The overlap between irritable bowel syndrome and organic gastrointestinal diseases

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Irritable bowel syndrome (IBS) is a common functional bowel disorder characterised by symptoms of recurrent abdominal pain associated with a change in bowel habit. This condition is one of the most frequent reasons to seek a gastroenterology consultation in primary and secondary care. The diagnosis of IBS is made by identifying characteristic symptoms, as defined by the Rome criteria, and excluding organic gastrointestinal diseases that might otherwise explain these symptoms. Organic conditions that can be mistaken for IBS include coeliac disease, inflammatory bowel disease (IBD), colorectal cancer, and, in those with diarrhoea-predominant symptoms, chronic gastrointestinal infections, microscopic colitis, and primary bile acid diarrhoea. The concept of small intestinal bacterial overgrowth being associated with IBS is shrouded with controversy and uncertainty, mainly because of invalid tests due to poor sensitivity and specificity, potentially leading to incorrect assumptions. There is insufficient evidence to link IBS-type symptoms with exocrine pancreatic insufficiency or with symptomatic uncomplicated diverticular disease, since both are hampered by conflicting data. Finally, there is growing appreciation that IBS can present in patients with known but stable organic gastrointestinal diseases, such as quiescent IBD or coeliac disease. Recognising functional gut symptoms in these individuals is paramount so that potentially harmful escalations in immunosuppressive therapy can be avoided and attention can be focused on addressing disorders of gut–brain interaction. This Review endeavours to aid clinicians who practise adult gastroenterology in recognising the potential overlap between IBS and organic gastrointestinal diseases and highlights areas in need of further research and clarity.

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Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that manifests with symptoms of abdominal pain and altered bowel habits in the absence of abnormal findings on routine clinical tests that could explain the symptoms.[1–3] The pathophysiology of IBS is unknown, but the prevailing hypothesis pertains to a disorder of gut–brain interaction with various factors of relevance, either alone or in combination. These factors include visceral hypersensitivity, abnormal gastrointestinal motor function, altered gastrointestinal mucosal and immune function, abnormalities in the gut microenvironment, and altered CNS processing.[4,5]

On the basis of a meta-analysis published in 2020, the global prevalence of IBS in 53 studies that used the Rome III criteria, from 38 countries and comprising 395 385 participants, was 9·2% (95% CI 7·6–10·8).[6] By contrast, pooled IBS prevalence among six studies that used the Rome IV criteria, from 34 countries and comprising 82 476 individuals, was 3·8% (95% CI 3·1–4·5).[6] The marked difference in IBS prevalence rates between the Rome III and Rome IV criteria can be mainly explained by the former being characterised by abdominal pain or discomfort at least 3 days a month in association with altered bowel habit, whereas the contemporaneous and more stringent Rome IV iteration characterises IBS as abdominal pain at least one day per week in association with altered bowel habit. To date, two large population-based studies have concurrently evaluated the prevalence of IBS using the Rome III and Rome IV criteria in tandem within the same cohort of participants.[7,8] A cross-sectional study across the USA, Canada, and the UK comprising 5931 adults found IBS to affect 9% of the population when the Rome III criteria were applied, but this value decreased to 4·6% with use of the Rome IV criteria.[7] A global study on the epidemiology of functional gastrointestinal disorders, including 30 countries from six continents and 73 076 adult respondents, yielded similar results for IBS.[8]

The first presentation of a patient with IBS to a physician usually takes place between the age of 20 years and 40 years, with a decrease in reporting among older patients.[9,10] In clinical practice, IBS accounts for almost a third of all gastroenterology cases seen in primary care, with a subsequent third of these being referred onto secondary care for further evaluation.[9] The economic burden of IBS is considerable, with calculations from the USA noting total direct and indirect expenditures exceeding US$20 billion.[11] Considerations for reducing direct costs associated with IBS include establishing an early diagnosis, primarily through recognising key symptoms, and minimising inappropriate and repeated investigations for potential organic pathology.[12] An estimated quarter of all colonoscopies are done for inappropriate reasons, of which individuals with IBS represent a third.[13,14]

The symptoms of IBS

The cardinal symptoms of IBS, as currently outlined by the Rome IV criteria, are chronic recurrent abdominal pain associated with an altered bowel habit.[5] The abdominal pain should be present for at least 1 day per week in the past 3 months, with onset at least 6 months before diagnosis. Moreover, the abdominal pain has to be associated with at least two of the following three symptoms: related to defecation, associated with a change in frequency of stool, or associated with a change in form

