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Utility of wireless motility capsule and lactulose breath testing in the evaluation of patients with chronic functional bloating

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ABSTRACT

Background: The precise aetiology of chronic bloating remains poorly understood and underlying gastroparesis, small bowel bacterial overgrowth and colonic inertia may, individually or collectively, play a role.

Aims: In this retrospective cohort analysis of symptomatic patients with chronic persistent bloating, we determined the clinical utility of wireless motility capsule and lactulose breath test in further defining the underlying aetiology for functional bloating.

Methods: Consecutive patients with chronic bloating underwent clinical assessment, wireless motility capsule testing and lactulose breath testing using standard protocols.

Results: 52 patients qualified for inclusion in this analysis, fulfilling Rome III criteria for functional bloating. Most patients (54%) had an abnormal wireless motility capsule study; of those, 11.5% had evidence of gastroparesis, 7.7% had small bowel transit delay, 15.8% had colonic inertia, 3.8% had delayed gastric and small bowel transit, 5.6% had combined gastric and colonic transit delay, 3.8% had delayed small bowel and colonic transit, and 5.6% had delayed gastric, small bowel and colon transit times. Using clinical questionnaires the median scores for bloating, constipation and eructation were not significantly different. Neither constipation nor eructation was specific to gastroparesis or colonic inertia but bloating was numerically more prevalent and severe in patients with delayed small bowel transit. 40% of patients had positive lactulose breath test but had no distinguishing clinical characteristics.

Conclusions: Chronic functional bloating may reflect underlying gastroparesis, small intestinal bacterial overgrowth or colonic inertia. Wireless motility capsule and lactulose breath test are useful in the assessment of patients with bloating and should be considered during evaluation.

INTRODUCTION

Bloating is defined as a feeling of gaseousness or abdominal fullness, particularly after meals. The term abdominal distention is reserved for patients who exhibit a visible increase in abdominal girth. Eructation, burping or belching, imply the expulsion of excess gas from the stomach and they may or may not be related to bloating.[1] Bloating is quite prevalent and compromises the quality of life. In a US population survey, 31% of respondents met Rome I criteria for functional bloating.[2] Bloating is also a prevalent symptom of patients with irritable bowel syndrome (IBS).[3] In another population study, symptomatic respondents reported significantly more missed days from work, social or household activities.[4]

Small intestinal bacterial overgrowth (SIBO) is defined as the presence of excessive bacteria in the small intestine. Symptoms of SIBO are non-specific and include bloating, abdominal distension or discomfort, diarrhoea, and fatigue.[5] These symptoms likely reflect not only the degree of bacterial overgrowth and related mucosal inflammation but also the underlying cause, such as small bowel dysmotility and delayed transit.[6] Lactulose breath testing (LBT) is a widely used method for the diagnosis of SIBO and, if positive, allows for antimicrobial therapy aiming at bacterial eradication and symptom relief.

The wireless motility capsule (WMC; Smartpill, Medtronic, Sunnyvale, California, USA) is an ambulatory non-invasive and non-radioactive diagnostic sensor that continuously samples intraluminal pH, temperature and pressure as it moves through the gastrointestinal tract. Studies have shown that the estimated interparticipant coefficients of variation (COV) for gastric emptying time (GET) with WMC in health and gastroparesis are 28% and 34%, respectively (not different); the interindividual COV in small bowel transit time (SBTT) for health, gastroparesis and constipation are

33%, 33% and 37%, respectively; the COV in healthy, gastroparetic and constipated participants are 1, 0.93 and 0.99, respectively.[7] This new technology has permitted routine quantification of transit in all gut regions in a single test and it has been increasingly used for the diagnosis of gastroparesis and slow-transit constipation (colonic inertia).[7 8]

Since underlying gastroparesis, SIBO or chronic idiopathic constipation could all be underlying aetiologies for chronic persistent bloating, we examined the utility of WMC and LBT in clarifying the diagnosis and guiding therapy. We found that, through the use of these tests, a significant proportion of patients with functional bloating exhibit objectively demonstrable abnormalities that can be targeted and treated selectively and effectively.

