RESEARCH LETTER

Comparing Small Intestinal Bacterial Overgrowth and Intestinal Methanogen Overgrowth: A Single-Center Retrospective Cohort Study

Small intestinal bacterial overgrowth (SIBO) refers to a clinical syndrome of maldigestion associated with excessive or regionally inappropriate bacteria in the small intestine. Symptoms typically associated with SIBO include bloating, abdominal pain, and diarrhea, but prior data have consistently suggested that presenting complaints correlate poorly with a formal SIBO diagnosis by hydrogen breath testing (BT) with either glucose or lactulose.[1,2] Increasing attention to exhaled methane (CH_4) and its clinical association with constipation has led several practitioners to approach intestinal methanogen overgrowth (IMO), or methane-positive SIBO, as a clinically distinct phenomenon.[3,4]

Current treatment paradigms are based on relatively small studies that suffer from heterogeneous diagnostic and outcome measures. National consensus guidelines recommend antibiotics as the preferred treatment for SIBO, though optimal regimens have not been established.[4] Various agents and dosing schedules have been used in the past, with the logic that polymicrobial colonies will be at least partially susceptible to multiple antimicrobial agents.[5]

Recent research has suggested that the IMO's phenotypic distinctions imply parallel therapeutic distinctions. A 2010 retrospective study reported that, among patients with CH_4-positive BT, the combination of rifaximin and neomycin was superior in efficacy to either agent alone (85% vs 63% and 56%, respectively).[6] A 2014 study by the same group randomized 31 patients with irritable bowel syndrome with constipation and CH_4 levels $\geq$3 ppm on BT to neomycin/placebo or neomycin/rifaximin combination and found that the antibiotic combination was superior to neomycin alone at alleviating constipation and bloating but not abdominal pain.[7] Herein, we report our own institutional experience with SIBO/IMO diagnosis and treatment, comparing the aforementioned antibiotic combination to rifaximin monotherapy.

All patients undergoing BT at the University of Pennsylvania from February 2019 to March 2020 were included in this study. All BT were performed with lactulose and interpreted according to the 2017 North American consensus, which defines hydrogen (H_2) positivity as a rise of $\geq$20 ppm above baseline before 90 minutes and CH_4 positivity as a value of $\geq$10 ppm at any testing time point.[8] Tests with elevated baseline hydrogen levels were excluded from the analysis for H_2 correlations but were included in the analysis for CH_4 testing. Initial symptoms and response to initial antibiotic treatment were evaluated via chart review according to a 5-point subjective clinical scale (worsening, no improvement, minimal improvement, moderate improvement, or resolution). Analysis was limited to primary courses of antibiotic treatment; repeat courses were infrequent and excluded. Successful treatment was defined as moderate improvement or resolution of symptoms. Secondarily, we queried the association of BT-based diagnoses of SIBO and IMO with presenting clinical symptoms, comorbid diagnoses, and the use of selected medications. Statistical analysis was performed with chi-squared tests, paired two-tailed Student's *t*-tests, two-sample *t*-tests, and analysis of variance as appropriate based on variable type. (Stata version 16, College Station, TX).

336 patients (73.6% female) with a median age of 54 (interquartile range 38, 67) underwent BT over the designated study period. 114 (33.8%) patients were CH_4-positive (IMO). Of the 222 CH_4-negative patients, 87 (39.2%) were H_2-positive (SIBO). Among all patients who underwent BT at our facility during the study, 201 (59.8%) were positive by one or both gases. 92 were H_2-negative, and 43 were equivocal. Antibiotic treatment data were available for 176 patients, and symptom response data were available for 153 patients. The median follow-up interval between BT and documented symptom response was 126 days (interquartile range 51–228 days). Among the 74 patients with IMO who had treatment and symptom response data, 48 (64.9%) were treated with rifaximin monotherapy, 11 (14.9%) were treated with rifaximin and neomycin, 15 (20.3%) were treated with other regimens (Figure). There was no significant difference in response to therapy between the rifaximin monotherapy and the rifaximin plus neomycin groups (58.3% vs 45.4%; $P = .51$). In the SIBO group, 58 had treatment and response data. The majority of SIBO patients were treated with rifaximin monotherapy (n = 43, 74.1%), among whom 28 (48.8%) were deemed successfully treated. There was no significant difference in the treatment response to rifaximin monotherapy between the SIBO and IMO subgroups ($P = .405$).

