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Original Article

Alternative Gastrointestinal Conditions Identified in Patients Meeting Rome IV Criteria for Irritable Bowel Syndrome or Functional Diarrhea Referred to Secondary Care: A Prospective Study

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ABSTRACT

Introduction: Organic gastrointestinal (GI) disorders can be missed in individuals with irritable bowel syndrome (IBS). This study investigated the frequency of organic disorders in patients with diarrhea-predominant IBS or functional diarrhea and the impact of treatment for any identified alternative diagnoses.
Methods: Between April 2019 and March 2020, the results of comprehensive investigations, including blood and fecal tests, a 75selenium homophobic acid taurine scan, a breath test, and endoscopies performed on consecutive eligible patients, were recorded. Symptom burden was reassessed after treatment for any GI conditions identified.
Results: 66 (15 males) consecutive patients were included. Two patients (3%) were diagnosed with colonic malignancy; 21 (38%) had bile acid diarrhea; one (1%) had pancreatic exocrine insufficiency; and 31 (54%) had small intestinal bacterial overgrowth. 21 patients (32%) had at least two GI diagnoses. Significant improvement in symptoms occurred following treatment ($p<0.0001$).
Conclusions: Multiple co-existing conditions were detected in many of these patients, with one-third of the cohort having more than one abnormal test. When these alternative diagnoses were treated, patients reported significant symptomatic improvement. Larger studies are required to validate our findings, and these patients' investigative and management pathways should be amended accordingly.

1. Introduction

Although international consensus-derived criteria recommend that patients can be diagnosed with irritable bowel syndrome (IBS) if they have specific symptoms, 'red flags' are absent. There is no serological evidence of inflammation or coeliac disease, many studies suggest that an alternative gastrointestinal (GI) disorder can frequently be identified in patients confidently diagnosed with IBS. These include bile acid diarrhea (BAD), cancer, carbohydrate malabsorption, coeliac disease, infectious diarrhea, inflammatory bowel disease, microscopic colitis, pancreatic exocrine insufficiency (PEI), and small intestinal bacterial overgrowth (SIBO). However, studies report widely differing prevalences of these conditions [1].

There are no published studies on people whose symptoms meet diagnostic criteria for IBS that investigate participants for all the conditions listed above and report the change in symptoms using patient-reported outcome measures when such a condition is diagnosed and treated.

In this study, we recorded the alternative diagnoses detected in a consecutive series of patients with diarrhea-predominant IBS (IBS-D) and functional diarrhea (FD) following comprehensive investigations. We also measured changes in their symptoms and quality of life, prospectively following lifestyle advice when necessary and standard treatment of all alternative conditions detected.

2. Methods

Our Clinical Governance and Research and Innovation Departments of the United Lincolnshire Hospitals National Health Service Trust approved this study as a prospective clinical service evaluation. It was not considered to require written informed consent by the patients as all tests conducted fall within the standard investigative pathway comprehensively to look for potential aetiologies in chronic diarrhea in these patients.

We recorded investigation results and outcomes following intervention in patients newly referred to our "diarrhea clinic" by their GPs for secondary care management of persistent GI symptoms.

Between April 2019 and March 2020, we identified consecutive adults prospectively aged $\geq$ 18 and $\leq$ 50 years old who had symptoms fulfilling the Rome IV criteria for IBS-D or FD but no "red flag" symptoms at the time of their first clinic visit in Lincoln

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Table 1: First and Second-Line Investigations

First-line Investigations
Blood Tests
Full blood count
Bone profile
C-reactive protein
Erythrocyte sedimentation rate
Liver function tests
Tissue transglutaminase antibody with immunoglobulins
Thyroid function tests
Urea and electrolytes
Vitamin B12 and folate
Stool Tests
Microbiological culture
Pancreatic faecal elastase-1
Faecal calprotectin
Guaiac faecal occult blood (FOB)
Breath Tests and Imaging
Lactulose hydrogen breath test (HBT)
SeHCAT scan
Gastroscopy with duodenal biopsies (if no upper GI endoscopic investigation within past 12 months)
Endoscopy-Based Tests
Flexible sigmoidoscopy with left-sided mucosal biopsies (if no lower GI endoscopic investigation within past 12 months), if:
• Negative FOB, and
• Faecal calprotectin < 50 μg/g
Or Colonoscopy with colonic biopsies, if:
• Positive FOB, or
• Faecal calprotectin > 250 μg/g
Second-line Investigations
Lactose hydrogen breath test
Fructose hydrogen breath test
Fasting gut hormone profile

FOB, Faecal occult blood; HBT, Hydrogen breath test.