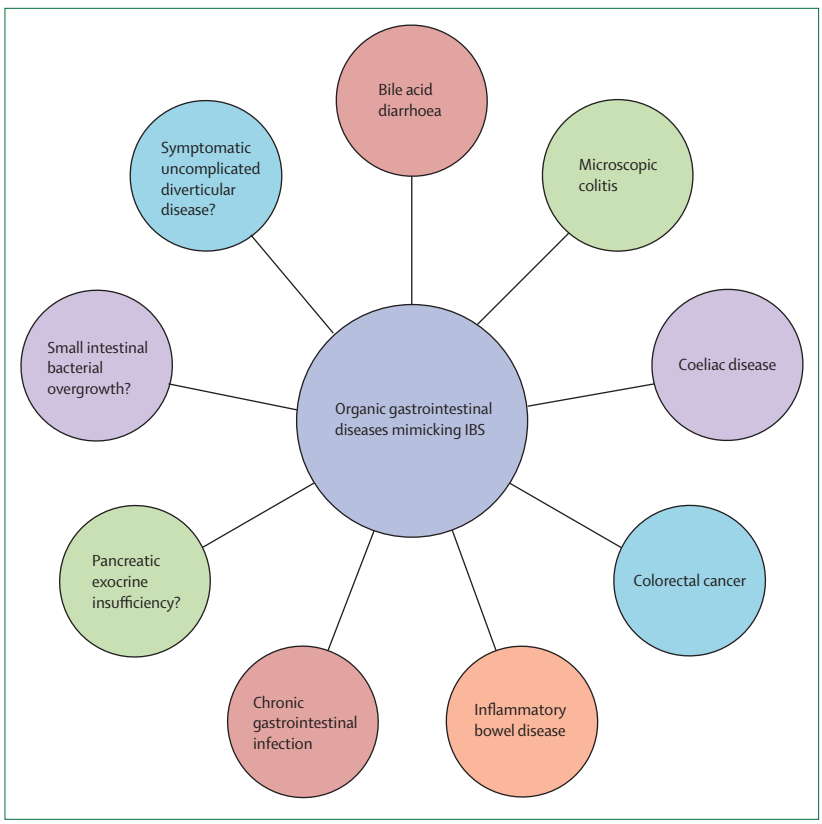

Figure 1: **Organic gastrointestinal diseases that mimic the symptoms of IBS**
IBS=irritable bowel syndrome.

(appearance) of stool. Depending on the predominant bowel habit on days of abnormal stool pattern, IBS can be further subdivided, with relative equal distributions of a third, into IBS with predominant diarrhoea (IBS-D), constipation (IBS-C), or mixed bowel habits (IBS-M), with the remaining few termed as unclassified IBS.[7] Patients commonly also report abdominal bloating and distension, although these symptoms are not a prerequisite for the diagnosis of IBS.[5]

Other features that aid a diagnosis of IBS include the presence of symptoms compatible with another functional gastrointestinal disorder (emanating from other gastrointestinal regions, such as the oesophagus or gastroduodenum), which can be seen in about a third of IBS cases and correlate positively with increased health impairment and health-care use.[15] Moreover, patients with IBS commonly report somatic symptoms, which are medically unexplained extraintestinal complaints.[16] Prevalent somatic symptoms include back pain, limb pain, headaches, chest pain, dizziness, fainting spells, palpitations, breathlessness, menstrual cramps, dyspareunia, insomnia, and lethargy. There is also a substantial overlap with other functional somatic syndromes, in particular fibromyalgia (a chronic somatic pain disorder), interstitial cystitis (a chronic pelvic pain syndrome with symptoms referable to the bladder), and chronic fatigue syndrome.[16] Finally, psychological distress is frequently associated with IBS, which emphasises the concept of a bidirectional relationship between the gut and the brain.[17] In a third of individuals a mood disorder precedes gut symptoms, but in two-thirds gut symptoms precede the mood disorder.[17]

Organic gastrointestinal diseases that mimic symptoms of IBS

Although it is important to recognise the characteristic symptoms of IBS, as defined by the Rome criteria, these symptoms are not specific and could present as a feature of an organic gastrointestinal disease. Validation studies report that symptom-based criteria perform only modestly in distinguishing IBS from organic gastrointestinal diseases, although these criteria can be enhanced by incorporating the presence of psychological and non-gastrointestinal somatic symptoms, and normal blood and stool tests.[18–20] Organic gastrointestinal diseases that can mimic the symptoms of IBS are colorectal cancer, inflammatory bowel disease (IBD), coeliac disease, and, in the context of IBS-D type symptoms, chronic gastrointestinal infection, primary bile acid diarrhoea, and microscopic colitis. The role of small intestinal bacterial overgrowth (SIBO), pancreatic exocrine insufficiency, and symptomatic uncomplicated diverticular disease and their link to IBS remain shrouded with uncertainty (figure 1).

