & Singh, R. Functional dyspepsia is associated with $GN\beta_3$ C825T and CCK-AR T/C polymorphism. *Eur. J. Gastroenterol. Hepatol.* **28**, 226–232 (2016).
23. Gatta, L. & Scarpignato, C. Systematic review with meta-analysis: rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth. *Aliment. Pharmacol. Ther.* **45**, 604–616 (2017).
24. Liu, Z. et al. Ileocolonic anastomosis after right hemicolectomy for colon cancer: functional end-to-end or end-to-side? *World J. Surg. Oncol.* **12**, 306 (2014). (ISSN: 1477-7819).
25. Nyam, D. C., Pemberton, J. H., Ilstrup, D. M. & Rath, D. M. Long-term results of surgery for chronic constipation. *Dis. Colon. Rectum* **40**, 273–279 (1997).
26. Wofford, S. A. & Verne, G. N. Approach to patients with refractory constipation. *Curr. Gastroenterol. Rep.* **2**, 389–394 (2000).
27. da Luz Moreira, A., Kiran, R. P. & Lavery, I. Clinical outcomes of ileorectal anastomosis for ulcerative colitis. *Br. J. Surg.* **97**, 65–69 (2010).
28. Nieuwenhuis, M. H. et al. Genotype-phenotype correlations as a guide in the management of familial adenomatous polyposis. *Clin. Gastroenterol. Hepatol.* **5**, 374–378 (2007).
29. Lerch, M. M. Postoperative adaptation of the small intestine after total colectomy and J-pouch-anal anastomosis. *Dis. Colon. Rectum* **32**, 600–608 (1989).
30. Cummings, J. H. et al. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut* **28**, 1221–1227 (1987).
31. Ringel-Kulka, T. et al. Altered colonic bacterial fermentation as a potential pathophysiological factor in irritable bowel syndrome. *Am. J. Gastroenterol.* **110**, 1339–1346 (2015).
32. Miller, L. S. et al. Ileocecal valve dysfunction in small intestinal bacterial overgrowth: a pilot study. *World J. Gastroenterol.* **18**, 6801–6808 (2012).
33. Roland, B. C. et al. Low ileocecal valve pressure is significantly associated with small intestinal bacterial overgrowth (SIBO). *Dig. Dis. Sci.* **59**, 1269–1277 (2014).