County Hospital, UK. Patients were excluded from this study if they had undergone any previous abdominal surgery (except appendicectomy, inguinal/femoral hernia repair, or Caesarean section). Patients were also excluded if they were pregnant or breastfeeding or had a history of coeliac disease, cancer, inflammatory bowel disease, or pancreatic disease.

All clinic patients were investigated similarly, so this study did not reflect a change in clinical practice. If the physical examination was unremarkable, first and second-line investigations were arranged accordingly (**Table 1**).

Before each appointment, all patients completed a Patient Reported Questionnaire and the Gastrointestinal Symptom Rating Scale (GSRS), (**Supplemental material**). This questionnaire is validated for patients with functional bowel symptoms [2, 3, 4]. In this study, a (≥30% reduction in the overall GSRS score is considered a good response to treatment with significant symptom improvement [5]. The GSRS questionnaire was modified by adding two 11-point visual analog scales evaluating the quality of life and the impact of GI symptoms on quality of life and a Bristol Stool Chart assessing the patient's 'best' and 'worst' bowel frequencies and stool forms. In addition, to avoid missing relapsing and remitting symptoms [6], we asked patients to complete the questionnaire based on their symptoms over the preceding month rather than the two weeks originally specified. Some questions were shortened, and 17 additional symptoms were added to allow for a more holistic assessment. All these additional items were deemed clinically relevant, and their inclusion allowed a more holistic assessment of the patient's overall symptom burden. They can be categorized into three major domains – upper GI, lower GI, and perianal symptoms. In addition, two visual analog scales evaluating the quality of life and the impact of GI symptoms on quality of life and a Bristol Stool Chart assessing the patient's 'best' and 'worst' bowel frequencies and stool forms were included in the questionnaire. All these modifications made to the original questionnaire give a better reflection of patients' overall GI burden and have been adopted in clinical practice by Professor Andreyev, an experienced clinician and Professor in gastroenterology.

2.1. Dietary factors

The dietary fiber intake of all patients was assessed at the baseline using a questionnaire that contains 31 items **(Supplemental material)**. A potential maximum of 41 points can be scored; one point is approximately equivalent to 1.5g of fiber; therefore, a score (≤10 suggests a low dietary fiber intake, whereas a score (≥20 indicates a high dietary fiber intake. Recommendations were made, and leaflets on dietary fiber were given to those with a low or high dietary fiber intake.

A questionnaire Supplemental material assessed total daily caffeine intake. An intake of (≥400 mg/day was considered high, and these patients were advised to try reducing their caffeine intake.

All patients were asked to complete an Alcohol Use Disorders Identification Test (AUDIT), a validated screening tool detecting early signs of excessive alcohol use [7]. Patients who scored (≥8 on the questionnaire were recommended to reduce their alcohol intake.

2.2. Treatments used

All patients were provided with written information for all treatments prescribed and were given a face-to-face follow-up appointment one month after starting treatment to assess response until the start of the first national lockdown following the outbreak of coronavirus 2019, when follow-up appointments were conducted via telephone.

All patients with BAD were recommended to reduce their total daily fat intake to 20% of their daily calorie intake [8, 9]. With moderate to severe BAD (SeHCAT 7-day retention 0%-<10%), patients were also prescribed cholestyramine 4 g sachets and asked to titrate the dose up to a maximum of three sachets a day, taken with food, according to the response. If not tolerated, colesevelam was offered instead, starting with one 625mg tablet with food and titrating up to a maximum of seven tablets daily in split doses. Patients with mild or borderline BAD (SeHCAT 7-day retention 10-20%) were initially treated with diet alone; if that was not adequate or could not be maintained long-term, a sequestrant was offered [10].

