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Small Intestinal Bacterial Overgrowth in Patients with Interstitial Cystitis and Gastrointestinal Symptoms

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Abstract *Purpose* Interstitial cystitis (IC) often coexists with irritable bowel syndrome (IBS). IBS may be explained by small-intestinal bacterial overgrowth (SIBO), which increases immune activation and visceral hypersensitivity. This prospective pilot study tested hypotheses that IC patients with gastrointestinal (GI) symptoms have SIBO, that nonabsorbable antibiotic use improves symptoms, and that improvement is sustained by prokinetic therapy. *Methods* Consecutive IC patients with GI symptoms had lactulose breath testing (LBT). Those with abnormal results received rifaximin 1,200–1,800 mg/day for 10 days then tegaserod 3 mg/nightly. Questionnaires addressed IC and GI global improvement. *Results* Of 21 patients, 17 (81%) had abnormal LBTs. Of 15 patients treated, GI global improvement was moderate to great in 11 (73%) and sustained in ten (67%). IC global improvement was moderate to great in six (40%) and sustained in seven (47%). *Conclusions* A majority of IC patients and GI symptoms had an abnormal LBT suggesting SIBO. Rifaximin improved symptoms, which was sustained by tegaserod.

Keywords SIBO · Interstitial cystitis · IBS · Rifaximin

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Introduction

Interstitial cystitis (IC) is a debilitating, chronic syndrome of unknown etiology characterized by pelvic pain, increased urinary frequency, abnormal urgency to void, and dyspareunia [1]. By convention, IC is viewed as a disorder that coexists with irritable bowel syndrome (IBS). In a survey of 2,405 patients with IC, IBS was the second most commonly listed medical condition other than allergies [2]. These two conditions may share common pathophysiology, as IC is present in 40–60% of patients with IBS, and 38% of patients with IC also have IBS [1, 3]. Inflammatory cells, cytokines, substance P, neural growth factor, and neural plasticity are possible explanations for visceral hypersensitivity in both syndromes [4–9].

Evidence is now available to support the role and treatment of small-intestinal bacterial overgrowth (SIBO) in IBS [3, 10–12]. SIBO is an abnormal expansion of the indigenous bacterial population of the distal gut into the more proximal regions of the small intestine. Abnormal bacterial fermentation, a basic feature of SIBO, can be detected using the lactulose breath test (LBT). Three randomized, placebo-controlled, double-blind studies have shown significant improvement of IBS symptoms after treatment with neomycin [11], a poorly absorbed antibiotic, and rifaximin, a nonabsorbable antibiotic that spares the colonic bacterial flora to target those in the small intestine [12, 13]. As maximal improvement occurred when abnormal bacterial fermentation was successfully eliminated by antibiotic treatment [11, 12, 14], SIBO appears to be the best explanation for the gastrointestinal (GI) symptoms of IBS (3).

Bacterial overgrowth is associated with increased intestinal permeability [15], bacterial translocation with exposure to bacterial antigens [16], and subsequent

activation of the host immune response [17]. Evidence for immune activation in IBS and IC include the following: (1) mast cells in bladder biopsies in IC [18]; (2) mast cells in the ileum, mast cells adjacent to colonic nerves, and lymphocytes in lamina propria and the myenteric plexus in IBS [6, 7, 19]; and (3) interleukin elevation in urine in IC [20] and in serum in IBS [21].

In one study, patients with IC had a mild response to broad-spectrum antibiotics despite sterile urine cultures, suggesting a possible role of bacteria in this condition [22]. In our pilot study, we tested two hypotheses: (1) IC patients with chronic GI symptoms have abnormal bacterial fermentation that suggests SIBO; and (2) a nonabsorbable, effective, small-intestine-targeting antibiotic improves IC and GI symptoms, with subsequent prokinetic therapy sustaining clinical improvement. Tegaserod, a 5-HT4 receptor agonist known to stimulate phase 3 of interdigestive motility [23], was used to delay relapse of bacterial overgrowth and, thus, treat the underlying cause of SIBO [24–26].

Methods

General design

This was a prospective, open-label, observational pilot study of patients with IC and chronic GI symptoms. The primary goal was to examine the effect of a nonabsorbable, small-intestine-targeting antibiotic treatment on GI and IC symptoms. An LBT was used to detect abnormal bacterial fermentation, considered indirect evidence of SIBO. Study procedures were approved by the Sterling Institutional Review Board (Atlanta, GA, USA).