Colorectal cancer

The probability of colorectal cancer in patients presenting with IBS-type symptoms is low, ranging from 0% to 2·7%.[21–25] An initial increase in risk for colorectal cancer in patients with IBS has been reported in three previous studies, although no association between the two conditions was seen after excluding the first year of follow-up.[26–28] These increased risks within the first year are likely to be explained by diagnostic confusion because of overlapping symptomatology.

IBD

The burden of IBD is rising globally, with worldwide prevalence surpassing 0·3%.[29] The pretest probability of IBD in patients presenting with symptoms compatible with IBS has been quoted as ranging from 0·4% to 3·5%,[21–24] although one study reported values as high as 15%.[25] Conversely, the pooled prevalence for IBS-type symptoms among patients with IBD in remission is 32·5% (95% CI 27·4–37·9), with an odds ratio of almost five compared with controls.[30,31]

Chronic gastrointestinal infections

Consideration that a possible infective cause might be underlying IBS-D type symptoms should always be suspected in patients who are immunocompromised or in those who live in, or have travelled to, high risk endemic areas.[32] Persistent diarrhoea occurs in about 3% of individuals travelling to low-income countries.[32] Infective

causes are commonly protozoal (eg, *Giardia* and *Cryptosporidium*), with helminths, viruses, and bacterial pathogens less commonly implicated.[32] An Italian study noted *Giardia* to be present in 6·5% of suspected IBS cases,[33] whereas a Swedish study found three cases (about 1·5%) of chronic gastrointestinal infection in a series of 205 consecutive cases referred to a gastroenterology unit for assessment of chronic diarrhoea.[34] In this cohort, IBS-D was the most common diagnosis after a thorough clinical evaluation. The US Centre for Disease Control and Prevention recommend that stool testing for giardiasis should be done in people who have drunk contaminated water (eg, lakes, rivers, and streams), travelled to endemic areas, had contact with animals who have the disease, had exposure in day-care settings, and in men who have sex with men. Observations have also linked colonic spirochetosis with IBS, and in particular with the diarrhoeal subtype, but whether this condition is the cause of the symptoms has yet to be established.[35–37]

Finally, postinfectious IBS is important and defined as the development of IBS following an episode of gastroenteritis. A systematic review and meta-analysis of 45 studies, comprising 21421 individuals with infective enteritis, found that 10·1% developed postinfectious IBS.[38] The highest prevalence occurred after protozoal infections (41·9%), then bacterial infections (13·8%), and the lowest prevalence was with viral infections (6·4%). The overall risk of developing IBS within the first 12 months was four times higher in patients exposed to an enteric infection than in non-exposed controls. However, after 12 months, the relative risk of having IBS was twice as high in exposed versus non-exposed individuals, suggesting that in a subset of patients the symptoms of postinfectious IBS disappear over time. In fact, after a viral enteric infection there was no difference in the prevalence of IBS compared with non-exposed controls after 12 months. Risk factors associated with the development of postinfectious IBS include female sex, severity of infective enteritis, use of antibiotics, and the presence of psychological distress.[38]

Coeliac disease

Contemporary epidemiological studies recognise that coeliac disease is common, with a prevalence of about 1% of the general population.[39] Moreover, many patients with coeliac disease do not present with the classical description of malabsorption, but rather with heterogeneous and non-classical symptoms, including those mimicking IBS, which might be seen in almost 40% of patients with coeliac disease.[39,40] Conversely, a systematic review and meta-analysis showed a pooled prevalence of biopsy-proven coeliac disease of 3·3% among individuals with IBS-type symptoms, with an odds ratio of 4·5 compared with healthy controls, and this finding was consistent across all IBS subtypes.[41] Most international guidelines recommend testing for coeliac disease in individuals presenting with suspected IBS,[42–44] a concept supported by cheap tests (ie, coeliac serology) for a common condition in which a gluten-free diet leads to a substantial improvement in symptoms and quality of life.[39]

