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ORIGINAL ARTICLE

Double-Blind Randomized Controlled Trial of Rifaximin for Persistent Symptoms in Patients with Celiac Disease

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Abstract
Background Small intestinal bacterial overgrowth (SIBO) is one cause of a poor response to a gluten-free diet (GFD) and persistent symptoms in celiac disease. Rifaximin has been reported to improve symptoms in non-controlled trials.
Aims To determine the effect of rifaximin on gastrointestinal symptoms and lactulose-hydrogen breath tests in patients with poorly responsive celiac disease.
Methods A single-center, double-blind, randomized, controlled trial of patients with biopsy-proven celiac disease and persistent gastrointestinal symptoms despite a GFD was conducted. Patients were randomized to placebo ($n = 25$) or rifaximin ($n = 25$) 1,200 mg daily for 10 days. They completed the Gastrointestinal Symptom Rating Scale (GSRS) and underwent lactulose-hydrogen breath tests at weeks 0, 2, and 12. An abnormal breath test was defined as: (1) a rise in hydrogen of $\geq$20 parts per million (ppm) within 100 min, or (2) two peaks $\geq$20 ppm over baseline.
Results GSRS scores were unaffected by treatment with rifaximin, regardless of baseline breath tests. In a multivariable regression model, the duration of patients' gastrointestinal symptoms significantly predicted their overall GSRS scores (estimate 0.029, $p < 0.006$). According to criteria 1 and 2, respectively, SIBO was present in 55 and 8% of patients at baseline, intermittently present in 28 and 20% given placebo, and 28 and 12% given rifaximin. There was no difference in the prevalence of SIBO between placebo and treatment groups at weeks 2 and 12.
Conclusions Rifaximin does not improve patients' reporting of gastrointestinal symptoms and hydrogen breath tests do not reliably identify who will respond to antibiotic therapy.

Keywords Celiac disease · Small intestine · Clinical pharmacology · Diarrhea · Malabsorption · Microbiology · Symptom score or index

Introduction

Celiac disease is an immune-mediated enteropathy that is triggered by the ingestion of gluten. Adherence to a gluten-free diet (GFD) is the only treatment currently available [1]. However, 7–30% of patients fail to respond to a GFD and require further evaluation [2–4].

Small intestinal bacterial overgrowth (SIBO) has been demonstrated to be a potential cause of a poor response to a GFD in up to two-thirds of patients, although the exact prevalence is debated [5–9]. Jejunal aspirate culture with $>10^5$ colony-forming units per milliliter (CFU/ml) of bacteria is considered the gold standard for SIBO diagnosis, but is technically difficult to obtain and is poorly reproducible [10]. In clinical practice, SIBO is typically diagnosed using non-invasive breath testing which, depending on the type of breath test, may vary widely in sensitivity and specificity [11, 12]. Symptoms may overlap with celiac disease and include diarrhea, bloating, and

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abdominal pain. Treatment of SIBO in patients with poorly responsive celiac disease with antibiotics has been shown to be successful in alleviating symptoms in small, observational studies [6, 7, 13, 14].

Rifaximin is a rifamycin derivative that inhibits bacterial RNA synthesis. It is an ideal agent for treating SIBO as it has broad efficacy against aerobic and anaerobic bacteria, but only minimal absorption from the gastrointestinal tract and a favorable side-effect profile even at high doses [15–17].

This study seeks to evaluate symptom and breath test improvement in patients with poorly responsive celiac disease after treatment with rifaximin in a randomized, placebo-controlled trial.

