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TITLE PAGE

Title: Rational Investigations in Irritable Bowel Syndrome.

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Abbreviations:

BAD	bile acid diarrhoea
CRC	colorectal cancer
CRP	C-reactive protein
DRE	digital rectal examination
ESR	erythrocyte sedimentation rate
FC	faecal calprotectin
FBC	full blood count
HBT	hydrogen breath test
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IBS-D	irritable bowel syndrome with diarrhoea
MC	microscopic colitis
NSAIDs	non-steroidal anti-inflammatory drugs
PPIs	proton-pump inhibitors
SeHCAT	23-seleno-25-homotaurocholic acid
SIBO	small intestinal bacterial overgrowth
TFTs	thyroid function tests

ABSTRACT

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder, which accounts for a substantial proportion of a gastroenterologist's time in the outpatient clinic. However, there is variability in approaches to diagnosis and investigation between physicians, dependent on expertise. Many patients express disappointment over the lack of a patient-centred approach. Consequently, there have been calls for the care of IBS patients to be standardised, a process which aims to promote high-quality and high value care. Making an early diagnosis, based on a clinical assessment of symptoms, whilst limiting use of investigations, are key tenets of this process. Exhaustive investigation to exclude all organic pathology is unnecessary, and may be counterproductive. Routine blood tests in suspected IBS have low yield, but are an acceptable part of routine practice. All patients should have coeliac serology tested, regardless of their predominant stool form. Patients with diarrhoea should have a faecal calprotectin measured, and should proceed to colonoscopy to exclude inflammatory bowel disease if this is positive. Beyond this, the need for investigations should be made on a case-by-case basis, contingent on the reporting of known risk factors for organic pathology. Colonoscopy should be considered in any patient with alarm features for colorectal cancer, and in those whose clinical features are suggestive of microscopic colitis. A SeHCAT scan should be considered in patients with IBS with diarrhoea, a third of whom may actually have bile acid diarrhoea. There is no role for routine hydrogen breath tests for lactose malabsorption or small intestinal bacterial overgrowth.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder, with an estimated population prevalence of 10%, [1] which more commonly affects women [2] and younger individuals. [1] Patients with IBS experience abdominal pain in association with a change in the frequency or form of their stools, and are subdivided according to their predominant stool form into IBS with diarrhoea (IBS-D), constipation, or a mixed stool pattern. [3] The aetiology remains unclear, but a variety of factors have been implicated, including genetics, visceral hypersensitivity, disordered gastrointestinal motility, abnormalities of the brain-gut axis, and alterations in the gut microbiome. [4] Although the identification of these potential pathophysiological mechanisms has yet to yield any useful diagnostic strategies for clinical practice, it does cast doubt on the concept that IBS is a purely functional condition.

Nonetheless, whatever uncertainties exist in our understanding of IBS, what is clear is that this disorder has a substantial impact on patients, many of whom report considerable impairment of quality of life as a consequence of their symptoms, [5] and face daily challenges with working [6] and socialising. [7] This, in conjunction with other factors, [8, 9, 10, 11] such as the severity and chronicity of symptoms and fear of underlying organic disease, make individuals with IBS likely to seek the advice of a doctor. Up to 80% will consult in primary care, [10, 11] the majority of whom will be managed in this setting, [12] but some will be referred for a specialist opinion. [8] Consequently, patients with IBS account for between 10 and 25% of a gastroenterologist's workload in the outpatient clinic. [13] This highlights the importance of implementing a logical and evidenced-based approach to investigation and diagnosis.

Guidelines for the management of IBS advocate that a diagnosis is made on clinical grounds, without the need for exhaustive investigations in an attempt to rule out all possible organic pathology. [14, 15] Nevertheless, and due in part to the potential uncertainty that may surround the diagnosis, many physicians still consider IBS to be a diagnosis of exclusion. [16] Although undertaking extensive testing may offer both the physician and the patient some reassurance, repeatedly normal investigations may instead make the patient feel that the cause of their symptoms remains elusive, or that organic disease has been "missed". In preference, making an early and positive diagnosis of IBS following cogent use of limited investigations, together with a clear explanation, may help patients better accept the diagnosis and facilitate earlier treatment, [17] as well as minimise associated healthcare costs. [18] Indeed, direct care costs are considerable, estimated to be between £90 to £316 per patient per year in the UK, [19] and close to $1 billion per annum in the USA. [20]

Unfortunately, patients with IBS often perceive a lack of a patient-centred approach to their care, and management strategies can vary between physicians, dependent on expertise. Consequently, there have been recent calls to standardise the management of patients with IBS, with a focus on early diagnosis, rational investigation, and timely treatment, aiming to improve the overall quality and value of care in IBS. [21] Accordingly, this review endeavours to present a practical and evidence-based approach to diagnosing and investigating IBS to assist physicians in their day-to-day clinical practice.

