

# Recognizing and treating a new entity on the quality-of-life front: small intestinal bacterial overgrowth

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Gastrointestinal (GI) complications are widely recognized radiation-associated toxicities for patients undergoing cancer therapy. Emerging data suggest that small intestinal bacterial overgrowth (SIBO) contributes to numerous GI disorders. Recognizing this, our institution evaluates patients undergoing abdominopelvic radiotherapy (RT) for SIBO if they develop diarrhea or related symptoms. A retrospective case review was conducted over the initial 10-month period in which SIBO testing by glucose and lactulose breath tests was employed in the radiation oncology department. Of 30 patients with GI symptoms undergoing breath testing, 17 (57%) exhibited positive results consistent with SIBO. Sixteen patients with positive results and two with negative results, who were treated on an empiric basis, received rifaximin (Xifaxan) 800–1,200 mg/d during RT and for several weeks afterward. Of these patients, 94% and 81% experienced partial and global relief, respectively, of SIBO-associated GI symptoms. To our knowledge, this is the first published report demonstrating an association between SIBO and RT. Our findings emphasize the need to further examine the diagnosis and treatment of SIBO in this patient population.

According to an American Cancer Society estimate, more than 650,000 new diagnoses of abdominopelvic malignancy were made in the United States in 2006.<sup>1</sup> This constitutes just less than 50% of all malignancies diagnosed and includes those with a primary origin in the gastrointestinal (GI) tract (excluding the esophagus), gynecologic organs, and other genitourinary organs. However, this number does not include skin cancers, soft-tissue sarcomas, or hematologic malignancies, many of which are also localized within the abdominopelvic region, nor does it include nonabdominopelvic primary malignancies with subsequent metastasis to this region. When all such diagnoses are considered, more than half of the cancers reported in the United States involve the abdomen and pelvis to some degree. Many malignancies within the abdomen and pelvis require radiotherapy (RT), typically combined with chemotherapy, as an essential component of curative or palliative treatment. Currently, early detection of many of these malignancies is suboptimal. In such cases, the viability of resection as single-modality curative treatment is poor at best. For example, in the case of pancreatic cancer, 80%–95% of patients present with local or regionally advanced disease or metastases, rendering the tumors unresectable.<sup>2</sup> Of the remaining 5%–20% of patients who are treated

surgically, less than one-third will have a resection with pathologic margins that are completely free of tumor.<sup>2</sup> These and other factors necessitate highly aggressive therapy, generally including RT, which frequently re-

## KEY POINTS

Small intestinal bacterial overgrowth (SIBO) contributes to gastrointestinal (GI) complications of abdominopelvic radiotherapy.

Patients with GI symptoms can be assessed for SIBO using glucose and lactulose breath tests.

In our retrospective study, treatment with the nonsystemic antibiotic rifaximin was associated with alleviation of SIBO symptoms in our retrospective study.

Additional investigation of the prevalence of SIBO as a complication of RT/chemoradiotherapy and of the benefits of rifaximin or other appropriate antibiotic therapy is warranted.

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sults in small bowel toxicity and other GI complications.

Small bowel toxicity resulting from RT for abdominopelvic malignancies is a complex phenomenon that manifests clinically as dyspepsia, diarrhea, cramping, abdominal pain, bloating, and nausea. Damage to mucosal surfaces of the small intestine occurs early in the course of RT and may be followed by an “adaptive phase,” during which histologic changes are less pronounced, but clinical symptoms generally continue or worsen. A study specifically addressing this mucosal reaction time course showed that acute GI symptoms are not solely the result of direct mucosal damage by RT and likely involve a less obvious phenomenon.<sup>3</sup>

Potential contributors to this constellation of symptoms are numerous. Animal studies have demonstrated dramatic alterations in small bowel motility, both acutely and chronically, following RT doses larger than those administered in clinical practice,<sup>4,5</sup> as well as meaningful alterations in motility after administration of clinically relevant doses.<sup>6</sup> A study in patients with gynecologic malignancies demonstrated an overall decrease of 20% in orocecal transit time following external-beam RT doses of 45–50 Gy.<sup>7</sup> Extrapolation from animal studies suggests that this overall decrease in transit time likely is associated with paroxysms of faster propulsion, both anterograde and retrograde, throughout the irradiated portions of the GI tract. In addition, intestinal denudation by radiation directly results in loss of absorptive function and barrier integrity, leaving the patient susceptible to bacterial colonization, invasion, and associated inflammation.<sup>8</sup>