Table 2: Baseline Characteristics of the 66 Patients in the 'Diarrhoea' Clinic

Characteristic	Male	Female	Total
Number of patients (n)	15	51	66
Age, median (range)	34 (20–50)	34 (18–50)	34 (18–50)
BMI, mean (± SD)	27.7 (±5.6)	29.4 (±6.4)	29.0 (±6.3)
Ethnicity			
White	13	50	63 (95%)
Asian	1	1	2 (3%)
Black	1	0	1 (2%)
Rome IV Criteria			
IBS-D	10	34	44 (67%)
FD	5	17	22 (33%)
Duration of symptoms (months), median (range)	60 (6–240)	36 (6–360)	36 (6–360)
Questionnaires			
Fibre intake (points), mean (±SD)	14.4 (±4.3)	12.5 (±4.4)	13.2 (±4.3)
Caffeine intake (mg), median (range)	200 (16.25–1725)	206.5 (9.75–780)	201.25 (9.75–1725)
AUDIT score, median (range)	4 (1–11)	2 (0–14)	3 (0–14)

Patients diagnosed with PEI were prescribed 25,000-unit Creon® (pancrelipase) capsules and advised to take 50,000–75,000 units with main meals and 25,000–50,000 units with snacks or any drinks except for water, black tea, and black coffee.

If SIBO was diagnosed following a breath test, patients were offered seven days of rifaximin 550mg twice daily for hydrogen (H2) positive tests or rifaximin 550mg and neomycin 500mg twice daily for methane (CH4) positive tests [11, 12].

Patients diagnosed with villous atrophy were advised to follow a gluten-free diet. Those diagnosed with lactose or fructose malabsorption were advised to avoid lactose or fructose from their diet. Both groups were also referred to the dieticians for further advice.

Overflow diarrhea was treated with two doses of Picolax® sachets followed by a 7g sachet of Normacol® granules (sterculia), to be taken once or twice daily long term.

2.3. Statistics

Descriptive statistics were used to describe the identified baseline demographics and prevalence rates of GI conditions. For both categorical and continuous variables, normally distributed data were expressed as mean (SD), and non-normally distributed data were expressed as median (range). Paired scores were compared using Wilcoxon non-parametric tests to determine changes in total GSRS, quality of life, and impact of GI symptoms on life quality between baseline and follow-up. All statistical analyses were conducted using Stata SE 16 (StataCorp LLC, USA). A two-sided alpha level of 0.05 was used to test for statistical significance.

3. Results

3.1. Patient Demographics

Between April 2019 and March 2020, 66 consecutive patients were included, 44 (67%) meeting the Rome IV criteria for IBS-D and 22 (33%) FD. The majority were female (77%), with a median age of 34 years old; they had been symptomatic for a median of three years at presentation. Four patients had a high dietary fiber intake (range 20-22), and 18 had a low dietary fiber intake (range 2-10). 15 patients consumed>400 mg caffeine daily (median 517.25 mg/day, range 450-1725). Eight patients scored ≥ 8 (range 9-14) on the AUDIT questionnaire **(Table 2)**.

The mean total GSRS baseline symptom score was 31 ± 12. Abdominal pain, bloating, diarrhea, fecal urgency, and a sense of incomplete emptying were the dominant symptoms. The prevalence of baseline individual GI symptoms and bowel frequencies are shown in **(Figure 1)** and **(Figure 2)**. Baseline stool forms varied between types 4 and 7. Almost all patients with predominant type 7 stool had occasions when they passed type 4 stool.

3.2. Investigation Findings and Outcomes of Treatments (Table 3) (Supplemental material)

3.2.1. Blood tests

All blood tests were normal except for one patient with iron deficiency anemia. Urinalysis, upper and lower GI endoscopies, and small bowel capsule endoscopies were normal. His anemia was attributed to his poor diet.

3.2.2. Stool tests

Stool samples for microbiology and calprotectin were produced by 64 patients. None grew pathogens. Three patients had a raised fecal calprotectin between 100 and 250 µg/g in their initial and repeat stool samples, but no endoscopic evidence of inflammatory bowel disease was found.

Two FOB tests were positive. At colonoscopy, one patient had an adenocarcinoma in her sigmoid colon. No cause for the positive FOB was found in the other.