Methods

Celiac disease patients with persistent symptoms despite adherence to a GFD were enrolled at the Celiac Disease Center at Columbia University between October 2006 and April 2008. Symptoms included indigestion, diarrhea, constipation, gas, bloating, abdominal pain, and cramping. Patients were eligible if they were 18 years or older, had a biopsy-proven diagnosis of celiac disease, and had persistent symptoms while on a GFD for at least 3 months, although most patients enrolled had been on a GFD for a median of 3.2 years. All patients were followed by a certified nutritionist on staff at the Celiac Disease Center with extensive experience with celiac disease. The nutritionist designed detailed, individualized diet plans for each patient and regularly reviewed food intake diaries, medications, supplements, and other potential sources of gluten. All patients enrolled in the study were considered to be strictly adherent to a GFD by both the physician and nutritionist caring for them. Patients were excluded if they were pregnant or lactating, had other gastrointestinal diagnoses (including inflammatory bowel disease, microscopic colitis, pancreatic insufficiency, giardiasis, enteropathy associated with T cell lymphoma, other causes of malabsorption), renal or hepatic insufficiency, tuberculosis or a positive tuberculin skin test and infection with other mycobacterial diseases, recently used medications over the past month that could affect gastrointestinal symptoms (including antibiotics, bismuth compounds, antispasmodics, antidiarrheal agents, antimotility agents, prokinetic agents, 5HT3 antagonists, 5HT4 agonists, immunomodulators, pancreatic supplements), or had an allergy or potential for the emergence of drug resistance to rifampicin and rifamycin compounds. Esophagogastroduodenoscopy and colonoscopy with biopsy was performed in all patients prior to enrollment in the study, either at our institution or at an outside institution. Patients on probiotics were asked to stop the medication 5 days prior to enrollment. Patients on PPIs were not excluded. The study was approved by the Columbia University Medical Center Institutional Review Board and registered at www.clinicaltrials.gov, number NCT01137955.

The study was designed as a randomized, double-blind, placebo-controlled, two-group parallel trial. Patients were randomized to receive either treatment with rifaximin 1,200 mg daily for 10 days or placebo, matched for size and color, in a 1:1 ratio. Assignment of a random subject number for rifaximin or placebo was generated in advance by Salix Pharmaceuticals who provided the study drug and placebo, and dispensed by the Columbia University Medical Center research pharmacy. The research pharmacy maintained a randomization log and patients were sequentially designated a number as they were enrolled. Patients and clinicians were blinded to the therapy until after the study was completed. The Gastrointestinal Symptom Rating Scale (GSRS), a validated seven-point questionnaire [18], was used to evaluate gastrointestinal symptoms at weeks 0, 2, and 12. The GSRS evaluates five symptom areas, including abdominal pain, reflux, indigestion, diarrhea, and constipation. Individual scores are calculated for each symptom area and the mean of the scores is used to derive an overall GSRS score. A lactulose-hydrogen breath test (Micro Direct Hydra H2) was performed at weeks 0, 2, and 12. Patients were instructed to avoid antibiotics 1 month prior to testing. The day before, the patients were placed on a dietary restriction, which excluded beans, bran, high-fiber cereals, and the night before excluded sugary sauces, salads, broccoli, pastas, ice cream, and pudding. Patients were instructed to not eat or drink after 11:00 P.M. and to brush their teeth with only water, and not paste, on the morning of the test. Patients were prohibited from cigarette smoking, sleeping, gum chewing, and exercise 1 h prior to and during testing. Patients ingested 10 g of lactulose and had breath samples taken every 20 min for 120 min. A test was considered positive using two different criteria adapted from the literature. Criteria 1 was defined as a rise in hydrogen of $\geq$20 parts per million (ppm) within 100 min [19, 20]. As patients with celiac disease may have elevated baseline hydrogen levels that could affect breath test interpretation [21], criteria 2 was defined as two peaks $\geq$20 ppm over the baseline hydrogen level within 100 min [22, 23]. A patient was considered "normal" if the breath test was normal at weeks 0, 2, 12; "intermittent SIBO" if the breath test was initially normal but later became abnormal; "persistent SIBO" if the breath test was abnormal at weeks 0, 2, 12; "non-sustained response" if the breath test was abnormal at week 0, became normal at week 2, but then became abnormal again at week 12; and "sustained response" if the breath

test was abnormal at week 0 and then remained normal at weeks 2 and 12.

