

Perspectives

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Opinion: Refractory inflammatory bowel disease—could it be an irritable bowel?

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Abstract

Patients with IBD who are apparently in remission—as indicated by normal blood tests, endoscopic findings and ultrasonography results—often continue to experience symptoms. Furthermore, despite these negative findings, there is a temptation to increase their anti-inflammatory medication in the hope that this approach would lead to some improvement. However, this strategy often seems to fail and can sometimes lead to adverse events. Consequently, when evidence of continuing inflammatory activity is lacking it might be appropriate to consider the possibility of co-existent IBS in these patients and to treat them for this condition. Dietary manipulation, antispasmodic agents, antidepressants (especially of the tricyclic variety) and even behavioural treatments might result in a worthwhile improvement of symptoms.

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Introduction

Unfortunately, unlike in IBD, there are no diagnostic tests or biomarkers for IBS and consequently diagnosis is entirely symptom-based and after exclusion of other possibilities. Therefore, it might seem logical to assume that once a diagnosis of either ulcerative colitis or Crohn's disease has been made, a patient could not have IBS and this possibility might not be considered in subsequent patient consultations.

The diagnosis of IBS has traditionally been based on the symptoms of abdominal pain, bloating and a disturbance of bowel function. However, many patients also suffer from a series of noncolonic symptoms such as lower back pain, constant lethargy, nausea, early satiety and a range of urinary and gynaecological features.¹ These symptoms are important because not only do they add to the burden of the illness but they are also diagnostically useful. The more non-colonic symptoms a patient experiences, the more likely they are to be suffering from IBS.² This condition is notoriously common worldwide and epidemiological studies indicate that its prevalence is ~15%,³ although this varies from country to country. This Perspectives article examines the relationship between IBS and IBD, and discusses how to diagnose and treat IBS in patients with co-existing IBD.

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Possible IBS–IBD association

If 15% of the population has IBS then it seems reasonable to predict that 15% of any disease group will be similarly afflicted. Consequently, because there is no known reason why having IBD should protect an individual from IBS it might be expected that 15% of patients with IBD will have coexistent IBS. Our research group was the first to examine the prevalence of IBS in patients with ulcerative colitis in remission and found that 33% of these patients reported symptoms consistent with IBS.⁴ Subsequently, four studies from other groups confirmed an increased prevalence of IBS in patients with ulcerative colitis, although one showed that the prevalence did not seem to be raised ([Table 1](#)).^{3,5,6,7,8,9,10,11} In Crohn's disease, the prevalence of IBS is 26–60% and the prevalence seems to be at the higher end of that range in patients who had undergone some form of surgical intervention.^{5,6,7} Previous surgery is likely to confuse the interpretation of any residual symptoms and, in our opinion, 30–40% is probably a more accurate reflection of the prevalence of IBS in Crohn's disease. Therefore, it seems that patients with IBD who are apparently in remission have at least double the likelihood of developing IBS that would be expected by chance. The term IBD–IBS has been proposed for this clinical scenario.¹¹

[Table 1 | Prevalence of IBS-like symptoms in IBD that is in remission](#)

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Reasons for IBD–IBS association

IBS is a condition in which a number of factors seem to underlie the symptoms ([Box 1](#)). A large proportion of patients with IBS can link the onset of their condition to the occurrence of an enteric infection, which has led to a suggestion that the inflammation resulting from an infection might have a pathophysiological role in the subsequent development of IBS.¹² Evidence is accumulating to show, at least in some individuals, that low-grade inflammation persists after the infection has resolved and is associated with the development of symptoms of IBS.¹² Furthermore, there is also growing support for the view that the interaction between the neural control of gastrointestinal function and the immune system,¹² along with genetic influences,¹³ might also be important in the pathogenesis of IBS. It seems possible, therefore, for IBD-associated inflammation to have a similar effect, especially when IBD is in remission and inflammation is minimal.