Study population

Consecutive patients with IC and chronic GI symptoms ($n = 44$) seen in follow-up visits over a 4-month period at a urology practice at Washington University were referred to the gastroenterology practice conducting the study. To be eligible, patients with IC must have had chronic, active, unexplained GI symptoms, including abdominal pain, bloating, postprandial fullness, flatulence, diarrhea, and/or constipation, for at least 3 months. The IC diagnosis was based on a history of pelvic pain, urinary frequency, and urinary urgency, with other urological diseases excluded by a prior cystoscopy and urine culture. Patients were excluded if they had an active organic GI disease, including celiac disease, pancreatic insufficiency, Crohn's disease, and ulcerative colitis, on the basis of medical history, physical exams, antitissue transglutaminase antibody for celiac disease, and a review of colonoscopy records at study entry.

LBT

Breath samples were collected before ingestion of 10 g of lactulose (Kristalose, Cumberland Pharmaceuticals Inc., Nashville, TN, USA) and every 20 min for 180 min thereafter. This is a nondigestible starch in 240 ml water. Breath samples were analyzed for concentrations of hydrogen and methane using a gas chromatograph (QuinTron DP plus, QuinTron Instrument Company, Milwaukee, WI, USA). The criteria for a normal pattern of bacterial fermentation were "no rise of breath hydrogen or methane concentration before 90 min of lactulose intake with a definitive rise never more than 20 ppm during 180-min measurement" [10]. As hydrogen and methane are produced exclusively by bacteria, abnormal bacterial fermentation is detected when the pattern of gas excretion is different from the criteria for normal bacterial fermentation. Examples of criteria for abnormal bacterial fermentation include a gas profile with a rise in hydrogen and/or methane concentration of more than 20 ppm above baseline during the 180-min breath test or a flat-line hydrogen profile with a rise of no more than 5 ppm of hydrogen over baseline for 180 min and absence of methane excretion.

Open-label treatment

If patients had SIBO, determined by detection of abnormal bacterial fermentation, they were offered treatment with rifaximin (Xifaxan; Salix Pharmaceuticals, Inc., Morrisville, NC, USA) 1,200 or 1,800 mg/day for 10 days. The higher dose was administered to patients with a flat-line response or those with a hydrogen rise greater than 60 ppm. As SIBO is characterized by a chronic relapsing clinical course and impaired cycling of interdigestive motility [25], time to relapse was delayed by prescribing tegaserod (Zelnorm; Novartis Pharmaceuticals Corp., East Hanover, NJ, USA) 3 mg nightly following completion of the rifaximin course.

Symptom questionnaires

At baseline, eligible patients completed a GI symptom questionnaire using a 7-point Likert scale consisting of 0 not at all; 1 hardly; 2 somewhat; 3 moderately; 4 a good deal; 5 a great deal; and 6 a very great deal. Responses to these questionnaires were used to determine activity and

subsequent change of GI symptoms with treatment and to identify the predominant bowel complaint according to the Rome II classification for IBS. Patients completed a questionnaire on which they were asked to describe their global response (greatly improved, moderately improved, mildly improved, or no improvement) of IC and GI symptoms after completing a 10-day course of rifaximin and at follow-up at least 2 months later. The follow-up marked the conclusion of the observational period for each patient. Duration of IC symptoms and the timing of onset of bladder and GI symptoms were also assessed. In addition, the presence of comorbid conditions of fibromyalgia and restless legs syndrome was determined.

Data analysis

The primary endpoints were the percentage of patients with an abnormal LBT result and the percentage of patients with moderately or greatly improved global symptoms immediately after antibiotics (day 11) and at the follow-up visit. Descriptive statistics were used to summarize data for patients with baseline and follow-up data. Comparisons were made using the Wilcoxon signed ranks test (SPSS).

Results

Patient demographics

Twenty-one women with IC (mean age 49 years; range 19–81 years) were included. Mean IC duration was 7 (range 1–20) years. In 13 patients, IC symptoms started after GI symptoms. In six patients, IC symptoms started before GI symptoms. In the remaining two patients, the order of onset was unknown. Seventeen (81%) of the 21 patients with IC and GI symptoms had an abnormal LBT result. Of these 17 patients, an elevated peak hydrogen concentration was found in 11 (65%), with a mean rise of 43 ppm above baseline and mean time to peak of 128 min. Elevated methane was found in one patient. Five (29%) of 17 patients had a flat-line hydrogen profile with a mean hydrogen rise of 3 ppm. Fifteen of these 17 patients with abnormal LBT results received rifaximin for the treatment of SIBO.