Statistical Analysis

The primary outcome measured was GSRS score improvement after treatment with rifaximin compared to placebo. Hydrogen breath test improvement was measured as a secondary outcome. Demographic and baseline clinical characteristics were analyzed using Mann–Whitney–Wilcoxon tests for continuous measures that were not normally distributed and Chi-square tests for categorical measures. Differences in GSRS scores between groups (rifaximin versus placebo) were measured using *t* tests. Breath test data were analyzed using Chi square tests. A two-tailed alpha level of 0.05 was considered significant. Analysis was performed and reported as intention-to-treat. We estimated that $n = 22$ per group would have 90% power to detect a difference of 0.3 points from the GSRS score and based on an attrition rate of 10–15% we enrolled $n = 25$ subjects to each group. All analyses were performed using SAS software (SAS Institute, Cary, NC, Version 9.1).

Results

Participants

Fifty patients were enrolled and randomized to either rifaximin or placebo. Completion of the study was achieved by 21 patients in the placebo group and 20 patients in the treatment group. Dropouts occurred at weeks 0 ($n = 1$), 2 ($n = 5$), and 12 ($n = 3$), primarily for non-adherence to medication or study visits (Fig. 1). The mean age was 42.7 (range 20–75) years and the majority of participants, 68%, were female. On average, patients had been on a GFD for 3.8 years. The placebo and rifaximin groups were similar in age, sex, and other baseline characteristics (Table 1). Participants tolerated the study medications without any complications.

Gastrointestinal Symptom Scores

Overall GSRS scores were similar between placebo versus rifaximin groups at baseline. There were no significant differences in GSRS symptom specific scores (abdominal pain, reflux, indigestion, diarrhea, and constipation) found between rifaximin and placebo groups at weeks 2 and 12 (Table 2). After stratifying for the presence of SIBO at baseline, there was no difference in terms of GSRS scores between the placebo and rifaximin groups (data not shown).

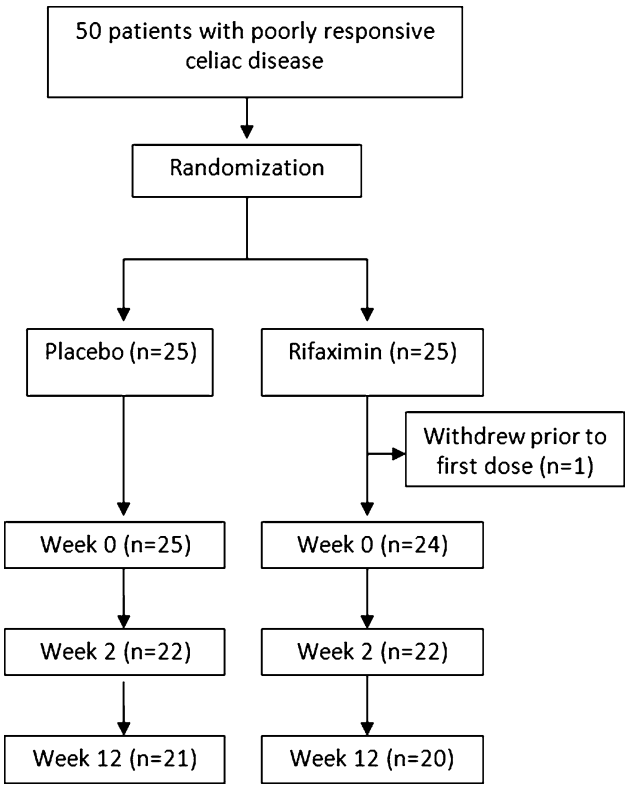

Fig. 1 Flow diagram of patients in each phase of the study

In a multivariable regression model, the number of years a patient had gastrointestinal symptoms was found to be a significant predictor of overall GSRS scores (estimate 0.029, $p < 0.006$), when controlling for treatment group, length of time with a diagnosis of celiac disease (in years), and duration on a GFD (in years). In a model examining GSRS sub-scores, the duration of gastrointestinal symptoms also significantly predicted GSRS reflux (estimate 0.057, $p < 0.0001$) and indigestion scores (estimate 0.029, $p < 0.04$). Additionally, while all patients in the study were adherent to a GFD, the longer amount of time that a patient had been on a GFD, the more likely it was for the patient to have lower GSRS reflux (estimate -0.076, $p < 0.007$), and constipation scores (estimate -0.098, $p < 0.009$).