MAKING A DIAGNOSIS OF IBS

A general approach

Making a diagnosis of IBS begins with a good clinical history. Questions should focus on establishing whether a patient has the cardinal symptoms of IBS: abdominal pain, often related to defaecation, which is associated with either a change in stool frequency, a change in stool form, or both. [3] Chronicity of symptoms should also be assessed, with attention paid to the presence of any alarm (red flag) features, such as weight loss or rectal bleeding. These raise concern for colorectal cancer (CRC), and require urgent lower gastrointestinal investigation, as per NICE guidance (Table 1). [22] However, alarm features have only modest accuracy for predicting CRC, with sensitivity ranging from 5% for detection of an abdominal mass to 64% for rectal bleeding, [23] and many patients with IBS will endorse them. [24] Similarly, symptoms that are often felt to be associated with new onset inflammatory bowel disease (IBD) do not perform particularly well, with sensitivities ranging from 14.5% for mucus PR to 53% for abdominal pain once a week or more. [25] Older patients (>50 years) presenting with a change in their bowel habit are likely to require further investigation before a diagnosis of IBS can be made.

Enquiring about a patient's medical history is also important. In a patient with loose stools, a history of cholecystectomy or right hemi-colectomy may suggest they have bile acid diarrhoea (BAD), rather than IBS-D. A family history of IBD, coeliac disease, or CRC may also be relevant. Review of the patient's medications might suggest drug-induced constipation, for example secondary to opiates, or diarrhoea occurring as a side-effect of a drug such as metformin or an anti-depressant, particularly selective serotonin re-uptake inhibitors. Alternatively, it may identify use of non-steroidal anti-inflammatory drugs

(NSAIDs) or proton-pump inhibitors (PPIs), which might indicate a diagnosis of microscopic colitis (MC), or NSAID-induced enteropathy.

Physical examination, including digital rectal examination (DRE), should be conducted to assist exclusion of organic gastrointestinal disease. A normal examination may be reassuring to both the physician and the patient, but, taken in isolation does not confirm a diagnosis of IBS. In patients with obstructive defaecation-type symptoms, pelvic dyssynergia should be considered; a DRE demonstrates paradoxical anal contraction on straining. [26]

Symptom-based diagnostic criteria

Manning and colleagues were the first to propose a method for diagnosing IBS based on the presence of certain gastrointestinal symptoms reported by the patient [27]. These led on to the development of the Rome criteria which, over the past 20 years, have emerged as the accepted gold-standard for the diagnosis of IBS. The most recent iteration, Rome IV, were published in 2016, [3] (Table 2) and include a number of changes compared with their predecessor, the Rome III criteria. [28] Unfortunately, their performance in diagnosing IBS is unclear, as they have not been validated in routine clinical practice. The Rome III criteria performed only modestly in previous validation studies in both the UK and Canada, [29, 30] although this can be augmented by incorporating blood results and other items from the clinical history. [30]

The Rome criteria were developed through a consensus of expert opinion among gastroenterologists and allied academics in the field of IBS. [3, 28] In primary care, surveys show that very few physicians are aware of, or use, symptom-based diagnostic criteria, [31] yet they are still able to diagnose IBS with confidence, using a pragmatic approach. [32]

Nevertheless, management guidelines for IBS in both primary and secondary care recommend their use. [14, 15]

ROLE OF INVESTIGATIONS IN SUSPECTED IBS

Careful deployment of investigations is important (see Figure 1), as it has been suggested that use of extraneous testing may reinforce abnormal illness behaviour. [17] A randomised controlled trial of a positive diagnostic strategy compared with exhaustive investigation in 302 patients with suspected IBS demonstrated higher costs and an extremely low yield for organic disease with exhaustive investigation, no difference in terms of effect on symptoms, and similar rates of patient satisfaction. [33]