PATIENTS AND METHODS

Patients: This retrospective cohort study was approved by the Institutional Research Board of El Camino Hospital and was conducted at the Neuro-gastroenterology and Motility Center of Silicon Valley Gastroenterology, in Mountain View, California, USA, a community-based referral practice. The study was considered exempt from the need for individual informed consent from participating patients. We included patients identified as suffering from chronic bloating (International Classification of Diseases (ICD)-10 code: R14.0), flatulence (ICD-10 code: R14.1), eructation (ICD-10 code: R14.2) and gas pain (ICD-10 code: R14.3). The Rome III criteria for functional bloating and IBS were used. Specifically, patients should experience recurrent feeling of bloating or visible distention for at least 3 days per month, onset of symptoms at least 6 months prior to presentation and presence of symptoms for at least 3 months. Patients should have insufficient criteria to establish a diagnosis of IBS or functional dyspepsia. Diagnostic criteria for IBS were recurrent abdominal pain or discomfort at least 3 days per month in the past 3 months associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool and onset associated with a change in form (appearance) of stool.[9]

Inclusion criteria: Included were patients who, after chart review that included symptom questionnaires, were fulfilling Rome III criteria for functional bloating and who had undergone both WMC and LBT. *Exclusion criteria*: Excluded from this analysis were patients fulfilling IBS criteria using the Rome III classification, and those with neurological conditions affecting motility, such as collagen vascular diseases, connective tissue diseases, endocrine disorders or opioid use (figure 1).

Patient questionnaires: On initial clinical evaluation, every patient included in the study had filled out a gastrointestinal symptom questionnaire that was reviewed in detail. In particular, the frequency and severity of bloating, constipation and eructation were recorded using a 0–3 scale, where 0 represents no symptoms, 1 mild and infrequent symptoms, 2 moderate and frequent symptoms, and 3 severe and daily symptoms.[10]

Lactulose breath testing: A 10 g lactulose load is orally administered to the patient, and exhaled breath gases are analysed at 15 min intervals. An increase in H_2 of 20 parts per million within 60–90 min is diagnostic of SIBO. Elevated fasting levels of H_2 and CH_4 have also been shown to be highly specific; a positive test required an elevated breath hydrogen concentration within 90 min, two distinct peaks and an increase >20 ppm.[11]

Wireless motility capsule: Briefly, the test starts with the ingestion of a meal to initiate the postprandial motility pattern following an overnight fast. The meal consists of a SmartBar (260 kcal, 2% fat, 2 g fibre), followed by 120 mL water. Immediately after the meal, the patient swallows the capsule with 50 mL water. Patients are then released and they are given the data receiver and a diary for recording bowel movements, food intake, sleep and gastrointestinal symptoms. Physical restrictions include no strenuous activities and refrain the use of medications that could affect gastrointestinal motility (ie, prokinetics) or pH (ie, proton pump inhibitors). Since food may alter gastric emptying, patients are asked to fast for 6 hours after capsule ingestion, after which they ingest a regular meal in order to allow for the evaluation of the fed response. Patients are then instructed to continue

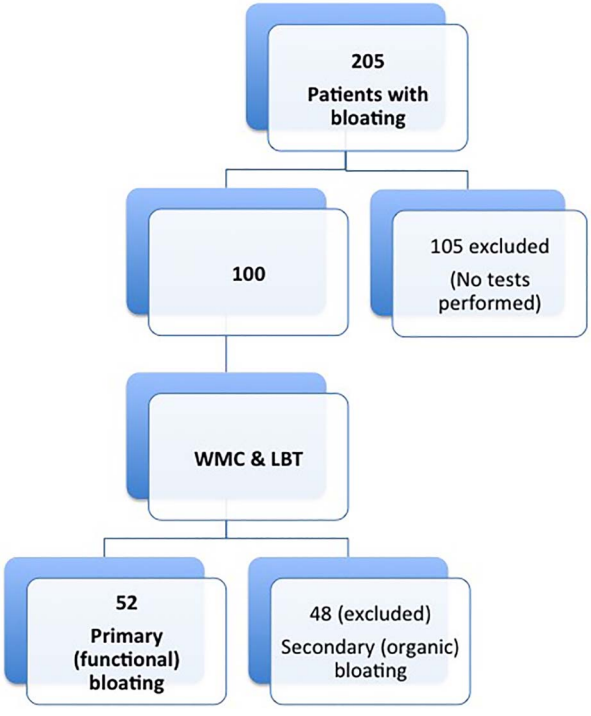

Figure 1 Study flow. Excluded patients either did not undergo WMC and LBT or were found to have other secondary diagnoses to explain chronic bloating. Only patients with chronic functional bloating based on Rome III criteria were analysed. LBT, lactulose breath testing; WMC, wireless motility capsule.