Microscopic colitis

Microscopic colitis used to be considered rare, but recent studies suggest a pooled worldwide incidence of almost 10 cases per 100000 people per year.[45] Microscopic colitis has a female preponderance, with a ratio reaching 9:1, and is characterised by diarrhoea that is sometimes accompanied by abdominal pain.[45] Hence, microscopic colitis presentation might conceivably overlap with suspected IBS-D. Moreover, similar to IBS-D, the condition shows normal to near-normal findings at colonoscopy, and thus can be missed unless colonic biopsies are taken to identify its characteristic histological pattern.[45] A systematic review and meta-analysis reported that up to a third of patients with microscopic colitis have symptoms compatible with IBS-D.[46,47] Conversely, the presence of microscopic colitis in suspected IBS-D reaches 9·8% (95% CI 4·4–17·1), with a pooled odds ratio 6·5 times higher than for non-diarrhoeal controls (95% CI 1·66–25·5).[46,47] Other groups have reported a much lower prevalence of microscopic colitis in individuals with non-constipated IBS (about 1·5%),[23] although arguably they might have underestimated its prevalence by considering patients with IBS-D and IBS-M, thereby diluting the patient pool, and restricting biopsies to the rectosigmoid colon.[23] Restricting biopsies to a specific area might miss the disease in 18–34% of cases.[48] Hence, awareness of microscopic colitis as a cause of IBS-D type symptoms is important, particularly because misdiagnosis with subsequent delays to appropriate therapy can be experienced by up to a third of patients.[49] A large multicentre, case-control study found that age older than 50 years, nocturnal stools, weight loss, diarrhoea of less than 12 months duration, recent introduction of new drugs (in particular, selective serotonin reuptake inhibitors, proton pump inhibitors, and non-steroidal anti-inflammatory drugs), and comorbid autoimmune diseases were associated with an increased risk of microscopic colitis.[50] These factors might guide physicians towards carefully selecting which patients with suspected IBS-D should undergo colonoscopy, with biopsies specifically looking for microscopic coltis.[50,51]

Bile acid diarrhoea

Patients with a history of cholecystectomy, terminal ileal disease or resection, or pelvic radiotherapy are at risk of bile acid malabsorption and this condition might present with symptoms mimicking IBS-D and functional diarrhoea.[52,53] However, there are emerging data to suggest that even in the absence of the aforementioned risk factors, between one in three and one in four patients with symptoms compatible with IBS-D and functional diarrhoea have primary bile acid diarrhoea, in whom most will be categorised as being moderate to severe in nature.[54–56] The high prevalence of primary bile acid

diarrhoea is seen to a similar extent irrespective of use of the Rome III or IV criteria.[56] Moreover, colonic bile acid exposure correlates with bowel habit and colonic transit time, thereby supporting their role in symptom generation.[57] A simple and highly sensitive method of testing for bile acid diarrhoea is via the ^{75}selenium homocholic acid taurine (^{75}SeHCAT) test, in which retention of radiolabelled bile acids of less than 10–15% after 7 days is abnormal. The ^{75}SeHCAT test is available in the UK, Canada, and some European countries, but not in the USA. There are ongoing advances in detecting bile acid diarrhoea through alternate means, such as serum FGF-19, central for homoeostatic regulation of hepatic bile acid synthesis, and serum 7α-hydroxy-4-cholesten-3-one, a precursor of bile acid synthesis.[53] A study from the USA reported that 38% of patients with IBS-D had increased levels of serum bile acid precursors compared with healthy controls.[58] More recently, a large retrospective study from the USA found that of 936 patients with chronic unexplained diarrhoea, over 50% had increased faecal bile acid excretion whereas, in comparison, other diagnostic tests performed for organic diseases (eg, endoscopies and cross-sectional radiological imaging) had a yield of less than 10%.[59]

Unfortunately, given the limited availability of these tests, excluding primary bile acid diarrhoea is not currently within the routine investigational algorithm for IBS-D type symptoms. However, for patients with easy access to testing, seeking a diagnosis of primary bile acid diarrhoea seems reasonable, because open-label treatment with bile acid sequestrants improves gastrointestinal symptoms (particularly for those with severe disease) and reduces diagnostic investigations over the subsequent 5 years.[60] Some clinicians without resources to test for bile acid diarrhoea might consider a therapeutic trial of a bile acid sequestrant, although this approach might be limited by the palatability of bile acid sequestrant and clinical uncertainty regarding diagnosis.[56,61,62] In such circumstances, selecting the patient with the highest pretest probability of primary bile acid diarrhoea might be a thoughtful option, with data suggesting that individuals who are overweight or obese are potentially reasonable candidates in view of the prevalence of primary bile acid diarrhoea in this cohort reaching almost 60%, compared with around 20% who were of normal weight.[56]

Further acceptance of the primary bile acid diarrhoea model in IBS-D will be guided by randomised controlled trials to determine whether bile acid sequestrates are superior to standard IBS-D therapies (eg, diet, loperamide, antispasmodics, and tricyclic antidepressants).

SIBO

Contrary to initial enthusiasm strongly linking SIBO and IBS, data have been weak, leading to scepticism, and consequently, routine testing for SIBO in IBS is not recommended.[63] Case-control studies evaluating the prevalence of SIBO in IBS and healthy participants have shown conflicting results.[63] Moreover, the tests available in routine clinical practice to diagnose SIBO, such as small bowel aspirate or the glucose and lactulose hydrogen breath test, have poor sensitivity and specificity.[63–65] For example, a positive lactulose hydrogen breath test is likely to be a consequence of rapid oral-caecal transit with ensuing colonic fermentation as opposed to SIBO.[64] Similar shortcomings have been shown with the glucose hydrogen breath test.[65] Hence, interpreting the effect of interventions on the basis of these tests is fraught with uncertainty and in need of further clarification. Future studies in this field should revolve around use of non-culture molecular techniques, with data showing mixed results.[66–68]