3.2.3. Pancreatic FE-1 <500ug/g

65 patients had their FE-1 level tested; one (1.5%) had severe PEI (FE-1 (≤100 µg/g). The CT scan of her pancreas was unremarkable. This patient also had moderate BAD. 11 patients (17%) had an equivocal FE-1 (200-500 µg/g). Of the 12 patients, 10 (83%) had IBS-D, and two (17%) had FD. They had a mean (SD) body

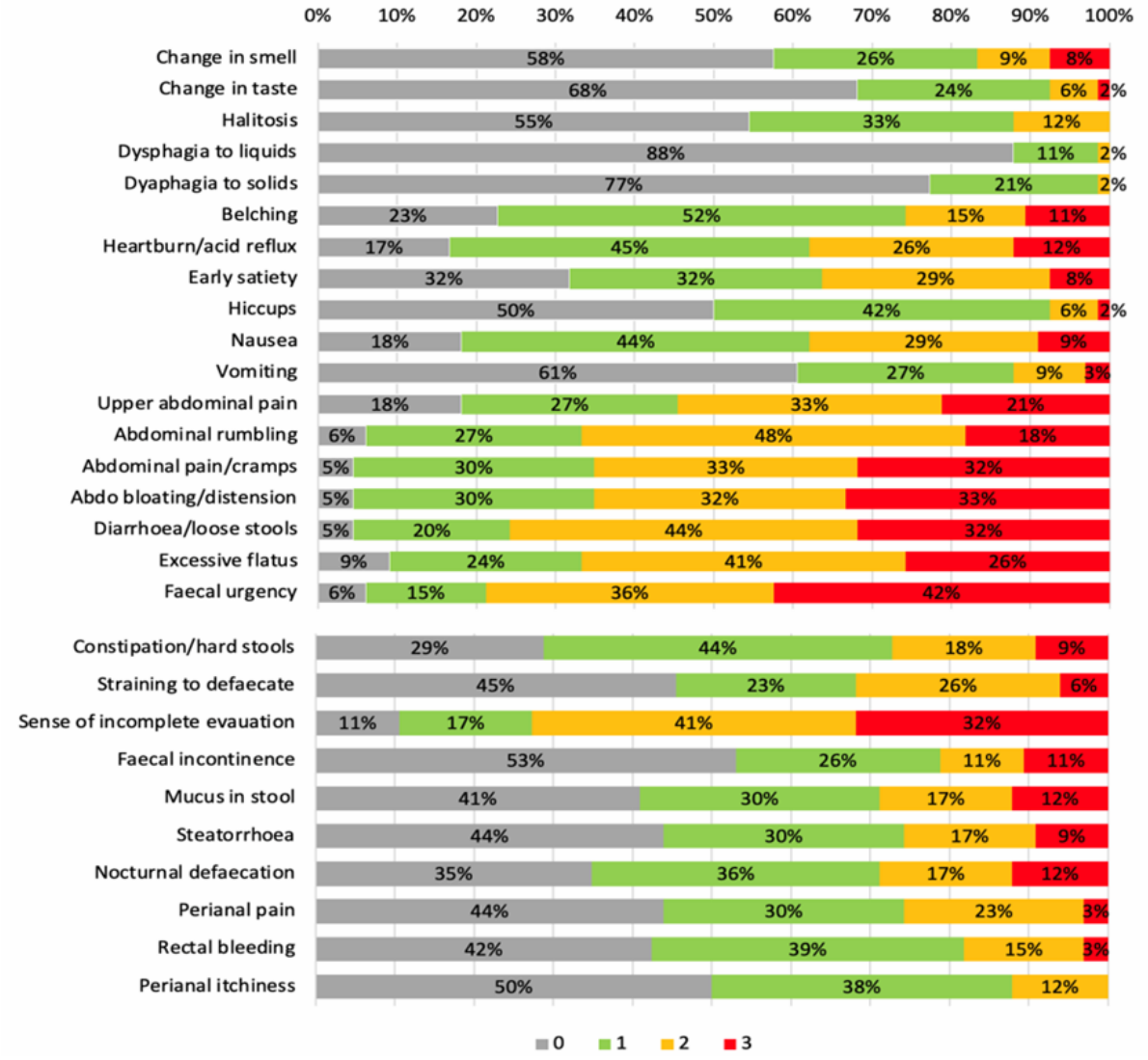

Figure 1: The GI symptoms and function reported by the 66 patients at baseline. GSRS, Gastrointestinal Symptom Rating Scale.

mass index of 29.3 (7.4). Four also had SIBO, and four were also diagnosed with BAD.

Of interest was that four of the ten patients with a FE-1 of 200-500 µg/g treated with Creon® reported a good clinical response **(Supplemental material)**. The median GSRS score reported by the patients benefiting from Creon® reduced from 38 (range 27-48) at baseline to 32 (range 10-42) at follow-up (p= 0.04). Changes in quality of life score and the impact of GI symptoms on quality of life were not statistically significant (p= 0.24 and 0.15, respectively).