Routine blood tests

A panel of routine blood tests is commonly performed in patients with suspected IBS, often when they are first assessed, and frequently prior to a referral to a gastroenterologist. However, in a study of 300 people with suspected IBS, measurements of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) identified only 3 patients with organic disease, all of whom had IBD, [34] and only one instance of organic pathology, biopsy-proven coeliac disease, following analysis of a full blood count (FBC). A meta-analysis of studies demonstrated a CRP <0.5mg/dL in patients with typical IBS symptoms conferred a <1% risk of IBD, whereas ESR was of little clinical utility. [35] Another study evaluating the yield of an FBC and serum biochemistry in 196 patients with IBS detected no cases of organic disease. [36] In a pooled analysis of data from five studies examining yield of thyroid function tests (TFTs) in IBS, 91 of 1860 patients with IBS (4.2%) had an abnormal result; [37] the background prevalence of abnormal TFTs in the general population is almost

identical. Overall, routine blood tests have a low yield in suspected IBS, but are an acceptable part of everyday clinical practice; a normal CRP appears to be reassuring.

Testing for coeliac disease

British Society of Gastroenterology guidelines for the management of coeliac disease recommend serological screening for the condition in any patient with suspected IBS. [38] A recently updated meta-analysis identified 12 case-control studies, recruiting patients with suspected IBS and healthy controls, in whom testing for possible coeliac disease was conducted. [39] Overall, odds of positive coeliac serology was almost three times higher, and odds of biopsy-proven coeliac disease more than four times higher, in patients with suspected IBS compared with healthy controls. This was the case irrespective of the patient's predominant stool form. These findings support serological screening for coeliac disease among all patients with IBS-type symptoms in secondary care. However, the yield in population-based studies was lower; [40, 41] the role of screening in a community setting remains uncertain.

Faecal calprotectin (FC)

Inflammatory bowel disease is an important differential for patients with suspected IBS-D. However, undertaking a colonoscopy, which is invasive and time-consuming, in all patients is neither feasible nor desirable, as it will be normal in a large proportion of those tested. [42] Faecal calprotectin (FC), a protein found in the cytosol of inflammatory cells, can be detected in stool, [43] and provides a non-invasive method for detecting possible IBD, and prioritising need for colonoscopy. Typically, this strategy is employed in primary care, as recommended by NICE and, until recently, a cut off of ≥50 mcg/g was used for referral. [44]

In a meta-analysis of six studies, including 671 adults with suspected IBD, all of whom underwent FC testing and colonoscopy, the authors reported a pooled sensitivity and specificity of FC for the diagnosis of IBD of 93% and 96% respectively. [45] Using FC to screen those with suspected IBD would lead to a 67% reduction in the number of patients requiring colonoscopy but, in a small proportion of individuals, a diagnosis of IBD will be delayed due to a false negative result.

In primary care, lower gastrointestinal symptoms are common, but prevalence of IBD is low. Consequently, a 50 mcg/g cut off for abnormal FC results in a high proportion of false positive tests among patients with IBS. [46] An updated FC pathway, advocated by NHS England and endorsed by NICE, [47] has been evaluated in over 1000 adult primary care patients with lower gastrointestinal symptoms. [46] In patients with no alarm features, normal routine bloods, and negative coeliac serology, a FC cut off <100 mcg/g identified IBS with 98% certainty. For a FC of >100 mcg/g, repeat testing was recommended, with a referral to gastroenterology if persistently elevated. Overall, FC testing in patients with diarrhoea can facilitate a positive diagnosis of IBS-D without recourse to colonoscopy, whilst identifying the minority with possible IBD who require further investigation.

Colonoscopy

Despite advice to the contrary, colonoscopy is commonly performed in patients with suspected IBS. A national survey in the USA highlighted that around 25% of all colonoscopies were performed in patients with typical symptoms of IBS. [48] In a prospective case-control study, enrolling 466 patients with suspected non-constipated IBS without alarm features there was no significant difference in the prevalence of structural abnormalities of the colon, when compared with 451 controls undergoing colonoscopy for

CRC screening or polyp surveillance. [49] There were seven cases of MC, but no cases of CRC, and only two individuals were found to have IBD.

A cross-sectional survey of over 4000 patients undergoing colonoscopy for assessment of lower gastrointestinal symptoms demonstrated no significant difference in the prevalence of organic disease between 203 patients who met the Rome III criteria for IBS and 3975 individuals who did not. [50] Overall, 21 cases of organic disease were identified in those with suspected IBS, including five cases of CRC. However, around 70% of the cohort meeting Rome III criteria were over 50, and all five CRCs occurred in this group. These findings support lower gastrointestinal investigation in older patients with IBS-type symptoms.

