A review of rifaximin and bacterial overgrowth in poorly responsive celiac disease

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***Abstract*:** A proportion of patients with celiac disease have a poor response to a gluten-free diet, which may be due to small-intestinal bacterial overgrowth (SIBO). Treatment with rifaximin is often used in the clinical setting, but there is limited literature to support this practice. In addition, challenges in the diagnosis of SIBO confound response interpretation. Our recent placebo-controlled trial did not demonstrate any improvement in gastrointestinal symptoms after treatment with rifaximin and casts doubt on the utility of lactulose–hydrogen breath testing for SIBO in this population.

***Keywords*:** gluten-free diet, breath tests, questionnaires, small intestine

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Poorly responsive celiac disease

Celiac disease that is poorly responsive to a gluten-free diet (GFD), or sometimes called non-responsive celiac disease, is defined as persistent gastrointestinal symptoms despite dietary adherence for 12 months. It occurs in up to 30% of patients and is typically due to gluten contamination [Leffler *et al.* 2007; Abdulkarim *et al.* 2002; Trier *et al.* 1978; Rubin *et al.* 1970]. When not due to residual gluten in the diet, symptoms may persist because of the existence of either alternate or concurrent gastrointestinal disease, including malabsorptive, inflammatory, infectious, and oncologic disorders (Table 1) [Abdallah *et al.* 2007; Abdulkarim *et al.* 2002; Fine *et al.* 1997; O'Mahony *et al.* 1996]. Only infrequently do symptoms persist because of true refractory celiac disease, defined as persistent symptoms and villous atrophy despite dietary adherence for up to 12 months, as determined by a nutritionist [Green and Cellier, 2007; Daum *et al.* 2005; Abdulkarim *et al.* 2002; Cellier *et al.* 2000; Ryan and Kelleher, 2000].

Small-intestinal bacterial overgrowth (SIBO) has been suggested as one potentially reversible cause of poorly responsive celiac disease in up to two thirds of patients, although the true prevalence is debated and may actually be much lower, as low as 11% in one study that used jejunal aspirate cultures to diagnose SIBO [Rubio-Tapia *et al.* 2009; Rana *et al.* 2007; Tursi *et al.* 2003; Abdulkarim *et al.* 2002; Prizont *et al.* 1970]. Treatment of SIBO in patients with poorly responsive celiac disease using antibiotics has been shown to be successful in alleviating symptoms [Rana *et al.* 2007; Ghoshal *et al.* 2004; Tursi *et al.* 2003; Roufail and Ruffin, 1966]. However, this has been demonstrated primarily in small, observational studies, typically using breath testing as opposed to with the gold standard, jejunal aspirate cultures.

Small-intestinal bacterial overgrowth

Traditionally, patients with SIBO typically have either an abnormality in their gastrointestinal anatomy or motility. Symptoms include bloating, gas, diarrhea, abdominal pain, and can result in malabsorption, weight loss, and anemia [Gasbarrini *et al.* 2009]. Recently, SIBO has been suggested to be highly prevalent amongst patients with diarrhea predominant irritable bowel syndrome (IBS), but the evidence is conflicting [Ford *et al.* 2009; Walters and Vanner, 2005; Pimentel *et al.* 2000]. The underlying mechanism for SIBO in celiac disease is still uncertain and may be due to alterations in motility, which has been shown to improve in some cases with a GFD [Bassotti *et al.* 2008; Tursi, 2004; Chiarioni *et al.* 1997]. There are also a number of radiologic signs that support the presence of conditions that can predispose to SIBO, including dilated bowel loops, changes in mucosal folds, and the presence of free fluid [Tomei *et al.* 2005; Fraquelli *et al.* 2004; Rettenbacher *et al.* 1999].

Table 1. Causes of poorly responsive celiac disease.

Gluten contamination (~30–50% of cases)
Dietary nonadherence, accidental ingestion (medications and foods containing gluten)
Inflammatory
Ulcerative jejunitis, collagenous colitis, lymphocytic colitis
Malabsorptive
Pancreatic insufficiency, lactose or fructose intolerance, protein losing enteropathy, refractory celiac disease
Infectious
Tropical sprue, parasitic infections, SIBO
Oncologic
Lymphoma
Irritable bowel syndrome

SIBO, small-intestinal bacterial overgrowth.