3.2.4. Lactulose HBT

57 patients underwent lactulose HBT, and 31 (54%) were positive, 52% with a rise in H2, 39% with a rise in CH4, and a 3% rise in both gases. Of the patients with an abnormal HBT, 24 (77%) met the criteria for IBS-D and seven (23%) for FD. A second diagnosis was made in 18 patients: ten had BAD, seven PEI and one villous atrophy.

Following first-line antibiotic treatment, 12 (39%) patients with an abnormal HBT reported improvement in GI symptoms **(Supplemental material); the total** GSRS reduced from 30 (range 10-50) at baseline to 16 (range 1-47) (p= 0.0002). Quality of life and impact of GI symptoms on quality of life improved from a median baseline score of 5 (range 0-8) to 7 (range 2-10) (p= 0.004) and from a median baseline score of 8 (range 3-10) to 6 (range 1-10) (p= 0.001), respectively.

3.2.5. SeHCAT scan

56 patients underwent two scans, and 25 (45%) had a retention rate of (≤20% after one week. Three patients (5%) had severe BAD, nine (16%) had moderate BAD, nine (16%) had mild BAD, and four (7%) had borderline BAD. Of these 25 patients, 22 patients (88%) met the criteria for IBS-D and three (12%) for FD. A second diagnosis was made in 14 patients: four had PEI, and 10 had SIBO.

Improvement was reported by 18 of 23 treated patients **(Supplemental material)**. The median baseline GSRS of 35 (range 10-48) dropped to 17 (range 3-39) (p= 0.0005). The quality of life improved from a baseline median score of 6 (range 1-10) to 8 (range 3-10) (p= 0.0002); the impact of GI symptoms on life

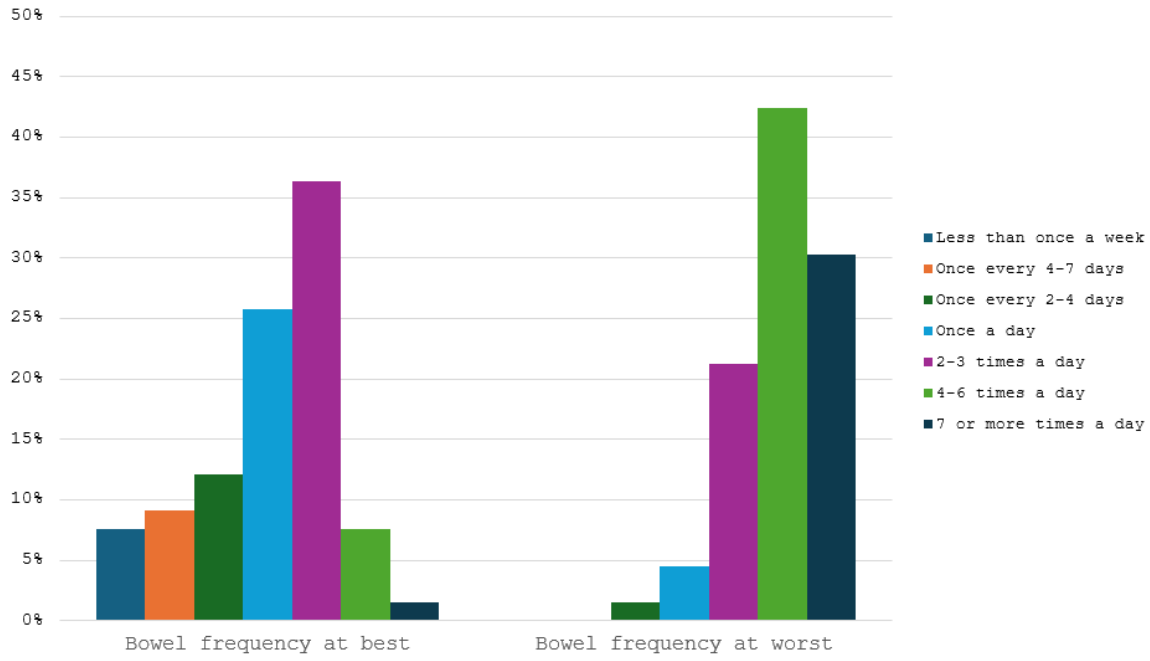

Figure 2: Bowel frequency reported by the 66 patients at baseline.

quality reduced from 8 (range 4-10) at baseline to 4 (range 0-8) ($p< 0.0001$).