Bloating was significantly more common in patients with SIBO compared to those with negative H_2-testing (70.4% vs 52.3%, $P < .01$). Constipation was more common in patients with IMO compared to those with negative CH_4 testing (43.9% vs 30.0%, $P = .02$). Surprisingly, the presence of vomiting was significantly associated with negative BT for both H_2 (7.0% vs 15.4%, $P = .03$) and CH_4 (14.8% vs 6.1%, $P = .02$). Mood disorders were more common in patients with H_2 positivity compared to H_2 negativity (69.0% vs 50.0%, $P = .03$) but not between CH_4 groups ($P = .72$). Any type of IBS prevalence was not different between H_2 or CH_4 groups (23.9% in H_2 positivity and 19.5% in CH_4 positivity, $P = .39$ and $P = .78$,

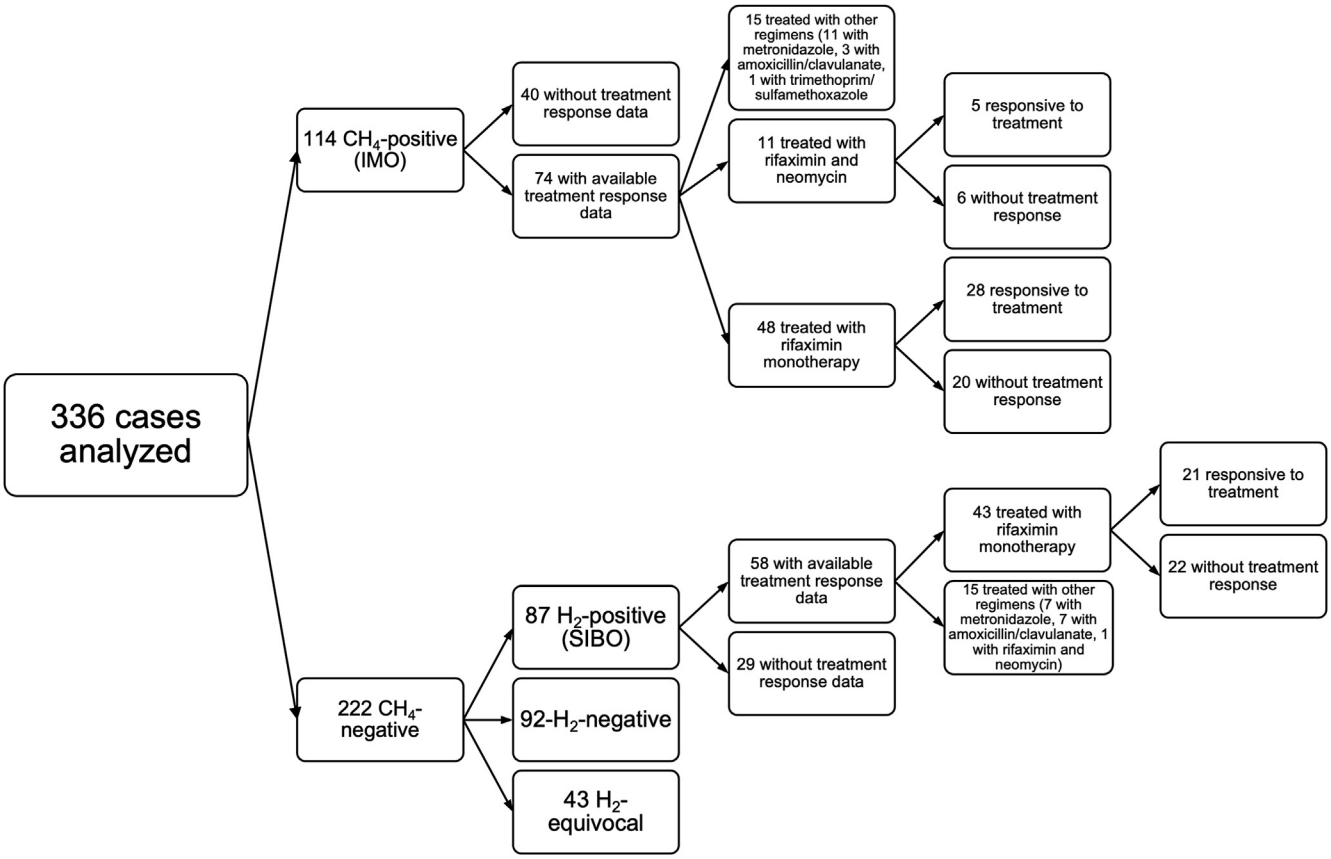

Figure. Diagram of responders stratified by breath test result and antibiotic regimen.

Table. Clinical Variables Associated With Positive Breath Testing in 336 Patients Between 2019 and 2020 at the University of Pennsylvania