The hypothesis fundamental to the current study is that radiation-induced and/or chemotherapy-induced dysmotility combined with barrier degradation predisposes patients to small intestinal bacterial overgrowth (SIBO), a condition in which abnormally high concentrations of enteric bacteria are

present in the small intestine. We further hypothesize that SIBO results in an exaggerated inflammatory response and a corresponding increase in RT-associated GI symptoms. Suppressing SIBO may decrease the undesirable inflammatory response, decrease GI symptoms, and improve quality of life.

### The role of SIBO: cause and effect

Published literature strongly supports the potential role of SIBO in the development of RT-associated adverse effects. As early as 1974, researchers described a “stagnant loop syndrome” in patients with small bowel radiation injury that was severe enough to necessitate intestinal bypass.<sup>9</sup> This study emphasized the importance of recognizing *Bacteroides* and *Escherichia coli* overgrowth and appropriately treating the overgrowth with antibiotic therapy.

In a subsequent study, researchers described the results of carbon-14 (<sup>14</sup>C) lactose breath tests in patients who were receiving radiation to the small bowel without surgery.<sup>10</sup> Patients were also compared based on the amount of small bowel included in the radiation portals. Those with greater amounts of small bowel inclusion had more than three times the amount of change in excreted tracer by the end of the study, compared with patients with smaller amounts of small bowel inclusion. The authors concluded that the increased degree of malabsorption directly reflected the amount of bowel included in the radiation field.

To some extent, the idea that malabsorption is caused by destruction of brush border enzymes is accepted as a legitimate explanation for the development of diarrhea in patients undergoing RT. However, more recent data support the interpretation that the results of the breath test study described above likely reflect early presentation of the test substrate to bacteria, not lactose malabsorption (ie, brush border enzyme loss).<sup>11</sup> Considering the early work involving <sup>14</sup>C lactose breath testing and new in-

terpretations of the results, evidence of SIBO in patients undergoing RT may already exist. However, this evidence is not broadly recognized as such, nor has this interpretation been described previously.

European groups have advocated homeopathic approaches to dealing with bacterial imbalances for decades, despite an absence of controlled studies addressing the causative factors. Studies have demonstrated the successful administration of *Lactobacillus acidophilus* as a means of preventing dysbiosis of gut flora in patients undergoing RT.<sup>12,13</sup> However, substances added to promote the growth of live cultures have been associated with untoward effects.<sup>12,13</sup> Antibiotic therapy for the management of GI symptoms resulting from RT has been suggested<sup>8</sup> but has not been evaluated to date in trials with an adequate patient population.

Recognizing the aforementioned factors that suggest SIBO as a likely cause of RT-associated diarrhea in patients with an abdominopelvic malignancy, we routinely evaluate patients undergoing RT for SIBO if they present with abnormal diarrhea, bloating, abdominal cramping, or similar GI symptoms. Glucose or lactulose hydrogen breath testing has become a standard diagnostic measure for SIBO in patients with GI symptoms presenting in gastroenterology practices.<sup>14</sup> This is a simple test in which a fasting patient ingests the relevant substrate (eg, glucose or lactulose), and expired air is analyzed for the presence of a higher than normal hydrogen concentration.<sup>15</sup> Excess hydrogen indicates substrate metabolism by small intestinal bacteria, rather than normal physiologic absorption of the carbohydrate or passage to the colon.<sup>11</sup> The current study was designed to retrospectively assess the degree of SIBO in patients undergoing RT who had an early onset of GI symptoms and to provide a preliminary determination of patient response to oral antibiotic therapy.