their regular diet and routine and to return the data receiver and diary after 5 days. Downloaded data are analysed using the display software.[7] The combinations of pH and temperature profiles are then used to calculate the GET, SBTT and colonic transit time (CTT). GET is defined as the time from capsule ingestion to its entry into the alkaline duodenal environment, and if longer than 5 hours, it is suggestive of gastroparesis.[12] SBTT is defined as the time from entrance into the duodenum to the capsule passage into the caecum, an event defined by a sustained pH drop of at least one pH unit that occurs as the capsule enters the caecum's more acidic environment. Normal SBTT should be 6 hours or less.[8] CTT is defined as the time from the capsule entry into the caecum to its passage from the body, manifested by a drastic temperature drop and normally it should be <59 hours.[13]

Statistical analysis

Data are presented with descriptive statistics of median values, SDs, IQRs and total ranges.

RESULTS

Figure 1 outlines the study flow. Over the period of 2/1/2014 and 2/1/2016, 205 patients were diagnosed with abdominal bloating. Of those, only 100 had undergone WMC and LBT and were reviewed in detail, while 105 were excluded either because the tests were not performed or because patients had one test and not the other. After chart review that included symptom questionnaires, 52 patients qualified for inclusion in this analysis, fulfilling Rome III criteria for functional bloating, while 48 were excluded because of IBS (using Rome III criteria), neurological conditions affecting motility (ie, Parkinson's disease, syringomyelia), collagen vascular diseases (ie, progressive systemic sclerosis), connective tissue diseases (ie, Ehlers-Danlos syndrome), endocrine disorders (ie, diabetes, hypothyroidism) or opioid use. The mean age of the cohort was 49 years (range 19–86); 11 males and 41 females.

Figure 2 depicts the WMC results. Most patients (54%) had an abnormal study; of those, 11.5% had evidence of gastroparesis (G), 7.7% had small bowel transit delay (S), 15.8% had colonic inertia, 3.8% had delayed gastric and small bowel transit (GS), 5.6% had combined gastric and colonic transit delay (GC), 3.8% had delayed small bowel and colonic transit, and 5.6% had delayed gastric, small bowel and colon transit times (GSC). The magnitude of delayed regional transit is shown in figure 3. The 14 patients with gastroparesis (isolated or mixed) had a median emptying time of 12.3 (SD 7; IQR 5.9–15.7; range 5.0–43.9) hours. The 11 patients with delayed SBTT (isolated or mixed) had a median transit time of 7.9 (SD 2; IQR 7.6–9.4; range 6.3–11.5) hours. Finally, the 16 patients with colonic inertia (isolated or mixed) had a median colonic transit of 76.5 (SD 25; IQR 69.3–85.9; range 62.7–89.9) hours. All these values reflect clinically significant transit delays, above the upper limits of normal for all three regional times tested with WMC.

Figure 4 shows the median scores for bloating, constipation and eructation as collected at baseline by clinical questionnaires. There were no significant differences among the eight groups defined by WMC. Although bloating was universally prevalent (100%) and numerically more severe (overall median score 2.2), constipation and eructation were prevalent throughout the groups, albeit at a lesser scale (65% and 61%, respectively) and lesser intensity (overall median scores 1.5 and 1.2, respectively). It is important to emphasise that neither constipation nor eructation were specific to the underlying diagnosis based on WMC, be it gastroparesis or colonic inertia. Nevertheless, the symptom of bloating was numerically more prevalent and severe in patients with delayed small bowel transit.