Breath Test Scores

Hydrogen breath test values amongst patients given placebo versus rifaximin were not significantly different (Fig. 2). Using criteria 1 to define a positive hydrogen breath test, which defines SIBO by the presence of an elevated hydrogen level $\geq$20 ppm above baseline, SIBO was seen in 55% (27/49) overall at the initiation of the study. There was no difference in the prevalence of SIBO between patients given placebo versus rifaximin at week 0 (64 vs. 46%, $p = 0.20$), week 2 (59 vs. 45%, $p = 0.37$),

Table 1 Basic patient information by placebo and rifaximin groups

	Placebo, $n = 25$*	Rifaximin, $n = 25$*
Mean age, years (SD)	43.4 (14.0)	41.9 (14.6)
Median duration of symptoms, years (IQR)	8.5 (10.8)	5.1 (15.6)
Median duration from diagnosis, years (IQR)	4.2 (4.6)	3.9 (3.9)
Median duration on GFD, years (IQR)	3.0 (5.9)	3.2 (3.1)
Duodenal biopsy Marsh grade 2 or higher prior to enrollment, *n* (%)	20 (80)	19 (76)

* There was no significant difference between groups

Table 2 GSRS scores by symptom area between placebo versus rifaximin

GSRS symptom area	Placebo*	Rifaximin*
Overall score (SD)		
Week 0	2.8 (0.9)	2.7 (1.1)
Week 2	2.4 (0.6)	2.3 (0.6)
Week 12	2.5 (0.8)	2.5 (0.8)
Abdominal pain		
Week 0	3.0 (1.0)	3.1 (1.6)
Week 2	2.4 (0.8)	2.6 (1.1)
Week 12	2.7 (1.0)	2.7 (1.1)
Reflux		
Week 0	1.9 (1.2)	1.9 (1.4)
Week 2	1.7 (0.8)	1.6 (0.9)
Week 12	1.7 (0.9)	1.9 (1.3)
Indigestion		
Week 0	3.6 (1.2)	3.6 (1.5)
Week 2	3.1 (0.8)	3.0 (0.9)
Week 12	3.3 (1.2)	3.3 (1.0)
Diarrhea		
Week 0	2.8 (1.8)	2.3 (1.6)
Week 2	2.1 (1.3)	1.8 (0.6)
Week 12	2.2 (1.4)	1.8 (1.3)
Constipation		
Week 0	2.5 (1.3)	2.7 (1.4)
Week 2	2.6 (1.4)	2.4 (1.1)
Week 12	2.6 (1.6)	2.7 (1.5)

* There was no significant difference between groups

and week 12 (52 vs. 60%, $p = 0.62$) (Fig. 3a). SIBO was intermittently present in 28% of patients receiving placebo and rifaximin (Table 3). When stratified by baseline breath test, there was no difference in the response to treatment between placebo and rifaximin by week 2 ($p = 0.68$) or week 12 ($p = 0.90$).

According to criteria 2, SIBO was present in only 8% (4/49) at initiation, which was a much lower prevalence than was found using criteria 1. Again, there was no difference in the prevalence of SIBO between patients given placebo versus rifaximin at week 0 (8% vs. 8%, $p = 0.97$), week 2 (14% vs. 9%, $p = 0.64$), and week 12 (14% vs. 0%, $p = 0.79$) (Fig. 3b). SIBO was intermittently present in 16% of patients overall (20% receiving placebo and 12% receiving rifaximin, Table 3). When stratified by baseline breath test, there was no difference in the response to treatment between placebo and rifaximin by week 2 ($p = 0.96$) or week 12 ($p = 0.77$).