One of the primary challenges of diagnosing SIBO is that there is no accepted, consensus definition. A jejunal aspirate culture with $>10^5$ colony-forming units per milliliter (CFU/ml) of bacteria is generally considered the diagnostic gold standard, but is it rarely performed in routine clinical practice because it is difficult to obtain, may become contaminated with oral flora, can miss distal or patchy disease, and is poorly reproducible [Quigley and Quera, 2006].

In clinical practice, SIBO is typically diagnosed using noninvasive breath testing to detect either radiolabeled carbon or, more conveniently, hydrogen or methane [Rana and Bhardwaj, 2008; Corazza *et al.* 1990]. The test is simple to conduct: for a hydrogen breath test, a carbohydrate, either lactulose or glucose, is ingested at the beginning of the study and exhaled hydrogen is measured and plotted at regular intervals. However, breath testing is not standardized and, consequently, has variable sensitivity and specificity. Variability exists from the dose of carbohydrate ingested to the diagnostic criteria used to determine SIBO. Classically, lactulose hydrogen breath tests have been considered to be positive for SIBO when two distinct hydrogen peaks are measured, an early peak for abnormal small-intestinal bacteria and a late peak for normal colonic flora [Gasbarrini *et al.* 2009]. However, depending on how the test is conducted, it can last for 90 minutes to over 2 hours, hydrogen measurements can be taken anywhere from every 5 minutes to 20 minutes, and the definition of an 'elevated' hydrogen level can be as low as 10 parts per million (ppm) to greater than 20 ppm above baseline [Gasbarrini *et al.* 2009; Khoshini *et al.* 2008]. This variability in methodology makes it difficult to compare the different studies reported in the literature.

As a result, some have advocated that a diagnosis of SIBO should be based not just on the results of diagnostic testing, but also on the clinical response after treatment, a 'test, treat, and outcome' approach that integrates the breath test result with the clinical context and then uses the patient's symptom response to antibiotics to confirm eradication of clinically relevant overgrowth [Khoshini *et al.* 2008]. Eradication of SIBO has been demonstrated with several antibiotics [Fan and Sellin, 2009] including rifaximin, which is minimally absorbed from the gastrointestinal tract and is generally well tolerated [Scarpellini *et al.* 2007; Lauritano *et al.* 2005; Pelosini and Scarpignato, 2005].

Trial of rifaximin for poorly responsive celiac disease

We conducted a two-group, parallel, randomized, double-blind controlled trial of rifaximin for poorly responsive celiac disease [Chang *et al.*] to determine whether rifaximin would improve gastrointestinal symptoms when measured using the Gastrointestinal Symptom Rating Scale (GSRS), a validated seven-point questionnaire that evaluates five symptom areas: abdominal pain, reflux, indigestion, diarrhea, and constipation [Midhagen and Hallert, 2003; Svedlund *et al.* 1988]. Lactulose–hydrogen breath test improvement was measured as a secondary outcome. Our study included patients who were 18 years or older with a biopsy-proven diagnosis of celiac disease, and persistent symptoms while on a GFD. Potential causes of persistent gastrointestinal symptoms, including infectious, inflammatory, medication-related, and other similar causes

Table 2. Summary of Gastrointestinal Symptom Rating Scale (GSRS) scores and hydrogen breath test results according to placebo and rifaximin groups.

	Placebo	Rifaximin
Overall GSRS score (SD)*		
Week 0 ($n = 25$, 24)	2.8 (0.9)	2.7 (1.1)
Week 2 ($n = 22$, 22)	2.4 (0.6)	2.3 (0.6)
Week 12 ($n = 21$, 20)	2.5 (0.8)	2.5 (0.8)
Interpretation of breath test results - Criteria 1, *n* (%)*		
Normal	5 (20)	7 (28)
Intermittent SIBO	7 (28)	7 (28)
Persistent SIBO	6 (24)	4 (16)
Normalization of breath test, not sustained	1 (4)	1 (4)
Normalization of breath test, sustained	2 (8)	1 (4)
Drop out	4 (16)	5 (20)
Interpretation of breath test results - Criteria 2, *n* (%)*		
Normal	14 (56)	15 (60)
Intermittent SIBO	5 (20)	3 (12)
Persistent SIBO	0 (0)	0 (0)
Normalization of breath test, not sustained	0 (0)	0 (0)
Normalization of breath test, sustained	2 (8)	2 (8)
Drop out	4 (16)	5 (20)