Figure 5 depicts the prevalence of SIBO by LBT positivity among the eight groups defined by WMC. Overall, 21/52 patients (40%) were positive and there were no distinguishing clinical characteristics that would suggest its presence. Nevertheless numerically, patients with isolated small bowel transit delay had an 80% prevalence of

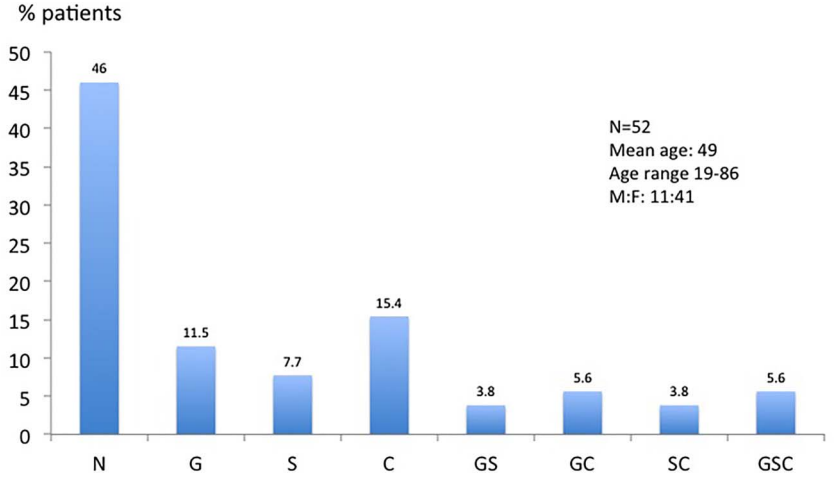

Figure 2 WMC results. Patients were classified as having N, G, S, C, GS, GC, SC or GSC. C, colonic inertia; F, female; G, gastroparesis; GC, combined gastric and colonic transit delay; GS, a combination of delayed gastric and small bowel transit; GSC, delayed gastric, small bowel and colon transit times; M, male; N, normal study; S, small bowel transit delay; SC, delayed small bowel and colonic transit; WMC, wireless motility capsule.

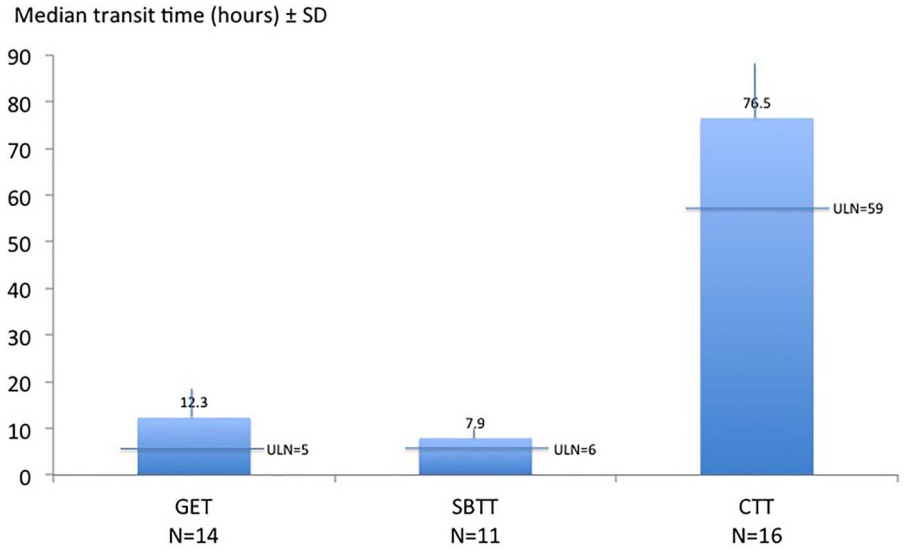

Figure 3 Magnitude of delayed regional transit by WMC. All values reflect clinically significant delays in transit above the ULN for all three regional times tested. SDs are shown. CTT, colonic transit time; GET, gastric emptying time; SBTT, small bowel transit time; ULN, upper limits of normal; WMC, wireless motility capsule.

SIBO, in contrast to other groups where the prevalence ranged from 0% to 40%. There was no significant correlation between SBTT and SIBO (p=0.85). Overall, 37/52 (71%) of patients had an underlying organic cause identified if investigated and only 15/52 patients (29%) had normal studies and remained undifferentiated.

DISCUSSION

The aim of our study was to determine any clinical utility in performing WMC and LBT in patients with chronic bloating. We have demonstrated that such patients cannot be further characterised on the basis of clinical history and symptom assessment since their symptoms overlap. In our study, out of the undifferentiated 52 patients with chronic functional bloating, 14 were diagnosed with gastroparesis, 11 with small bowel transit delay, 16 with colonic inertia and some exhibited combined abnormalities (multiregional dysmotility). Many of these patients were found to have SIBO in addition to their underlying dysmotility. Obviously, these results have therapeutic implications, since different targeted therapies can be applied, alone or in combination, for each patient.