3.2.6. Endoscopic assessment

Thirty-eight patients underwent gastroscopy with duodenal biopsies, 33 had flexible sigmoidoscopies, and t10had colonoscopies. Twenty-eight patients had their endoscopies canceled due to the coronavirus pandemic.

Two patients (3%) had negative coeliac serology but histological features of crypt hyperplasia with marked villous atrophy consistent with Marsh type 3b on the duodenal biopsies. Both patients reported a good symptomatic response after switching to a gluten-free diet, with their baseline GSRS improving from 39 to 11 and 40 to 27, respectively. Their quality of life also improved from 5 to 7 and from 2 to 5, respectively.

Two patients (3%) were found to have a Dukes B sigmoid adenocarcinoma, although only one initial FOB test was positive, and neither patient was anemic nor iron deficient. Both patients underwent curative surgical resection of their tumors, and follow-up appointments were arranged with the surgical team. No follow-up data were available for both patients.

3.3. Other findings

Overall, 21 (32%) patients had more than one cause found for their symptoms. 16 patients with unremarkable initial investigations underwent second-line investigations, with one patient identified with fructose malabsorption and referred for dietetic input. Lactose HBTs and tests for neuroendocrine tumors in the other 15 patients were unremarkable.

On revisiting the symptoms of these 15 patients at follow-up, eight patients gave a history of intermittent straining to defecate, a sense of incomplete emptying, and a short period of symptom relief after having the bowel preparation for their lower GI endoscopy. An abdominal X-ray was performed on these patients; three had colonic fecal loading. Overflow diarrhea with severe fecal impaction was diagnosed. Two of the patients were also found to have grade III hemorrhoids during their lower GI endoscopy and were referred for potential surgical intervention.

12 (21%), ten with IBS-D and two with FD had no abnormal tests. Two patients were started on amitriptyline with a good clinical response. Four were referred to dieticians for a trial of a diet low in fermentable oligo-, di-, mono-saccharides, and polyols. The other six did not want further input as their symptoms had spontaneously improved.

4. Discussion

This study demonstrates that a significant proportion of patients who fit the Rome IV diagnostic criteria for IBS-D or FD referred to a secondary care “diarrhea clinic” have at least one alternative diagnosis potentially accounting for their symptoms. Standard first-line therapies led to the alleviation or abolition of symptoms in many patients. Treating all identified alternative diagnoses was often required to achieve clinical improvement.

Many previous studies have examined the co-existence of one specific organic GI condition in patients with IBS-type symptoms, predominantly BAD and SIBO [1]. However, this is the first study that looks for a wide range of potential diagnoses. Our study has also considered the role of significant dietary indiscretion in contributing to symptoms, be it fiber, caffeine, or alcohol. In addition, our study is unique in objectively assessing treatment outcomes using patient-reported measures if any of these new diagnoses are made.

The prevalence of most of the conditions we identified is similar to data reported elsewhere in studies that have looked for the co-existence of one specific organic GI condition in patients with IBS-type symptoms [1]. The fact that the majority of patients reported a clinical response after appropriate treatments also suggests that the conditions were correctly identified. Thirdly, the response rates

Table 3: Investigations Undertaken and Number of Abnormalities Detected

Investigation	No. of Patients	Abnormalities Detected
First-line Investigations		
Baseline blood tests	66	1 iron deficiency anaemia
Stool Tests		
Microbiological culture	64	0
Faecal calprotectin	64	3
Pancreatic faecal elastase-1 (FE-1)	65	1 severe PEI ((≤100 μg/g)
Guaiac faecal occult blood (FOB)	64	2 positive
SeHCAT scan	56	25 BAD (7-day retention (≤20%)
Lactulose hydrogen breath test (HBT)	57	31 positive
Endoscopy		
Gastroscopy	38	2 villous atrophy on duodenal biopsies
Flexible sigmoidoscopy	33	2 sigmoid adenocarcinoma
Colonoscopy	10	0
Second-line Investigations		
Fructose HBT	16	1
Lactose HBT	15	0
Fasting gut hormone profile	15	0
Other Tests		
Abdominal X-ray	8	3 with radiological evidence of faecal loading*
Small bowel capsule endoscopy	1**	0

*Only three patients were treated with laxatives as they reported intermittent constipation-type symptoms with evidence of faecal impaction on abdominal X-ray.
**The one patient with iron deficiency anaemia underwent a small bowel capsule endoscopy.

we saw are similar to other large studies that have looked at the response of these individual conditions to treatment [10, 13, 12, 14].