Functional bowel symptoms of 17 of 21 patients met Rome II criteria for IBS. In this group of 17, 14 (82%) had an abnormal LBT result. Three patients had diarrhea, eight patients had constipation, and six had both diarrhea and constipation. Four of five patients with a flat-line hydrogen profile had diarrhea. Only one patient had detectable methane excretion, and she had constipation. Fibromyalgia was present in four patients, restless legs syndrome was present in four patients, and one patient had both fibromyalgia and restless legs syndrome.

Table 1 Gastrointestinal symptom response to small intestinal bacterial overgrowth (SIBO) therapy ($n = 15$)[a]

	Symptom			
	Pain	Bloating	Fullness	Flatulence
Baseline, mean ± SD	4.1 ± 2.0	4.7 ± 1.3	4.2 ± 1.7	4.6 ± 1.5
Follow-up (mean 122 days), mean ± SD	3.1 ± 1.8	3.3 ± 1.7	2.7 ± 1.8	3.0 ± 1.4
Comparison[b]	$P < 0.05$	$P = 0.005$	$P < 0.05$	$P < 0.01$

SD standard deviation, *SIBO* small intestinal bacterial overgrowth

[a] Scores according to Likert scale of 0–6; [b] Comparison based on Wilcoxon signed rank test

Table 2 Global improvement of interstitial cystitis (IC) and gastrointestinal (GI) symptoms

	Improvement *n*			
	Great	Moderate	Mild	None
IC				
Day 11	4	2	6	3
Follow-up (mean, 122 days)	2	5	5	3
GI				
Day 11	6	5	3	1
Follow-up (mean, 122 days)	4	6	4	1

Symptom improvement

For the 15 patients treated for SIBO, GI questionnaire scores for abdominal pain, bloating, fullness after meals, and flatulence significantly improved (Table 1). Global improvement of GI symptoms was moderate or great in 11 patients (73%) immediately after completion of a 10-day course of rifaximin (Table 2). This degree of symptomatic improvement was sustained in ten patients (67%) over a mean follow-up period of 122 (range 62–162) days. Global improvement of IC symptoms immediately after rifaximin treatment was moderate or great in six patients (40%; Table 2), with mild global IC improvement in six patients (40%). At the follow-up visit, seven patients (47%) had moderately or greatly improved IC status (Tables 2 and 3).

Discussion

In this open-label pilot study of patients with IC and functional GI symptoms, 17 (81%) of 21 patients had abnormal bacterial fermentation, suggesting the presence

Table 3 Clinical response to therapy and clinical variables

Patient initials	LBT result	Peak H_2 ppm	RFX/d (mg/day)	Global IC change at day 11	Global GI change at day 11	Global IC change at follow-up	Global GI change at follow-up
AD	H_2 high	44	1,800	Great	Great	Great	Great
NS	H_2 high	26	1,800	Great	Great	Moderate	Great
BS-1	H_2 high	115	1,800	None	Moderate	Moderate	Moderate
KR	H_2 high	82	1,800	Moderate	Moderate	Mild	Mild
RF	H_2 high	36	1,200	Moderate	Great	Great	Great
BS-2	H_2 high	25	1,200	Mild	Moderate	Mild	Great
GB	H_2 high	28	1,200	None	Great	None	Moderate
JH	H_2 high	24	1,200	Mild	None	Moderate	Moderate
CBK	H_2 high	28	1,200	Mild	Mild	Mild	Mild
NM	Methane	NA	1,200	Mild	Mild	Mild	Mild
EP	Flat line	NA	1,800	Great	Great	None	None
NM	Flat line	NA	1,800	Great	Moderate	Moderate	Moderate
AB	Flat line	NA	1,800	Mild	Great	Moderate	Moderate
GJ	Flat line	NA	1,800	None	Moderate	None	Moderate
ED	Flat line	NA	1,800	Mild	Mild	None	Mild

LBT lactulose breath testing, *H_2* hydrogen, *RFX* rifaximin, *IC* interstitial cystitis, *GI* gastrointestinal, *NA* not available

of SIBO. Fifteen of these 17 patients with an abnormal LBT result received a 10-day course of rifaximin, a non-absorbable, small-intestine-targeting antibiotic. At day 11, six (40%) of 15 patients reported moderate to great improvement in IC symptoms and another 40% reported mild improvement. Of the 15 patients, 73% reported moderate to great improvement of GI symptoms at day 11. As rifaximin is a nonabsorbable antibiotic that is not associated with a detectable change in the colonic (or urologic) bacterial flora [27], an antibiotic-sensitive mechanism located in the small intestine appears to be partly responsible for the IC and GI symptoms of these patients. As this observational study used open-label treatment and a generalized, nonvalidated questionnaire, confirmation of these results with a randomized, double-blind, placebo-controlled trial is necessary. Because of the complex nature of IC, it is unlikely that a single therapy targeting one aspect of this disorder will result in a complete response for all patients.