## Materials and methods

Patients who were undergoing RT and had GI symptoms of diarrhea, cramping, nausea, vomiting, bloating, or flatulence were evaluated to determine whether SIBO was present. Patients with breath test results suggesting SIBO were administered first-line therapy with rifaximin (Xifaxan) 400 mg two or three times daily (total of 800 or 1,200 mg per day), as described by Lauritano et al.<sup>16</sup> Treatment was continued throughout the course of RT and for 2–4 weeks following completion of RT. Rationale for the choice of rifaximin over other antibiotics and for this dosing regimen is detailed in the discussion section. Response to treatment was evaluated by patient-reported relief of presenting GI symptoms.

This retrospective analysis was performed after obtaining approval from the institutional review board of the University of Alabama at Birmingham. All patients who underwent RT and were evaluated for SIBO by a glucose or lactulose hydrogen breath test in a 10-month period, covering portions of 2005 and 2006, were included in the analysis. To the best of our knowledge, this represents all patients from the institution who were formally evaluated for SIBO that likely developed because of RT during this period.

Not all patients were evaluated using the same breath-test method. Patients evaluated early after initiation of this practice were tested using the glucose hydrogen breath test. This test has the advantage of high specificity at a cost of low sensitivity, as glucose is normally absorbed entirely in the proximal small bowel.<sup>17</sup> Thus, when testing with glucose, results for many patients with distal SIBO may be interpreted as false-negatives. Our recent practice has been to request the lactulose hydrogen breath test (LHBT), because lactulose is not absorbed in the gut.<sup>18</sup> We considered the time to development of elevated hydrogen in the interpretation of LHBT results and used a cutoff of

2 hours.<sup>18</sup> Given a previous study of orocecal transit time,<sup>7</sup> we deemed this a reasonable balance to minimize both false-positive and false-negative results. An elevation of  $\geq 12$  ppm hydrogen was interpreted as a positive result for SIBO, consistent with the predominant reference values (10–12 ppm) used in the literature.<sup>19</sup> Breath test results were available for hydrogen only. Methane is also recognized as a product of SIBO<sup>20</sup>; however, methane testing is not available at our institution.

Statistical analyses were performed using the GraphPad QuickCalcs (GraphPad Software, Inc., San Diego, Calif) online statistical analysis program in *t* test mode for continuously variable statistics and Fisher exact test mode for categorical data.

## Results

A total of 30 patients underwent RT and were assessed for SIBO during the 10-month study period. Demographic and treatment characteristics for the group as a whole are shown in Table 1. Salient features include the following: 21 patients (70%) had lesions for which radiation fields were characterized by the treating physician as principally abdominal, and 9 patients (30%) had fields characterized as principally pelvic. Of the entire group, 14 patients (47%) had pancreatic lesions. The mean radiation dose at which patients were tested for SIBO was 2,676 cGy (ie, the patient's radiation dose on the date the breath test was actually performed was on average 2,676 cGy). However, in some cases, there was a delay between the initial identification of SIBO symptoms and administration of the breath test, as scheduling delays were occasionally encountered. This suggests that symptoms were most often identified between the second and third weeks of RT. Of clinical symptoms suggestive of SIBO, the most common was diarrhea (63% of patients).

Four patients (13%) were administered a glucose breath test, and 26 pa-

**TABLE 1**

### Patient characteristics

Characteristics	Patients undergoing breath test (n = 30)
Mean age, years (range)	55.3 (19–79)
Age > 60 yr, n (%)	12 (40)
Male, n (%)	19 (63)
Mean body weight, kg	
Initially	75.6
At breath test	74.5
Cancer diagnosis, n (%)	
Pancreas	14 (47)
Rectum	6 (20)
Hepatobiliary	5 (17)
Other pelvic	3 (10)
Other abdominal	2 (7)
Radiation field, n (%)	
Principally abdominal	21 (70)
Principally pelvic	9 (30)
Concomitant chemotherapy, n (%)	
Total receiving chemotherapy	26 (87)
On regimen including capecitabine	22 (73)
Presenting GI symptoms, n (%)	
Diarrhea	19 (63)
Cramping	13 (43)
Nausea/vomiting	10 (33)
Bloating	10 (33)
Gas	7 (23)

GI = gastrointestinal

tients (87%) were administered LHBT. Breath test results were consistent with SIBO in 17 (57%), whereas 12 (40%) had negative results and 1 patient (3%) was intolerant of the test beverage (bloating, vomiting) and did not reliably complete the test. No differences in breath test results were attributed to sex, percentage of weight lost compared with baseline measurement, or chemotherapy regimen employed. Patients aged 60 years or younger represented 76% of those with positive test results but only 38% of those with negative test results ( $P = 0.04$ ). Of note, approximately 75% of both patients with positive results and those with negative results were on a chemotherapy regimen employing capecitabine (Xeloda), consistent with the fact that most patients evaluated had a GI primary malignancy.