An important finding was a relatively high response rate to treatment in patients with "borderline" SeHCAT results (between 15-20% 7-day retention) and in almost half of patients with a pancreatic FE-1, which lies between 200-500 μg/g. Many clinicians would consider these a normal result; however, these response rates support previously published data challenging the view that a SeHCAT scan is significant only if the level is below 10% or 15% 7-day retention [10, 15, 9]. Also, a recent study has confirmed that a significant proportion of patients with a FE-1 level of between 200-500 μg/g may also respond to pancreatic enzyme replacement therapy[16]; however, while experts do acknowledge that this is possible, clinical data are lacking [17].

One limitation of our findings is that this was a non-randomized study, and symptom scores were compared to baseline in the same individual. There were no matched controls. Therefore, improvements may be related to placebo effects, although many patients had had a variety of previous treatments in primary care that had no benefit. The patient population captured in this study likely represents more complex cases and may not represent the broader IBS population.

A second limitation was that the coronavirus outbreak in March 2020 caused major disruptions to clinics and non-urgent investigations, resulting in some patients in this study not having complete investigations. It is, therefore, likely that GI diagnoses were missed in some. Lockdowns may also have minimized symptoms for other patients as they stayed home. Others may not have received full or appropriate treatment due to delayed or telephone follow-up. Therefore, the findings generated from this study with a small sample size should be interpreted cautiously.

A third limitation is that a number of patients received multiple interventions, particularly with respect to any detected dietary indiscretion, and this study did not assess specifically the impact of advice given to correct these, particularly when another cause was also treated. So, some of the measured improvements in outcomes may have been related to wider lifestyle changes than just a specific prescribed medication.

The follow-up period varied and ideally would have been longer – those with only one alternative GI condition identified and reporting an excellent treatment response stayed in this study for a much shorter period than those who required more than one form of treatment for multiple GI diagnoses.

After first-line antibiotic therapy for SIBO, improvement was only seen in four in ten treated patients. Our normal practice in people with a positive HBT is to try a first-line treatment and then, if there is no response, a second-line treatment. If HBT is still positive and the patient remains symptomatic, a small bowel aspirate is performed to attempt to grow the organisms causing SIBO and obtain antibiotic sensitivities. This meticulous approach was discarded as a result of the pandemic. Important data suggest that normalization of a HBT following antibiotics correlates with good treatment outcome [18], so appropriate treatment for SIBO should

be the goal. Our data also show that it is essential to measure both H2 and CH4 during the HBT.

Our three patients diagnosed with overflow diarrhea did well after treatment. However, fecal loading is a subjective diagnosis with no clearly defined X-ray features, and it remains unclear whether the presence of fecal loading captured on a single abdominal film correlates well with symptoms.

Finally, although the validity of the GSRS is well-documented, we used a modified version which has not been validated. Nonetheless, the modified GSRS was repeated to assess all patients at baseline and following treatment, and this uniform assessment provides an objective short-term trajectory for each patient's symptoms.

5. Conclusions

Despite these limitations, our data suggest that organic GI conditions can be detected in a large proportion of patients who could be easily misdiagnosed as having IBS. This can be detrimental not only to the patients but also to healthcare and society. If our data are reproduced by others, this would require a fundamental reappraisal of clinicians' use of symptom-based diagnostic criteria.

Conflicts of Interest

The authors declare that they have no competing interests that could have influenced the objectivity or outcome of this investigation.

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Institutional Review Board (IRB)

This study was registered and approved as a prospective clinical service evaluation and quality improvement project (Registration No. L0141) by the Clinical Governance and Research and Innovation Departments of United Lincolnshire Hospitals National Health Service Trust on 27 March 2019. The study was also approved by the specialty Audit Lead on 21 March 2019. As this was classified as a service evaluation using standard investigative pathways for chronic diarrhea, formal research ethics committee approval was not required under NHS Health Research Authority guidance.

Large-Language Model

None

Authors Contribution

DP designed the study, collected and interpreted data, and drafted and revised the manuscript; GM designed the study and drafted and revised the manuscript; JA designed the study and drafted and revised the manuscript. All authors reviewed and approved the final manuscript.

Data Availability

All data generated or analyzed in this study are included in this published article.

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