*No statistically significant difference between placebo and rifaximin groups.
GSRS, Gastrointestinal Symptom Rating Scale; SD, standard deviation; SIBO, small-intestinal bacterial overgrowth.

were excluded; a complete list of exclusion criteria can be found in our full paper [Chang *et al.* 2011]. Patients were randomized to either treatment with rifaximin 1200 mg daily for 10 days ($n = 25$) or placebo ($n = 25$) and were assessed at weeks 0, 2, and 12 using the GSRS and breath testing. Owing to the lack of standardized diagnostic criteria for what constituted a positive breath test and the fact that patients with celiac disease can have elevated baseline hydrogen levels, [Corazza *et al.* 1987] we chose to evaluate our results using two different definitions adapted from the literature. Criteria 1 was defined as a rise in hydrogen of $\geq$20 ppm within 100 minutes [Sharara *et al.* 2006; Pimentel *et al.* 2003] and criteria 2 was defined using a more traditional double-peak interpretation of two peaks $\geq$20 ppm over the baseline hydrogen level within 100 minutes [Walters and Vanner, 2005; Pimentel *et al.* 2000].

GSRS scores were unaffected by treatment with rifaximin, regardless of baseline breath test results (Table 2). In a multivariable regression model, the duration of patients' gastrointestinal symptoms significantly predicted their overall GSRS scores (estimate 0.029, $p < 0.006$), whereas the duration that a patient had been on a GFD predicted lowered GSRS reflux and constipation subscores. This suggests that a GFD provides some incomplete degree of gastrointestinal symptom improvement in patients with poorly responsive celiac disease. In terms of the breath test results, 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%. According to criteria 1, SIBO was present in 55% at baseline, intermittently present in 28% given placebo, and in 28% given rifaximin. Using criteria 2, SIBO was not found as commonly as according to criteria 1, in only 8% of patients at baseline, while intermittently present in 20% given placebo and in 12% given rifaximin, over 12 weeks. There was no difference in the prevalence of SIBO between placebo and treatment groups at weeks 2 and 12 (Table 2).

There were a number of limitations to our study. Primarily, the study population was small and suffered from a relatively high rate of dropouts (18%, including one patient that left after randomization, but prior to the start of the study), although poorly responsive celiac disease itself is an uncommon entity. Also, breath testing can vary widely in its sensitivity and specificity in diagnosing SIBO, which could have limited the accuracy of our findings. In addition, we did not assess for methane production. However, our study clearly demonstrated that an empiric trial

of rifaximin is unlikely to improve gastrointestinal symptoms in patients with poorly responsive celiac disease, regardless of breath testing results. This may be in part due to an overestimation of the prevalence of SIBO in celiac disease, for which the use of antibiotics for gastrointestinal symptoms would obviously be ineffective. Our patients had lower rates of SIBO than previously reported, particularly when using criteria 2, which is more consistent with prevalence rates seen when using intestinal aspirate cultures to diagnose SIBO (8% in our study compared with 11% when using aspirate cultures) [Rubio-Tapia *et al.* 2009]. It may also be that patients with celiac disease have more resistant SIBO or multiple etiologies for their gastrointestinal symptoms, such that the treatment of SIBO alone would not be sufficient for symptom relief. It is very likely that a small proportion of patients with bloating and abdominal pain have intussusception and other alternate etiologies instead, as seen in our recent study [Gonda *et al.* 2010], and would benefit from evaluation with ultrasound, CT, or MR enterography. Unfortunately, we did not systematically incorporate imaging findings in our study and were unable to draw any conclusions regarding this. Of the patients who did test positively for SIBO, we found that it was both intermittent and difficult to eradicate with a conventional antibiotic course. In addition to exploring other causes of persistent gastrointestinal symptoms, one future approach for the treatment of SIBO in patients with celiac disease might be to combine rifaximin with another antibiotic, either concomitantly or sequentially.

Conclusions

Eradication of SIBO in patients with poorly responsive celiac disease is a common practice, but there is limited literature to support this. In our recent study, we found that the lactulose–hydrogen breath test was limited in its ability to identify which patients would respond to rifaximin and that the optimal diagnostic test for SIBO in celiac patients is still uncertain. Our findings cast doubt on the previously reported high prevalence of SIBO in celiac disease and question the practice of treating patients with poorly responsive celiac disease empirically for SIBO. Future directions of investigation should attempt to determine the true prevalence of and elucidate the mechanism behind SIBO in celiac disease.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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