The underlying pathophysiology of chronic bloating is multifactorial and challenging to decipher. Increased gas production, impaired gas transit and evacuation, or abnormal sensation have all been implicated and extensively studied.[1 14–18] Psychosocial distress may contribute to the overall symptom perception and its impact on the patient's quality of life.[19] SIBO is frequently implicated in symptom induction but not always explored or proven and often treated empirically with antibiotics, such as rifaximin.[20 21] Dietary measures and probiotics are extensively recommended.[1] Under the circumstances of a complex and multifaceted pathogenesis, targeting

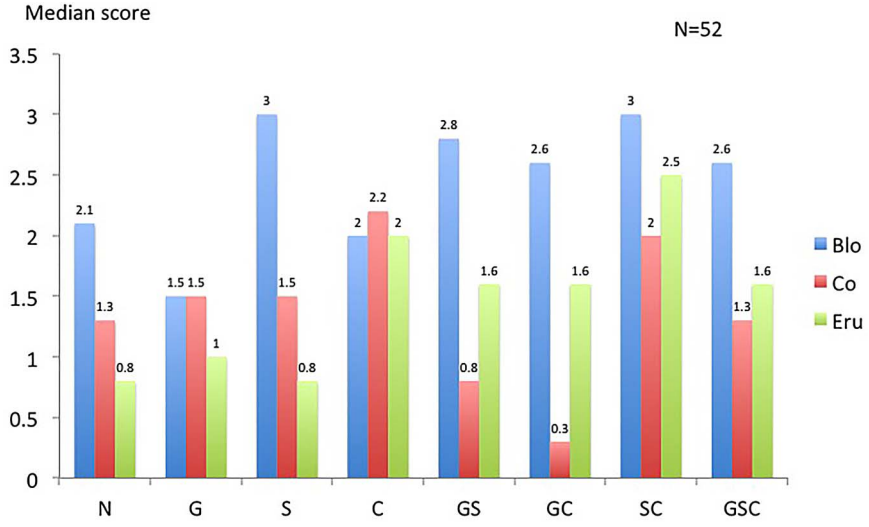

Figure 4 Median scores for Blo, Co and Eru as collected by clinical questionnaires. There were no significant differences among the eight groups defined by WMC. Patients were classified as having a N, G, S, C, GS, GC, SC or GSC. Blo, bloating; C, colonic inertia; Co, constipation; Eru, eructation; G, gastroparesis; GC, combined gastric and colonic transit delay; GS, a combination of delayed gastric and small bowel transit; GSC, delayed gastric, small bowel and colon transit times; N, normal study; S, small bowel transit delay; SC, delayed small bowel and colonic transit; WMC, wireless motility capsule.

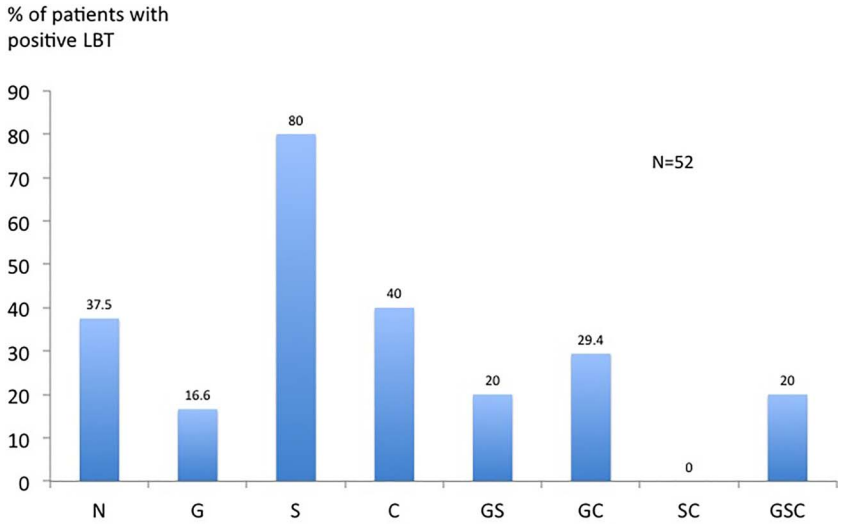

Figure 5 Prevalence of SIBO among the eight groups defined by WMC. Patients were classified as having N, G, S, C, GS, GC, SC or GSC. C, colonic inertia; G, gastroparesis; GC, combined gastric and colonic transit delay; GS, a combination of delayed gastric and small bowel transit; GSC, delayed gastric, small bowel and colon transit times; LBT, lactulose breath testing; N, normal study; S, small bowel transit delay; SC, delayed small bowel and colonic transit; SIBO, small intestinal bacterial overgrowth; WMC, wireless motility capsule.