The breath-test patterns seen in this study are suggestive of excess hydrogen sulfide gas production. Only one (6%) of 17 patients with IC and positive LBT results exhaled methane, in contrast with earlier studies of 254 patients with IBS and 85 patients with functional bowel syndrome (who did not have IC as their primary diagnosis), in whom methane was detected in 26% of all abnormal breath-test results in each group [25, 26]. In this study, five (29%) of 17 patients with positive LBT results had flat-line test results in contrast with flat-line results in 6% of patients with IBS and positive LBT results and 2% of patients with functional bowel syndrome and positive LBT results found in previous studies [25, 26]. In the past, a flat-line hydrogen pattern was attributed to the presence of "hydrogen non-producer" flora [28], but this is inconsistent with the fact that hydrogen producers, including Bacteroidetes and Firmicutes, represent >90% of the gut flora [29]. The dynamics of hydrogen generation and removal within the intestinal lumen may explain the flat-line phenomenon. Bacteria ferment nutrients, which produce hydrogen, and then the partial pressure of this gas rises in the lumen. In order to facilitate further fermentation, hydrogen must be removed from the gut by one or more of the following: (1) absorption into the mucosa with transportation to and elimination by the lungs; (2) passage of gas to the distal gut and elimination as flatus; and (3) conversion to methane by methanogenic microbes, conversion to hydrogen sulfide by sulfate-reducing bacteria, and rarely conversion to acetate by an acetogenic pathway [30]. Gas conversion pathways are competitive processes, and hydrogen sulfide is not produced in individuals excreting methane [30]. A flat-line hydrogen profile without methane excretion infers complete conversion to hydrogen sulfide. In the absence of bacterial overgrowth and excess fermentation, an efficient detoxification system in the colon [31] is able to rapidly remove this highly toxic gas [32].

With SIBO and the presence of excess sulfate-reducing bacteria, absorbed hydrogen sulfide may play local and distant roles in both IBS and IC. An association with bacteria-derived hydrogen sulfide functioning as gaseous neurotransmitters may provide an explanation for visceral hypersensitivity. In bladder tissues, hydrogen sulfide induces contraction of the detrusor muscle [33]. As this

effect is completely abolished by capsaicin desensitization or pretreatment with a combination of tachykinin NK1 and NK2 receptor antagonists, hydrogen sulfide is an activator of capsaicin-sensitive extrinsic sensory nerves and is involved in influencing neuronal sensitivity [34].

SIBO may also provide an explanation for the visceral hypersensitivity of IC and IBS by abnormal production of proinflammatory cytokines and immune-activated histological abnormalities [3, 6, 16]. The response to colorectal balloon distention has been used as a measure of visceral sensation in studies in both humans and animals [4, 35]. Bacterial antigens (lipopolysaccharides) were found to trigger GI mast-cell degranulation and visceral hypersensitivity in rats [35]. The role of bladder mast-cell degranulation in IC has been supported by elevated urinary tryptase [36] and beneficial effects of pentosan polysulfate, an inhibitor of mast-cell histamine secretion [37]. Systemic or bladder mast-cell degranulation by these factors could explain pelvic pain and altered bladder function. Increased intestinal permeability with translocation of bacteria and bacterial byproducts, food allergies, neuropeptides, and stress (via the effects of corticotropin-releasing factor) are all known triggers of GI mast-cell activation [38]. All of these factors are associated with SIBO [3]. Furthermore, animal data [39] demonstrate neuronal cross talk between the sensory nerves in the colon and bladder to provide another explanation for the overlap of IBS and IC. Finally, another link between mast cells and sensory nerves was suggested by showing that many substance-P-staining nerve fibers were in close proximity to mast cells in bladder and colonic biopsies obtained from a patient with both IC and IBS [40].

In summary, this study provides preliminary data to support the hypothesis that SIBO may be associated with IC. If excess bacteria in the small intestine were the trigger for the immune activation and visceral hypersensitivity seen in IC, then management of this vexing disorder could be dramatically improved by directing the diagnostic and treatment efforts toward SIBO. A randomized, double-blind, placebo-controlled study is currently underway to test this hypothesis.

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