Discussion

Prior small observational studies have demonstrated a high prevalence of SIBO in patients with poorly responsive celiac disease that is improved after treatment with antibiotics. Our study, the first double-blind, randomized, placebo-controlled trial of rifaximin for the treatment of SIBO in poorly responsive celiac disease, demonstrates a more modest prevalence of SIBO than previously reported that appears to be intermittent and difficult to treat with antibiotics.

In patients without celiac disease, rifaximin has been demonstrated to be effective for SIBO [16, 17, 24], yet we did not see improvement in the gastrointestinal symptoms of patients treated with rifaximin, as measured by the GSRS, a validated symptom assessment instrument that has been used in celiac disease [18, 25–28], not only in symptom areas that are more traditionally attributed to celiac disease, such as diarrhea, but also in other symptoms areas including reflux [29], abdominal pain, indigestion, and constipation [30]. Specifically, there was no improvement in the diarrhea score. It is unclear why our patients did not respond to treatment with rifaximin, as a recent multi-center trial of rifaximin for IBS demonstrated an improvement in gastrointestinal symptoms in 41% of patients treated with rifaximin compared to 32% of patients given placebo [31]. It is possible that IBS symptoms seen in celiac patients are caused by different mechanisms than those seen in non-celiac IBS patients. Interestingly, patients' duration of gastrointestinal symptoms resulted in higher overall GSRS scores, regardless of treatment, and adherence to a GFD for a greater duration lowered GSRS scores, specifically the reflux and constipation sub-scores, suggesting that a GFD provides some degree of

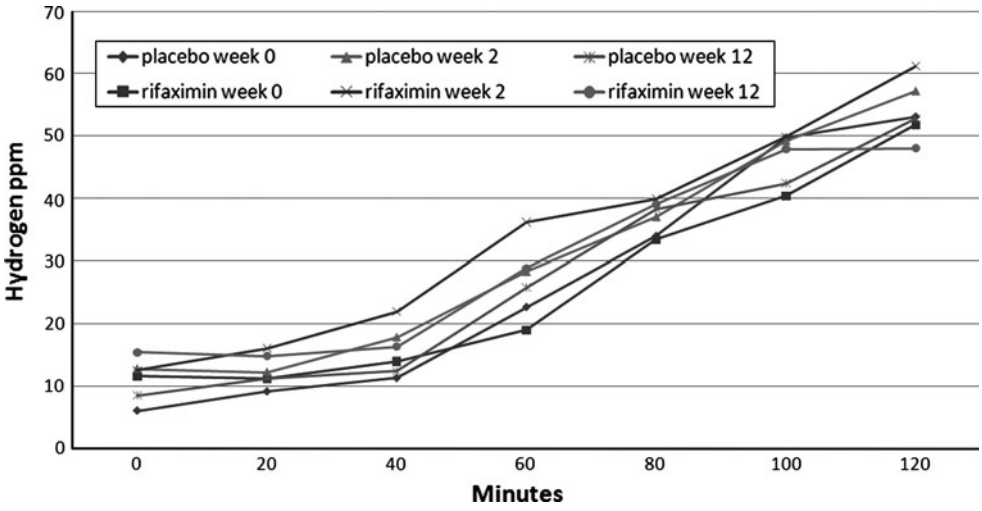

Fig. 2 Hydrogen breath test measurements for placebo and rifaximin at weeks 0, 2, and 12