[Box 1 | Multifactorial pathophysiology of IBS](#)

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Disturbance of the microbiota is one of the pathophysiological factors that is receiving an increasing amount of attention and evidence now exists that there might be subtle differences in the composition of the gut microbiota between people with or without IBS ([Box 1](#)).^{14,15} The composition of the gut flora is also disturbed in IBD,¹⁶ although it is still not fully understood whether, in IBS or IBD, these abnormalities are cause or effect, or a result of the various medications that these patients receive. However, examination of the microbiota of patients with IBS and IBD in remission would help to determine whether disturbance in gut flora could contribute to the apparent excess incidence of IBS in IBD. Interestingly, the microbiota can influence central nervous system function,¹⁷ a disrupted mucosa can lead to visceral sensitization¹⁸ and inflammation in the gut can activate intestinal secretion and alter gut motility.¹⁹ As such, IBD in remission shares many of the putative pathophysiological mechanisms considered to be important in IBS.

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Diagnosing IBS in IBD

Generally IBS is diagnosed positively with investigations being kept to a minimum, rather than being extensive, and on the basis of exclusion of realistic alternative diagnostic possibilities. This approach, which uses red flags to guide investigation,²⁰ has proved to be remarkably reliable^{21,22} as IBD has been found to be the correct diagnosis in ~2% of patients.²³

Contrary to the minimal investigation approach to the diagnosis of IBS, the diagnosis of IBS in IBD should only be contemplated if there is little or no evidence of active IBD.²⁴ Consequently, depending upon the site and nature of the disease, endoscopic evaluation as well as scanning techniques such as CT, MRI or ultrasonography should all support the diagnosis of clinical remission. Furthermore, levels of serological markers of inflammation such as C-reactive protein and erythrocyte sedimentation rate should also be normal. Bile-acid malabsorption²⁵ might need to be considered in patients with Crohn's disease, especially if there is a history of surgery. Whether structural changes identified by imaging in patients with Crohn's disease result from scarring or inflammation is not always clear, and a diagnostic decision should be made based on the whole clinical picture.

Sensitive techniques for detecting the products of inflammation in faeces have been developed. Calprotectin and lactoferrin are found within the cytosol or granules of polymorphonuclear neutrophils and can be easily identified in faecal samples; as such, both proteins are increasingly being used as a screening test for IBD, as well as a predictor of relapse in these patients.^{26,27,28} These tests are effective for distinguishing IBS from IBD, although there is still some dispute about what should be regarded as an ideal cut-off level. However, these faecal markers can be detected even if endoscopic examination shows apparently normal mucosa, which makes detection of these proteins indicative of ongoing low-grade inflammation. Consequently, this finding raises the problem of how much emphasis should be placed on a mildly positive test when considering the possibility of IBS in a patient with IBD in apparent remission.⁷ It seems reasonable to conclude that it is safe to treat a patient for IBS if they have negative inflammatory faecal markers, but perhaps a small

increase in these markers should not necessarily rule out the possibility of treating for IBS, although an acceptable range for recommending this approach needs to be defined. The use of granin detection in faeces²⁹ is interesting, but the utility of this test for diagnosing IBS in patients with IBD has yet to be defined.

If the patient does not have inflammatory markers, has negative results from colonoscopic investigations, but has continuing symptoms such as abdominal pain and bowel dysfunction, IBS should be considered—especially if bloating is a prominent feature. Bloating, which can be accompanied by visible distension, is characteristic of IBS³⁰ and should certainly raise suspicions if no evidence of structural change that could possibly lead to obstruction is present, even in inactive IBD. In addition, non-colonic symptoms, which our research group has shown are not prevalent in active IBD but are common in IBS, could also aid diagnosis (Table 2).² This finding has been confirmed in a study at a different research institute showing that such symptoms are more prevalent in IBS than in IBD.³¹ Therefore, an IBS-like syndrome should be suspected in a patient with IBD once clinically significant inflammatory disease activity has been excluded by a combination of investigation and clinical findings.

[Table 2 | Prevalence of noncolonic symptoms in patients with IBS and IBD](#)