Pancreatic exocrine insufficiency

The symptoms of chronic pancreatitis might include abdominal pain or diarrhoea (or both), and hence could conceivably mimic those of IBS-D. A single-centre prospective study of more than 300 patients with suspected IBS-D reported the prevalence of pancreatic exocrine insufficiency as 6% (based on a pancreatic faecal elastase concentration of ≤100 μg/g), with symptoms subsequently improving after open-label treatment with pancreatic enzyme supplements.[69] Although these preliminary data were promising, there were notably no cases of pancreatic insufficiency seen in the functional diarrhoea control group. Moreover, subsequent studies have not replicated these findings, instead noting low faecal elastase concentrations in only 1·5–2·3% of patients with IBS-D,[70,71] and in whom only a few showed changes consistent with chronic pancreatitis after endoscopic ultrasound or CT of the abdomen.[71] Hence, the concept of pancreatic exocrine insufficiency as a frequent cause for IBS-D type symptoms does not have a strong evidence base, but this condition should be considered in patients with a history of excess alcohol intake.[70,71]

Symptomatic uncomplicated diverticular disease (SUDD)

Proponents of the concept of SUDD describe it as lower gastrointestinal symptoms in individuals with diverticula but without evidence of diverticulitis. As such, an overlap with IBS has been suggested, although the symptoms of SUDD are purported to be more severe, last for longer than 24 h per occasion, and are restricted to the left lower abdomen.[72] The pathophysiology of SUDD is poorly understood, with some evidence to suggest altered colonic motility, visceral hypersensitivity, enhanced central-pain processing, microbiome alterations, or subclinical inflammation playing causative roles.[72] However, data to suggest an association between SUDD and gastrointestinal symptoms are unclear, with conflicting outcomes, and have not led to any new therapeutic approaches. A Swedish population-based case-control study found that SUDD becomes more prevalent with age (<40 years, 0·7%; 40–44 years, about 2%; 45–54 years, about 10%; 55–59 years, about 25%; >60 years, 30–40%) and only in

those older than 60 years is its presence associated with increased abdominal pain and IBS-D type symptoms.[73] By contrast, a case-control study from the USA found no association between the presence (or number) of colonic diverticulosis and mucosal inflammation or gastrointestinal symptoms, thereby casting doubt on the existence of SUDD as a clinical entity.[74] Future studies are needed to clarify these inconsistent findings.

Making a diagnosis of IBS

The Rome IV criteria recognise that a confident diagnosis of IBS cannot be based solely on symptoms and requires exclusion of organic pathology, but with a comprehensive approach, invasive tests should only be necessary in a subset of patients.[5] The Rome IV committee propose that physicians embark on a thorough, yet straightforward, clinical enquiry to identify any alarm features or specific symptoms (eg, persistent, frequent, watery diarrhoea refractory to initial symptomatic treatment) that raise suspicion of another disease, and that only in patients who are positive should further investigations be done (figure 2). The alarm features (panel) should be elicited via the clinical history, abdominal and digital rectal examination, and by performing a panel of basic laboratory tests (full blood count, C-reactive protein, coeliac serology, and faecal calprotectin in patients with diarrhoea predominance).[5] A meta-analysis found that normal C-reactive protein or faecal calprotectin has a high negative predictive value and essentially excludes IBD.[75] Stool analysis for microbiology should be considered in individuals with a history that suggests possible infectious cause.[5] Routine testing for thyroid function is not mandated because the prevalence of an abnormal result in suspected IBS is similar to that of the background population (about 6%).[22]

Evidence to support adopting a conservative and logical stepwise approach mainly comes from a large multicentre, cross-sectional study from the USA involving 466 patients with suspected non-constipated IBS and no alarm features, in whom colonoscopy yielded no cases of colorectal cancer, seven (1·5%) cases of microscopic colitis, and two (0·4%) cases of IBD.[23] The low diagnostic yield of colonoscopy in IBS-C without alarm features is also favourable, with a prospective multicentre study from Japan reporting no cases of colon cancer or IBD in individuals younger than 50 years.[24] However, a single-centre secondary care study[25] casts doubt on this approach after reporting that one in six (15·4%) patients with IBS without alarm features, irrespective of subtype, exhibit organic colonic pathology, predominantly IBD.[25] The discrepancy in outcomes among the aforementioned studies might be attributed to partial assessment of alarm features (eg, some studies have no data about family history of IBD, nor inflammatory markers within the blood or stool). Since, a large study evaluating diagnostic outcomes of colonoscopy in 646 patients with symptoms compatible with Rome IV functional bowel disorders, stratified comprehensively according to the presence or absence of alarm features, found no cases of colon cancer, IBD or microscopic colitis in those without alarm features.[76] By contrast, the diagnostic yield of organic disease at colonoscopy in those with alarm features ranged from about 6% in IBS-C, to about 9% in IBS-M, and highest at about 17% amongst IBS-D. The increased prevalence of organic disease in diarrhoeal versus constipation disorders was accounted for by microscopic colitis (5·7% *vs* 0·0%) but not IBD (7·2% *vs* 4·0%) or colorectal cancer (4·2% *vs* 2·3%).[76] However, it is worth emphasising that most studies evaluating diagnostic outcomes in IBS-D have tended to focus on excluding organic pathologies that are conceptually considered by clinicians to be the most concerning, as in coeliac disease, IBD, and colon cancer, with less emphasis placed on microscopic colitis and primary bile acid diarrhoea, both of which represent the largest proportion of organic pathology in individuals with suspected IBS-D and cause considerable health impairment, but which can be effectively treated.[47,55] Furthermore, in patients with