Patients with MC can present with similar symptoms to IBS, [51] but determining who should be referred for colonoscopy can be difficult. One study demonstrated that in patients with chronic diarrhoea, age ≥50 years, female sex, use of PPIs or NSAIDs, weight loss, and absence of abdominal pain were significantly associated with biopsy-proven MC. [52] In another study, presence of nocturnal stools and having diarrhoea for less than 12 months at presentation were also identified as independent predictors of MC. [53]

In spite of the low yield for organic pathology in suspected IBS without alarm features, some would argue a negative colonoscopy is reassuring for the patient. However, a study in 458 patients with IBS challenges this idea; there was no evidence of an independent association between a negative colonoscopy and reassurance, nor any evidence of an improvement in health-related quality of life. [54] On the basis of available evidence, performing a colonoscopy in younger individuals with suspected IBS, without alarm features, cannot be recommended as it has a very low yield for organic disease. It should be reserved

for older individuals or those with abnormal FC, alarm features, including a recent change in bowel habit, or features suggestive of MC.

23-seleno-25-homotaurocholic acid (SeHCAT) scanning

Bile acid diarrhoea is common; the population prevalence is approximately 1%. [55] It can be diagnosed using SeHCAT scanning, although access remains an issue in some parts of the UK. [56] Among patients with IBS-D, a substantial proportion may have BAD, making this an important differential diagnosis, particularly as it can be treated effectively with bile acid sequestrants.

A meta-analysis, published in 2009, suggested that one in four patients with symptoms compatible with IBS-D had evidence of BAD, defined as a SeHCAT retention of <15% at 7 days. [57] However, many of the included studies did not apply accepted symptom-based diagnostic criteria to define IBS, meaning that patients with chronic painless diarrhoea were likely included. This could have led to an overestimation of the prevalence of BAD. However, the findings of prospective studies using the Rome criteria are corroborative of this meta-analysis, with one study recruiting 118 patients with Rome III-defined IBS demonstrating BAD in 28 (23.7%) patients, [58] and another conducted in 141 patients with Rome II-defined IBS reporting moderate BAD, with a SeHCAT retention of <10%, in 26 (18.4%). [59] An updated meta-analysis, incorporating these studies with others using recognised diagnostic criteria to define IBS, reported a pooled prevalence of BAD in patients with IBS of 28%. [60]

Some clinicians may prefer to undertake a therapeutic trial of a bile acid sequestrant rather than requesting a SeHCAT scan. However, this approach risks missing a diagnosis of BAD if the dose used is suboptimal, or if patients discontinue treatment due to side-effects. In

one study, 44% of patients with BAD confirmed by SeHCAT testing failed to respond to colestyramine. [61] One study demonstrated that higher body mass index predicted presence of BAD in IBS-D; [58] however, it is unclear which other patient characteristics, if any, can discriminate patients with BAD from IBS-D. Overall, due to the relatively high yield, referring patients with suspected IBS-D for a SeHCAT scan, where available, is probably advisable.

Hydrogen breath test (HBT) for lactose intolerance

A HBT can be used to screen for lactose malabsorption, which, if associated with clinical symptoms, such as bloating and abdominal pain, is referred to as lactose intolerance. A recent meta-analysis of 14 case-control studies, the majority of which diagnosed lactose malabsorption using a HBT, reported that prevalence of lactose malabsorption was not significantly higher among those with IBS. [62] This remained the case when data were analysed according to the test used, as well as the dose of lactose ingested.

Four of the included studies presented data relating to the subjective assessment of lactose intolerance, [62] with patients with IBS being significantly more likely than controls to report the occurrence of symptoms when eating lactose-containing foods. Only three studies provided data for objective lactose intolerance, whereby symptoms were reported during or shortly after the test in patients with confirmed lactose malabsorption. [62] Those with IBS were significantly more likely to have objective lactose intolerance than healthy controls, but this analysis should be interpreted with caution, as there was significant heterogeneity between studies.

Knowledge of whether a patient with IBS also has lactose malabsorption does not appear to alter clinical outcomes. In one study of 161 patients with IBS, 23 (14.3%) identified

lactose as a potential trigger prior to HBT, and lactose malabsorption was confirmed in 47 (29.2%), [63] but during almost 4 years of follow-up there was no difference in rates of symptom persistence or resolution between those with confirmed lactose malabsorption and those without. In another study, 23 patients with suspected IBS with confirmed lactose malabsorption followed a lactose exclusion diet for 3 weeks; only 9 (39.1%) reported symptom improvement. [64] Current evidence does not support a role for routine exclusion of lactose malabsorption in IBS. In those reporting a dietary intolerance to lactose, referral to a dietitian for a trial of exclusion could be considered.