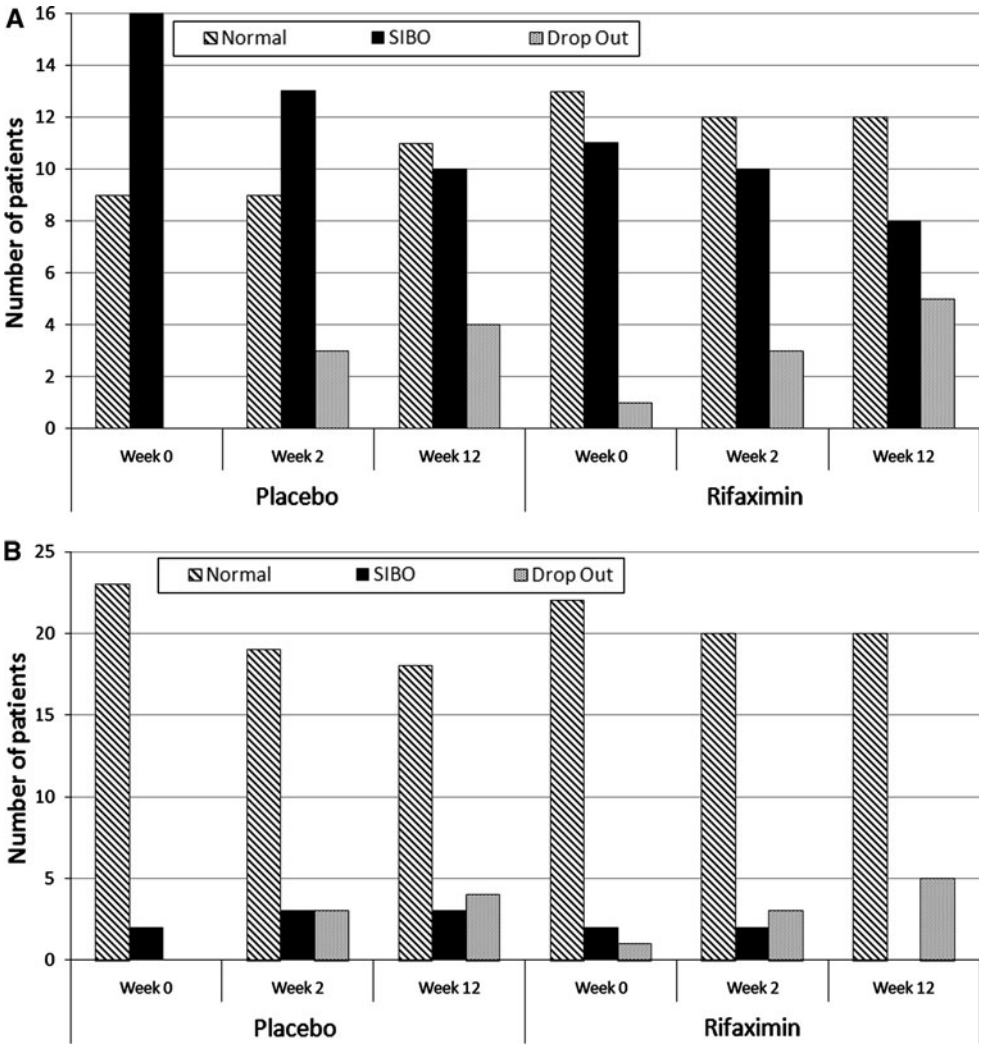

Fig. 3 **a** Patient breath test results "normal", "SIBO", and "dropout" as defined by criteria 1. **b** Patient breath test results "normal", "SIBO", and "dropout" as defined by criteria 2

gastrointestinal symptom improvement in patients with poorly responsive celiac disease. This would support recent evidence that these patients may often have SIBO concurrently with another cause for persistent symptoms, such as irritable bowel disease, microscopic colitis, or enteropathy-associated T-cell lymphoma [5, 32]. Our recent

Table 3 Breath test results of the placebo and rifaximin groups at the end of week 12

Group	Number (%)	
	Interpretation 1	Interpretation 2
Placebo, $n = 25$		
Normal	5 (20)	14 (56)
Intermittent SIBO	7 (28)	5 (20)
Persistent SIBO	6 (24)	0 (0)
Normalization of breath test, not sustained	1 (4)	0 (0)
Normalization of breath test, sustained	2 (8)	2 (8)
Dropout	4 (16)	4 (16)
Rifaximin, $n = 25$		
Normal	7 (28)	15 (60)
Intermittent SIBO	7 (28)	3 (12)
Persistent SIBO	4 (16)	0 (0)
Normalization of breath test, not sustained	1 (4)	0 (0)
Normalization of breath test, sustained	1 (4)	2 (8)
Dropout	5 (20)	5 (20)

study suggests that psychosocial factors are important in driving health care utilization in patients with refractory symptoms in tertiary care celiac centers [33]. This may have influenced the results of our current study.