Clinical variable, N (%)	H_2 positive (n = 142)	H_2 negative (n = 149)	*P* value (H_2)	CH_4 positive (n = 114)	CH_4 negative (n = 222)	*P* value (CH_4)
Nausea	28 (19.7)	36 (24.2)	.40	21 (18.4)	55 (24.7)	.22
Vomiting	10 (7.0)	23 (15.4)	.03	7 (6.1)	33 (14.8)	.02
Diarrhea	52 (36.6)	54 (36.6)	.90	36 (31.6)	86 (38.6)	.23
Constipation	44 (31.0)	62 (41.6)	.09	50 (43.9)	67 (30.0)	.02
Belching	21 (14.8)	19 (12.8)	.61	20 (17.5)	24 (10.8)	.09
Flatulence	28 (19.7)	26 (17.4)	.65	27 (23.7)	33 (14.8)	.05
Abdominal pain	91 (64.1)	103 (69.1)	.46	77 (67.5)	145 (65.0)	.72
Bloating	100 (70.4)	78 (52.3)	<.01	73 (64.0)	131 (58.7)	.41
IBS	34 (23.9)	29 (19.5)	.39	25 (21.9)	45 (20.2)	.78
Irritable bowel syndrome with constipation	7 (4.9)	5 (3.3)	.57	5 (4.4)	10 (4.6)	1.0
Inflammatory bowel disease	23 (16.2)	20 (13.4)	.51	7 (6.1)	39 (17.5)	<.01
Gastroparesis	9 (6.3)	12 (8.1)	.65	5 (4.4)	20 (9.0)	.19
Diabetes	22 (15.5)	28 (18.8)	.54	22 (19.3)	38 (17.0)	.65
Obesity (body mass index ≥30)	40 (28.2)	38 (25.5)	.60	31 (27.2)	59 (26.5)	.90
Migraine	23 (16.2)	21 (14.1)	.63	20 (17.5)	32 (14.3)	.52
Dysautonomia	3 (2.1)	5 (3.4)	.72	1 (0.9)	8 (3.6)	.18
Ehlers-Danlos syndrome	2 (1.4)	5 (3.4)	.45	1 (0.9)	6 (2.7)	.43
Abdominal surgery	58 (40.8)	56 (37.6)	.55	45 (39.5)	92 (41.3)	.82
Proton pump inhibitor use	63 (44.4)	81 (54.4)	.13	54 (47.4)	110 (49.3)	.73
H2 antagonist use	17 (12.0)	19 (12.8)	1.0	12 (10.5)	31 (13.9)	.40
Opiate use	18 (12.7)	13 (8.7)	.46	11 (9.6)	28 (12.6)	.48

respectively), nor was irritable bowel syndrome with constipation ($P = .57$ and $P = 1.0$, respectively), though inflammatory bowel disease was associated with CH_4 negativity (17.5% vs 6.1%, $P < .01$). Frequencies of other symptoms, diagnoses, and medication usages were statistically insignificant between groups (Table).

While our findings support the possibility of a symptomatic distinction between SIBO and IMO, we did not observe a difference in IMO response rates to rifaximin monotherapy versus its combination with neomycin. This study's limitations include its retrospective and nonrandomized design, similar to many of its predecessors, with the potential for selection and recall bias. We could not control for other clinical interventions initiated alongside or after antimicrobial therapy leading to symptomatic improvement, and while our sample size is comparable to prior studies of this type, our finding of no difference between the two IMO treatment types may reflect an underpowered analysis. Our study is also limited by the relatively poor performance characteristics of lactulose-based BT (sensitivity 31%–68%, specificity 44%–100%), which the North American consensus statement frames as acceptable in lieu of a true gold standard but which a more recent Asian-Pacific consensus statement suggests as inferior to glucose-based BT.[8,9]

That said, the discordance between our results and earlier data regarding combination therapy for IMO suggest caution against the rapid entrenchment of novel treatment paradigms. Other groups have suggested the utility of rifaximin monotherapy in treating IMO, including in a recent randomized placebo-controlled trial of 13 patients with constipation.[10] Our findings also highlight lingering questions around CH_4 BT, including, for example, the clinical importance of methane produced by organisms in the oral cavity or colon and/or more subtle distinctions among elevation time points. Larger cohort studies are needed on the optimal therapeutic response to abnormal BT, perhaps with the necessary burden of proof increasing in proportion to a given treatment's potential for misapplication.

B. E. ROSENTHAL[1]
B. ZOLL[1]
H. N. RYAN[2]
E. TOTO[2]
J. C. REYNOLDS[2]
N. K. AHUJA[2]
[1]Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
[2]Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, Pennsylvania

Correspondence:
Address correspondence to: Nitin K. Ahuja, MD, MS, Division of Gastroenterology and Hepatology, University of Pennsylvania, 3400 Civic Center Boulevard, 7 South Pavilion, Philadelphia, Pennsylvania 19104. e-mail: Nitin.Ahuja@pennmedicine.upenn.edu.

References

1. Baker J, et al. Am J Gastroenterol 2015;110:S1004–S1005.
2. Plauzolles A, et al. Clin Transl Gastroenterol 2023;14(4):e00556.
3. Hoegenauer C, et al. Nat Rev Gastroenterol Hepatol 2022;19(12):805–813.
4. Pimentel M, et al. Am J Gastroenterol 2020;115(2):165–178.
5. Shah SC, et al. Aliment Pharmacol Ther 2013;38(8):925–934.
6. Low K, et al. J Clin Gastroenterol 2010;44(8):547–550.
7. Pimentel M, et al. Dig Dis Sci 2014;59(6):1278–1285.
8. Rezaie A, et al. Am J Gastroenterol 2017;112(5):775–784.
9. Ghoshal UC, et al. Indian J Gastroenterol 2022;41(5):483–507.
10. Ghoshal UC, et al. Indian J Gastroenterol 2018;37(5):416–423.

2772-5723
https://doi.org/10.1016/j.gastha.2023.07.001

Received March 27, 2023. Accepted July 6, 2023.

Conflicts of Interest:
The authors disclose no conflicts.

Funding:
The authors report no funding.

Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Data utilized herein are available to other researchers upon request.

Reporting Guidelines:
Not applicable for this article type.