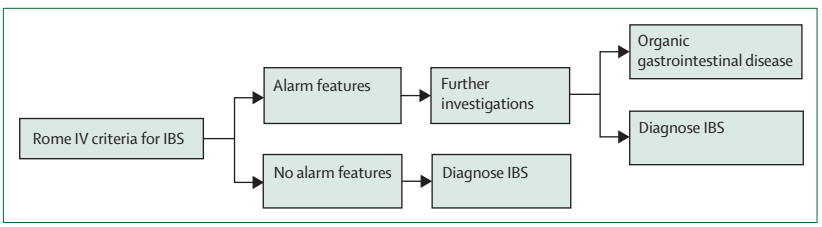

Figure 2: **Proposed diagnostic algorithm for patients with symptoms compatible with IBS**
In the presence of alarm features, further investigations should include an upper gastrointestinal endoscopy to obtain duodenal biopsies if coeliac disease is suspected, a colonoscopy to rule out colorectal cancer or IBD (and in those with IBS-D type symptoms, also microscopic colitis), and, where available, testing for bile acid diarrhoea in those with IBS-D type symptoms. Once IBS is diagnosed, the need for further or repeated investigations should be considered if patients do not respond to appropriate therapy or if new alarm features raise concern. IBD=inflammatory bowel disease. IBS-D=irritable bowel syndrome with diarrhoea.

***Panel*: Alarm features in patients with lower gastrointestinal symptoms that should prompt further investigations for organic pathology[1,2]**

- Age of symptom onset ≥50 years
- Recent change in bowel habit
- Rectal bleeding in the absence of documented bleeding haemorrhoids or anal fissures
- Unintentional weight loss
- Nocturnal pain or passage of stools
- Severe or progressively worsening symptoms
- History of cholecystectomy, terminal ileal resection, or pelvic radiotherapy
- Family history of colorectal cancer or inflammatory bowel disease
- Palpable abdominal mass or lymphadenopathy
- Evidence of iron deficiency anaemia on blood testing
- Positive coeliac serology
- Evidence of inflammation on blood or stool testing

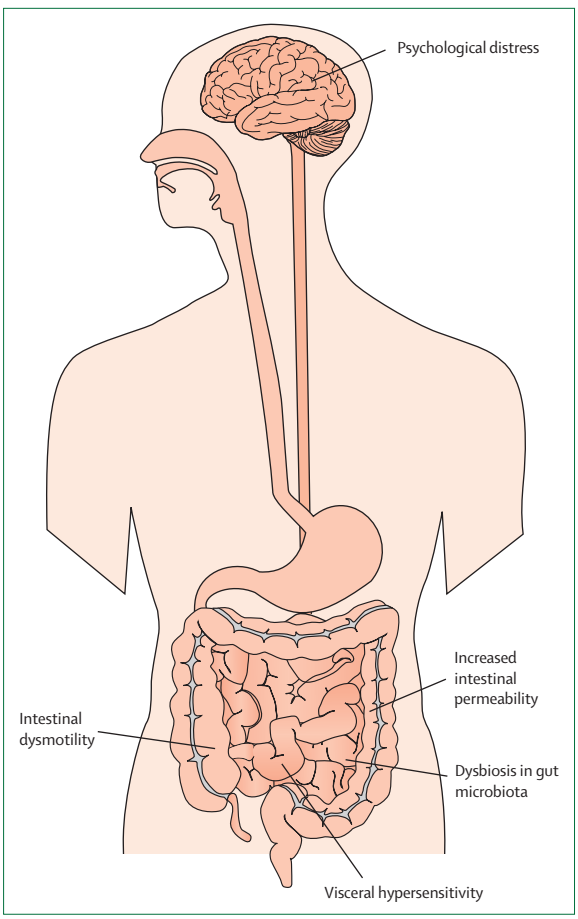

Figure 3: **Proposed pathophysiological factors of relevance for IBS-like symptoms in patients with inflammatory bowel disease in remission**
IBS=irritable bowel syndrome.

chronic non-bloody diarrhoea, these two diagnoses are the most common, after IBS-D and functional diarrhoea.[34] Hence, the true prevalence of organic pathology in patients with suspected IBS-D is yet to be clearly elucidated, but based on available evidence and inferences could be as high as 40% in patients attending secondary care settings.