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Treating IBS in IBD

Dietary approaches

Once the possibility of coexistent IBS is considered to be a viable option, then it is reasonable to offer specific treatment for IBS, particularly as the various approaches are extremely safe and not associated with major adverse effects. Fibre, especially the insoluble form, can exacerbate symptoms in patients with IBS and, therefore, its exclusion can often be beneficial (Table 3).³² Although fibre polysaccharides are fermented in the gut to produce short-chain fatty acids, which are thought to have beneficial effects on immune function in the intestine,³³ it might be reasonable to advise patients to restrict fibre intake when their IBD is in remission and they remain symptomatic. Our research group has previously shown that eating fruit can have a detrimental effect on IBS (Table 3).³² Notably, fermentable oligosaccharides, disaccharides, monosaccharides and polyols (known collectively as FODMAPs), which are common constituents in many fruits and vegetables, are now receiving considerable attention in relation to IBS. A diet that is rich in FODMAPs seems to exacerbate IBS symptoms and evidence is emerging that reducing the intake of these carbohydrates can have beneficial

effects.³⁴ Consequently, reducing FODMAP intake should be considered in quiescent IBD, especially as it has been proposed that FODMAPs might have a role in the pathogenesis of Crohn's disease.³⁵

[Table 3 | Symptomatic response to fibre sources in patients with IBS](#)



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Another area of great interest for research into IBS, as well as IBD, is the therapeutic potential of probiotics. Approximately two-thirds of probiotic trials in IBS indicate some degree of therapeutic potential,³⁶ although results in Crohn's disease have been disappointing,³⁷ unlike in ulcerative colitis.³⁸ Importantly, different probiotic bacteria can have completely different activities; therefore, if one is effective in IBS it might not necessarily be beneficial in IBD.

Pharmacological approaches

Antispasmodic agents are the main treatment for pain associated with IBS³⁹ and there is no reason not to use them for patients with IBD in whom IBS is suspected, although anticholinergic agents can sometimes cause constipation. Loperamide is useful for controlling diarrhoea associated with IBS, but it can actually precipitate toxic dilatation in acute IBD.⁴⁰ However, when the disease is in complete remission, the judicious use of loperamide is reasonable as it can have a positive effect on patients' confidence to venture away from the proximity of toilets. Laxatives are also perfectly acceptable treatments for patients with quiescent IBD and are especially useful in the proximal faecal loading that is common in patients with distal colitis and can be particularly uncomfortable for the patient, as well as being difficult to resolve.⁴¹

Antidepressants, particularly of the tricyclic variety, are probably the most effective medications for severe IBS and are particularly useful in the diarrhoea subgroup of the condition.⁴² As such, giving antidepressants is worth trying for patients with IBD who have apparently refractory IBS. However, vigilance is needed for the possibility of developing constipation that can occur with the use of this group of drugs.

The nonabsorbable derivative of the antibiotic rifampicin called rifaximin is receiving much attention in relation to treating IBS,^{43,44} particularly for symptoms of bloating and flatulence; use of this agent is based on the premise that the microbiota is disturbed in patients with IBS.⁴⁵ As a consequence of the emerging evidence that the gut flora is disrupted in IBD,¹⁶ the potential for rifaximin to treat this condition is being considered. Interestingly, rifaximin could have additional therapeutic effects in IBD independently of antibiotic actions as it can

act as a gut-specific ligand for the human nuclear receptor subfamily 1, group I member 2 (also known as pregnane-X receptor), which might regulate cytokine expression.⁴⁶ Rifaximin does not seem to predispose to *Clostridium difficile* infection and, therefore, could be a treatment for patients who have overlapping IBS and IBD.

Behavioural treatment approaches

A systematic review has shown that both hypnotherapy and cognitive behavioural therapy offer major benefits to patients with IBS⁴⁷ and the effects of hypnotherapy can last for a number of years. Furthermore, hypnotherapy improves some of the putative physiological abnormalities associated with IBS.⁴⁸ Consequently, such behavioural approaches are worth considering for patients with IBD who have symptoms indicative of IBS in whom other treatment modalities have failed. This recommendation is strengthened by the fact that there is data to indicate that hypnotherapy could also have benefits in IBD,^{49,50} as well as positively modulating some of the inflammatory mechanisms associated with IBD.⁵¹

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Conclusions

Accumulating evidence indicates that patients with IBD in remission who continue to have symptoms of abdominal pain, bloating and bowel dysfunction might actually have an IBS-like condition. Therefore, it seems reasonable to at least try conventional IBS treatment in these patients, as these approaches are unlikely to be harmful and could actually considerably improve symptoms—although, as yet, no trial data exists to support this view. This strategy seems to be a much more logical approach to managing this problem rather than immediately intensifying the use of medications aimed at modulating immune function.

Author contributions

All authors contributed equally to all aspects of the article.

Competing interests statement

The authors declare [competing interests](#).

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