We considered the possibility of false-negative results among our patients, and clinical suspicion led to empiric treatment with rifaximin in two

patients, despite negative LHBT results. One patient was not treated despite a positive breath test result. Of the patients treated with rifaximin, 16 had data sufficient to be analyzed, and 9 patients had two or more presenting symptoms. Of the analyzable patients, 15 patients (94%) experienced a subjective decrease in the severity of at least some clinical GI symptoms, whereas 13 of the 16 (81%) experienced a subjective decrease in the severity of all presenting symptoms. It should be noted that for seven of the patients in this latter analysis, global symptom relief constituted relief of only one symptom. Due to the retrospective nature of the study, additional characterization of treatment results was not possible. Administration of rifaximin was well tolerated, with patients experiencing few adverse effects, consistent with product labeling.

## Discussion

Few medical disciplines are as technology-driven as radiation oncology, and it can be easy to excessively depend on technology to solve all treatment-related maladies in this field. In recent years, quality-of-life research within this discipline has emphasized new technology, such as intensity-modulated radiation therapy (IMRT), to minimize treatment-related complications, de-emphasizing research that addresses those complications more directly and even more cost-effectively. In few cases is this truer than for GI adverse effects of RT. Indeed, the fact that some patients included in this study were treated with IMRT as a component of therapy emphasizes the need to consider issues such as SIBO even when optimal technologies have been employed. If one accepts the hypothesis that RT-related SIBO most likely results from abnormal peristalsis and that irradiation of even small amounts of bowel can cause such an abnormality, concern about the effective treatment of SIBO is quite rational.

As for the choice of SIBO treatment,

a nonsystemic antibiotic, such as rifaximin, is preferred. A lack of systemic absorption minimizes the potential for drug interactions as well as adverse effects commonly associated with systemic agents. The cost of rifaximin is similar to that of other proprietary antibiotics. It is currently available in the United States as a prescription drug indicated for the treatment of travelers' diarrhea caused by noninvasive strains of *E coli*. Although rifaximin has been available in Italy for more than 20 years and its efficacy has been demonstrated in the treatment of SIBO associated with other functional bowel symptoms (eg, irritable bowel syndrome),<sup>21,22</sup> this is, to our knowledge, the first published report demonstrating its utility in the oncology patient population.

We typically treat patients with antibiotics for the duration of RT and for a short time thereafter. In this study, we employed a sustained course of antibiotic treatment because the proposed factors that increase patient susceptibility to SIBO, namely altered motility and barrier degradation from chemoradiotherapy, are ongoing processes. Rifaximin is suitable for such sustained treatment, because long-term administration of the drug has been shown to be safe and well tolerated in the management of other conditions.<sup>23-27</sup>

We acknowledge that the present study suffers from problems inherent to any retrospective study. Further limitations include the heterogeneity of the patient population in terms of GI symptom presentation, variability in time between symptom onset and breath testing, use of two different breath test methods, and the use of patient-reported evaluations of treatment response. Nonetheless, the present data are evidence of a new entity in oncology, and members of our group are preparing to open a prospective study to rigorously test this evidence and the hypotheses described herein.

## Conclusion

SIBO is a relevant clinical concern

that may affect a substantial number of oncology patients. Unfortunately, the role of SIBO has gone largely unrecognized in this patient population. The dramatic 94% response rate for complete or partial symptom amelioration supports the effectiveness of the non-systemic antibiotic rifaximin in treating and managing SIBO symptoms in patients receiving RT. The results of this retrospective study warrant additional investigation into the prevalence of SIBO as a complication of chemoradiotherapy and the benefit of rifaximin therapy in the management of SIBO.

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