Tests for small intestinal bacterial overgrowth (SIBO)

Small intestinal bacterial overgrowth has been postulated as an aetiological factor in IBS. The prevalence of SIBO in suspected IBS has been reported to be almost 80% in some studies using lactulose HBT. [65] Understandably, such findings sparked considerable interest in the use of non-absorbable antibiotics, such as rifaxmin, for the treatment of IBS. However, a Swedish case-control study using jejunal aspirate and culture, often considered to be the gold-standard for diagnosing SIBO, cast doubt on this; [66] prevalence of SIBO was no higher in 162 patients with Rome II-defined IBS than in 26 healthy controls. Another case-control study reported that the prevalence of a positive lactulose HBT was equivalent between 224 patients with IBS diagnosed according to the Rome II criteria and 40 healthy controls. [67]

A meta-analysis of 12 studies concluded the prevalence of SIBO was highest when HBT was used, compared with jejunal aspirate and culture, but varied between patients with IBS and controls depending on threshold used to define a positive test. [68] Statistical

heterogeneity in the analyses was substantial, despite exclusion of small studies with fewer than 90 participants.

Whether a positive HBT in IBS truly represents SIBO, and hence whether SIBO is genuinely being missed in patients with IBS-type symptoms, is debatable. In a Canadian study, patients ingested a radio-labelled meal and 10g of lactulose simultaneously, and underwent subsequent scintigraphic scanning to estimate oro-caecal transit time, as well as a lactulose HBT. [69] The high rate of positive HBTs in patients with IBS appeared to be related to rapid intestinal transit; the rise in breath hydrogen corresponded to the time at which the meal entered the caecum in almost 90% of patients. Overall, therefore, current evidence does not support the use of testing for SIBO routinely in patients with suspected IBS unless there are other documented risk factors, such as previous gastric or intestinal surgery, intestinal dysmotility, or known structural abnormalities, [70] although prior surgery was associated with a 65% rate of false positive results in one study. [71]

CONCLUSION

The majority of patients with suspected IBS can be diagnosed confidently following a detailed history, eliciting the cardinal symptoms as described by the Rome criteria. Exhaustive investigation is not required and may be counter-productive. Routine blood tests are reasonable, although they have a low yield, and all patients should have serological testing for coeliac disease, irrespective of their predominant stool pattern. Any patient with suspected IBS-D should have a FC measured and, if this is positive, proceed to colonoscopy to exclude IBD. Need for further testing should then be assessed on a case-by-case basis, and guided by the presence of known risk factors for organic pathology. Colonoscopy should be considered in any patient reporting alarm features for CRC, and in those whose clinical features suggest a possible diagnosis of MC. A SeHCAT scan should be considered in patients with IBS-D, a third of whom may actually have BAD. There is no role for routine HBT for lactose malabsorption or SIBO, unless there are clear risk factors for the latter, although patients who report a dietary sensitivity to lactose may benefit from a dietitian review and a trial of dietary exclusion.

In conclusion, encouraging physicians to make an early positive diagnosis of IBS, limiting the need for clinical investigations, creates the opportunity for initiation of earlier symptom-specific treatment, whilst reducing associated healthcare costs. Adopting a standardised and evidence-based approach is vital to achieve high-quality and high-value care for patients with IBS.

Table 1: Alarm features raising concern for possible CRC. [23]

Refer adults for suspected colorectal cancer if:
Aged ≥ 40 with unexplained weight loss and abdominal pain
Aged ≥ 50 with unexplained rectal bleeding
Aged ≥ 60 with: - Iron deficiency anaemia - Change in their bowel habit - Tests show occult blood in faeces
Consider referring adults for suspected colorectal cancer if:
Aged < 50 with rectal bleeding **and** any of the following unexplained symptoms or findings: - Abdominal pain - Change in bowel habit - Weight loss - Iron deficiency anaemia
Adults of any age with an abdominal or rectal mass

Table 2: The Rome IV criteria for the diagnosis of IBS.

Rome IV IBS Diagnostic Criteria [3]
1. Recurrent abdominal pain, on average, at least **1 day per week** in the last 3 months and associated with two or more or the following:
a. **Related** to defaecation
b. Associated with a change in frequency of stool
c. Associated with a change in stool form
2. Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Figure 1: Suggested diagnostic algorithm for patients with IBS.

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