Application of the Rome criteria for IBS will have an important impact within primary care settings, whereby a substantial proportion of patients will be reassured because of mild symptoms and no alarm features, thus reducing downstream secondary care referral pressures and costs.[77] For example, screening with a faecal calprotectin within general practice can reduce the number of adults requiring colonoscopies by 67%.[78] However, although a combined panel of negative alarm features might provide reassurance, a single positive alarm feature will inevitably trigger consideration of an onward referral. In fact, about 80% of patients with IBS seen within gastroenterology clinics will exhibit at least one alarm feature, with the diagnostic yield of colonoscopy for organic pathology in this cohort ranging widely, from less than 10% to 30%.[25,76,79] Hence, the poor specificity of alarm features and their high false-positive rates are areas in need of further refinement,[80] and although the presence of certain alarm features (eg, older age, unintentional weight loss, and iron deficiency anaemia) are unlikely to alter investigation algorithms, others are under scrutiny and amenable to improvement. For example, a large proportion of faecal calprotectin tests within a primary care setting are in the indeterminate range of 50–250 µg/g; in these patients, IBD is unlikely.[81] In such instances, repeating the test after a few weeks is recommended because almost half will have test values that return to normal values, thereby providing reassurance and keeping patients in-house within primary care.[82] A raised C-reactive protein or erythrocyte sedimentation rate are highly non-specific and, in isolation, have little clinical utility.[75] Future studies in patients with IBS-type symptoms should endeavour to optimise the selection process for secondary care referrals and colonoscopy examinations by evaluating the combination pattern of alarm features.

There is also a subset of individuals with symptoms compatible with IBS who do not have alarm features, but who are still referred into secondary care, probably because of ongoing concerns, patient dissatisfaction, or poor quality of life.[10,83–85] A colonoscopy might be seen as a measure to reassure the patient or even the health-care provider.[86,87] However, a study in 458 patients found no independent association between a negative colonoscopy and reassurance or improved health-related quality in patients with IBS younger than 50 years.[86] In the future, this type of clinical scenario would benefit from an alternate approach whereby having a simple diagnostic biomarker to identify IBS will help quash any potential uncertainties that might still exist and avoid unnecessary colonoscopy investigations. However, diagnostic biomarkers for IBS are elusive, although there have been promising data to show that antibodies to bacterial toxins (cytolethal distending toxin and vinculin) might be novel biomarkers for the postinfectious IBS-D model. These biomarkers require further validation.[88]

Finally, a fundamental component of the Rome process is to encourage and empower clinicians to make a positive diagnosis of IBS once organic pathology has been appropriately excluded, rather than merely stating a list of negative investigation results.[12] Moreover, patients should not be subjected to repeated investigations (unless symptoms drastically change or are worrisome) because this strategy can foster abnormal illness behaviour, lead to the perception that the doctor is missing something, unnecessarily increase health-care costs, and delay appropriate treatment.[12] A randomised controlled trial comprising 302 patients with suspected IBS noted that making a positive diagnosis of IBS was cheaper than a strategy of exhaustive exclusion, did not miss any organic pathology over the subsequent 12 months, and was non-inferior in terms of patient

satisfaction, clinical symptoms, and quality of life.[89] Following a diagnosis of IBS, a patient has less than 5% risk of receiving an alternative organic diagnosis in the future.[90]

In summary, the Rome IV criteria for IBS guides clinicians towards recognising the cardinal symptoms of IBS followed by a logical and stepwise approach towards excluding organic pathology, so that exhaustive and repetitive investigations can be avoided. Thereafter, these guidelines encourage a confident diagnosis of IBS so that appropriate therapies can be initiated and the patient is left without uncertainty. However, clinicians should take testing for primary bile acid diarrhoea and microscopic colitis into consideration because they are among the largest potential mimicker of IBS with predominant diarrhoea. Further improvements are also needed to improve the specificity of alarm features so that non-diagnostic colonoscopies can be reduced, as well as to identify biomarkers to confirm the diagnosis of IBS, the latter of which would be particularly useful in those seeking further reassurances.