therapy in patients with bloating found to have specific abnormalities is poised to be more successful. In our study, for example, patients were treated for SIBO with antibiotics, for gastroparesis with metoclopramide or pyloric BoTox injections and, for colonic inertia, with lubiprostone and linaclotide. Such therapeutic efforts, however, were not formally assessed as part of our study given its retrospective nature and the lack of standardisation of the end points for each therapy. Prospective trials will be needed in order to examine the impact of such targeted therapies in patients with functional bloating further characterised by WMC and LBT, in comparison with those patients who remain undifferentiated and empirically treated. Given the multiregional dysmotility noted in our study, such trials will be challenging, since many patients may require multiple interventions (ie, metoclopramide for gastroparesis and linaclotide for colonic inertia). Further, proper instruments to accurately assess clinical response will need to be developed that will capture the specific elements of therapeutic response or lack thereof.

Abdominal distention, bloating and flatulence account for nearly one million office visits per year in the USA,[22] but frequently they are dismissed, minimised or empirically attributed to IBS requiring no therapeutic intervention. Therefore, such patients frequently find themselves searching for answers and solutions for their distress by visiting several practitioners and specialists, and undergoing repetitive imaging and endoscopic evaluations before a specific explanation for their bloating is found. Our study suggests that the usage of WMC and LBT can transform the non-specific symptoms of bloating, constipation and eructation into specific disorders of regional gut transit, such as gastroparesis, SIBO or colonic inertia, as well as multiregional dysmotility syndromes (figure 2). Indeed, less than one-third of our patients had normal studies and no explanation for their symptoms. In this regard, our data are consistent with that of other groups from large specialist referral centres using WMC[23–25] and/or LBT.[26 27]

There are some strengths and weaknesses in this analysis. First, since the study was conducted in a community-based cohort seeking more specific answers and options for a chronic, unexplained and troublesome symptom, its findings could be applicable to the general population with functional bloating. Second, the study carefully excluded other common diagnoses that would potentially explain chronic bloating, such as IBS and other states of disordered motility, thereby further characterising the phenotype of chronic functional bloating using Rome III criteria. Third, the performance of WMC and LBT led in many patients not only to a specific diagnosis but also therapy theretofore unavailable. However, the retrospective nature of our study does not allow us to accurately reflect on the precise prevalence and severity of the abnormalities we identified or the impact and true benefit of the treatment applied. For example, there were patients who were excluded because they either did not have both studies performed or they only had one or the other, mainly due to insurance authorisation or inability to swallow the WMC. A prospective study design using WMC and LBT, followed by standardised therapeutic intervention depending on the findings would be needed and, most likely, beneficial to many of these patients. Fourth, inherent limitations of the WMC in assessing SBTT (ie, due to unidentifiable pH landmarks) or of the LBT in assessing SIBO (ie, due to smoking, poor exhalation or prior abdominal surgery allowing colonic bacteria to colonise the small bowel) may challenge their validity. Although such scenarios are possible in large patient cohorts, in our limited patient sample, we did not encounter any such technical issues.[8 11 27]

In conclusion, chronic bloating may reflect underlying gastroparesis, SIBO or colonic inertia. In this cohort analysis, 54% of patients with functional bloating had abnormal WMC, identifying gastroparesis, delayed SBTT and colonic inertia (or combinations). Clinical symptoms are not sensitive or specific and up to 40% of patients with functional bloating have SIBO. Overall,

WMC and LBT are useful in the assessment of patients with bloating and should be considered during evaluation.

Competing interests None declared.

Ethics approval El Camino Hospital Institutional Review Board (IRB).

Provenance and peer review Not commissioned; externally peer reviewed.

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