Despite a lack in improvement of gastrointestinal symptoms, we would have expected a change in breath test results. One possible explanation for a lack of response to rifaximin is that hydrogen breath testing may overestimate SIBO prevalence. Some advocate the use of small intestinal aspirate cultures over breath testing. However, aspirate cultures are not perfect either as they may miss more distal or patchy areas of SIBO, are poorly reproducible, and are not widely used in clinical practice as they are difficult to obtain [10, 34]. Treatment with antibiotics in the practice setting is often initiated, for supposed SIBO for patients with poorly responsive celiac disease, without prior testing. This study questions the value of this practice.

Our prevalence of SIBO varied depending on the criteria used to define a positive hydrogen breath, ranging from 8 to 55% of patients at baseline, and intermittently present in 12–28%. In one study, small intestinal aspirate cultures demonstrated a much lower prevalence (11%) of SIBO amongst patients with poorly responsive celiac disease [5], which is consistent with our findings (8% at baseline) when using the more strict criteria 2 (two peaks $\geq$20 ppm over the baseline hydrogen level within 100 min). The mechanism by which patients with celiac disease develop SIBO is unclear, but one hypothesized mechanism is through decreased intestinal motility resulting in stasis and bacterial overgrowth [6]. This suggests that celiac disease predisposes patients to more-difficult-to-eradicate SIBO and that successful treatment may require a longer or intermittent course of treatment to produce a longstanding response.

There were several limitations to our study. Recruitment of patients with poorly responsive celiac disease can be difficult as the overall prevalence is low. As a result, the sample size was small and further diminished by a relatively high rate of dropouts (18%). This may have limited the power of our study and generalizability. However, prior to our study, the largest group of patients with celiac disease to be treated for SIBO in the literature was even smaller, only ten patients without a control group [6]. Despite our small sample size, we were still able to find a number of significant predictors in our multivariable regression analysis, indicating the relative strength of these associations. We also considered patients as poorly responsive to a GFD after 3 months, which may have been too brief of a trial period for mucosal healing, particularly in the seven patients in the placebo group and four in the rifaximin group who had been on a GFD for less than 1 year. However, this was unlikely to have significantly affected our findings as the median duration on GFD for the group overall was 3.2 years, and while patients who were adherent to a GFD for a longer duration were more likely to have lower GSRS reflux and constipation scores. This relationship was not demonstrated when stratifying by placebo versus rifaximin, and also did not impact breath test results.

Another limitation to the study was the use of hydrogen breath testing alone, which has a widely variable sensitivity and specificity in diagnosing SIBO. One alternative that might have enhanced the accuracy of hydrogen breath testing would have been to measure methane levels or to use small intestinal aspirate cultures. We chose to use hydrogen breath testing for its ease of administration and widespread use in routine clinical practice, and then

followed the patient's clinical status after treatment, utilizing a "test, treat, and outcome" method that has been recommended by some groups [35]. Until better tests are developed, the appropriate method of diagnosing SIBO will continue to remain controversial.

Our study demonstrated that a course of rifaximin did not improve symptoms in patients with persistent gastrointestinal complaints despite adherence to a GFD. Our patients with poorly responsive celiac disease had lower rates of SIBO than previously reported, and also had intermittent SIBO that was difficult to eradicate. Lactulose-hydrogen breath tests did not reliably identify which patients would have responded to antibiotic therapy and should be used judiciously in this patient population. The optimal diagnostic test for SIBO in celiac disease patients is uncertain and further investigation is needed on the mechanism behind SIBO in celiac disease, including motility and microbiologic studies. In addition, further studies of the mechanism of SIBO in this particular patient population are needed.

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Conflict of interest Drs. Peter Green, Matthew Chang, Maria Minaya, Jianfeng Cheng, Bradley Connor, Suzanne Lewis have no personal interests to declare.

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