IBS-like symptoms in patients with known organic gastrointestinal disease

Patients with an established organic gastrointestinal disease (eg, IBD) might have lingering lower gastrointestinal symptoms despite their organic disease being in histological remission. Escalating immunotherapy in this setting runs the risk of infective and neoplastic complications, plus increased health-care costs, with little clinical benefit. There is now appreciation that up to a third of patients with IBD with no active signs of inflammation will report predominantly lower functional gastrointestinal symptoms.[91] This observation was originally reported in the 1980s and has thereafter been corroborated by several groups.[30,31,92] In a 2020 systematic review and meta-analysis of 27 studies, comprising 3169 patients with IBD in remission, the pooled prevalence of IBS-type symptoms was 32·5% (95% CI 27·4–37·9).[31] Prevalence was lower when remission was defined by endoscopic assessment (23·5%, 17·9–29·6) or histological assessment (25·8%, 20·2–31·7) than when defined by validated clinical disease activity index (33·6%, 26·3–41·2). Hence, even when stringent criteria such as endoscopic or histological remission are used, about a quarter of patients with IBD in remission report IBS-type symptoms.[31] Moreover, symptoms compatible with IBS and other functional bowel disorders, such as functional constipation, functional diarrhoea, and functional bloating, are common in patients with IBD in deep remission.[93] From a clinical point of view, these findings are of great importance, since the presence of symptoms compatible with IBS or another functional bowel disorder in patients with IBD without signs of active disease is associated with increased health-care use, psychological comorbidity, and reduced quality of life.[93–98] The pathophysiological mechanisms by which IBS-like symptoms develop in quiescent IBD is not altogether clear, but might include intestinal dysmotility, visceral hypersensitivity, increased mucosal permeability, and psychological distress (figure 3).[91,95,98–102] The gut microbiome is considered to be an important factor in the pathophysiology of IBS,[103,104] but so far its relevance to IBS-type symptoms in patients with IBD in remission has not been established.[105] Currently, there are no general treatment recommendations for these patients, which is a consequence of the paucity of clinical trials specifically focusing on this patient group. However, a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet has been found to improve bowel symptoms and improve quality of life in patients with IBD in remission with IBS-like symptoms.[106,107] Hence, based on the available published literature, dietary interventions seem to be the most logical treatment option to offer to these patients. However, a large multiarm, randomised controlled trial of various management strategies (low FODMAP diet, amitriptyline, ondansetron, or loperamide) for ongoing diarrhoea in patients with stable ulcerative colitis is soon to begin in the UK and will hopefully shed further evidence as to how best to manage these patients (ISRCTN16086699). Up to a third of patients with coeliac disease have ongoing gastrointestinal symptoms compatible with IBS despite adhering to a gluten-free diet.[40] A randomised controlled trial found that in this patient group a short-term, low-FODMAP diet in addition to a gluten-free diet helped reduce gastrointestinal symptoms and improve mental well-being compared with a gluten-free diet alone.[108] The benefit of this dietary intervention seems to be as effective in patients with coeliac disease on a gluten-free diet but with ongoing gastrointestinal symptoms as it is in patients with non-active IBD with gastrointestinal symptoms and patients with IBS.[109] As a next step, it would be useful to compare other IBS-tailored therapies in patients with stable coeliac disease who have ongoing gut symptoms.

Search strategy and selection criteria

A PubMed search to identify peer-reviewed articles in English was done from database inception to Oct 12, 2020. Based on the authors expertise within the field, the search terms "irritable bowel syndrome" and "IBS" were used in combination with the "AND" operator for the terms "organic disease", "colorectal cancer", "inflammatory bowel disease", "gastrointestinal infections", "coeliac disease", "microscopic colitis", "bile acid diarrhoea", "small intestinal bacterial overgrowth", "pancreatic insufficiency", and "diverticular disease". All titles, abstracts, and reference lists from identified articles were assessed for relevance.

Conclusion

A bidirectional relationship exists between IBS and organic gastrointestinal diseases. In patients presenting with IBS-type symptoms, organic pathology should be

excluded by adopting a careful, cogent approach, which starts with the evaluation of alarm features and then proceeds accordingly. Conversely, patients with organic gastrointestinal disease with ongoing symptoms despite their disease being in histological remission might have overlapping IBS, which is important to recognise so that appropriately tailored therapy can be commenced and, more importantly, harmful escalations in immunosuppressive therapy can be avoided.

Contributors

IA and MS equally contributed and wrote, edited, and approved the final version of the manuscript.

Declaration of interests

MS has received unrestricted research grants from Danone, Glycom, and Ferring Pharmaceuticals; has served as a consultant or advisory board member for AstraZeneca, Danone, Nestlé, Almirall, Allergan, Albireo, Glycom, and Shire; and as a speaker for Tillotts, Menarini, Takeda, Kyowa Kirin, Biocodex, AlfaSigma, Shire, Allergan, and Almirall. IA declares no competing interests.

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