# Irritable Bowel Syndrome and Inflammatory Bowel Disease Overlap: Discussing the Dilemma

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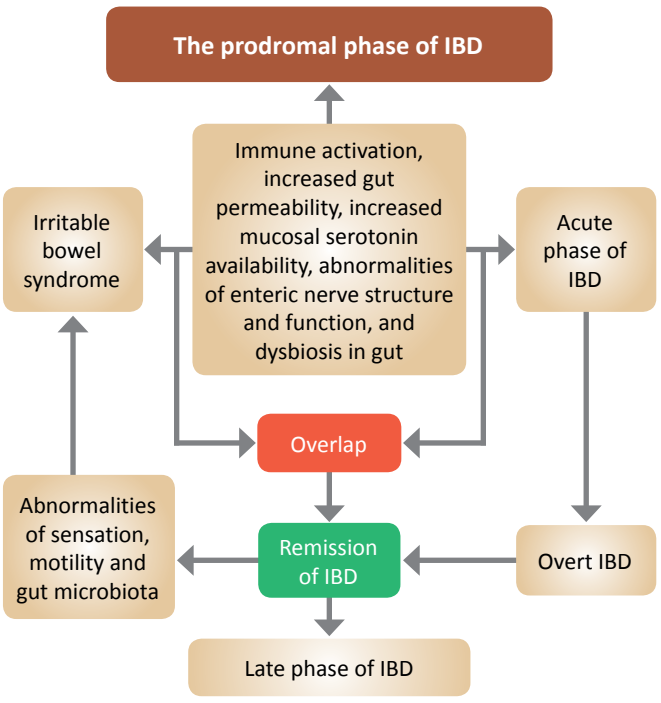
## Prologue

Irritable bowel syndrome (IBS), a common functional gastrointestinal disorder involving the gut-brain axis, and inflammatory bowel disease (IBD), a chronic relapsing inflammatory disorder, are both increasing in incidence and prevalence in Asia. Both have significant overlap in terms of symptoms, pathophysiology, and treatment, suggesting the possibility of IBS and IBD being a single disease entity albeit at opposite ends of the spectrum. IBS is characterized by a disordered gut-brain axis, but can develop following an enteric infection, and is associated with persistent immune activation that is also a feature of IBD. Of note, the considerable overlap of symptoms and colitis points to the possibility of IBS as a prodromal or mild subset of IBD, or IBD being pathologically related to the cause of IBS, or representing same pathophysiological spectrum of a disease.[1,2]

The acute phase of IBD with inflamed gut and often ulcerated mucosa which differs from the normal mucosa is characteristic of IBS. Detailed assessment has detected immune activation, increased gut permeability, increased mucosal serotonin availability, abnormalities of enteric nerve structure and function, and dysbiosis in gut microbiota in IBS - all features seen in IBD. Furthermore, approximately 1 in 3 patients with IBD in remission from inflammation still have persistent abnormalities of sensation, motility and gut microbiota, which may present with IBS-like symptoms. This two separate and distinct GI disorders share distinct commonalities, particularly at the extreme spectrum of both disorders–the prodromal phase of IBD and the late phase of IBD (Figure 1).[1,3]

**Figure 1: The proposed overlap of IBS-IBD[2,3]**




**Adapted from: 1.** Porter CK, Cash BD, Pimentel M, Akinseye A, Riddle MS. Risk of inflammatory bowel disease following a diagnosis of irritable bowel syndrome. *BMC Gastroenterol.* 2012;12:55. Published 2012 May 28. **2.** Spiller R, Major G1. IBS and IBD - separate entities or on a spectrum? *Nat Rev Gastroenterol Hepatol.* 2016 Sep 26;13(10):613-21.

## The IBS-IBD dilemma

The highlights of similarities and differences in IBS and IBD as disease per se is given as below:

### Ascertaining the similarities

***Brain-Gut Axis***

- There is a bidirectional interaction between the central nervous system and the enteric nervous system, which in turn modulates the gut function in both IBS and IBD[4,5]
- Both IBD and more particularly IBS are predisposed to psychological comorbidities such as anxiety and depression[4,5]
- Patients with IBD are associated with higher rates of anxiety and depression compared to the general population which can have negative impact on the quality of life and adversely affect the course of intestinal inflammation[4,5]
- In IBS, it has been reported that 50–90% of patients have or had at some point one or more common psychiatric condition, including major depressive disorder, generalized anxiety disorder, social phobia, somatization disorder, or posttraumatic stress disorder.[6] Inflammatory markers are also found to be elevated in patients who are depressed that further signifies immune dysregulation.[7]

***Genetic Factors***

- Recent advances in the genetic component have revealed tumor necrosis factor superfamily member 15 (TNFSF15), also

known as the TNF-SF15 gene contains a number of risk alleles that leads to altered expression of its gene product which acts as an autocrine factor inducing apoptosis, and inhibiting endothelial cell proliferation resulting in dysregulated immune response and subsequent chronic inflammation common to both IBS and IBD.[8,9]

***Microbiota***

- Patients with IBD and IBS may have an altered intestinal microbial composition compared with healthy individuals[10]
- Dysbiosis (abnormal gut microbiota) has been linked with several gastrointestinal diseases including IBD and IBS
- A recent study evaluating a dysbiosis index algorithm detected dysbiosis in 70% of treatment-naïve IBD patients and 73% of IBS patients, in comparison with only 16% of healthy subjects[11,12]
- The prevailing imbalance in gut bacterial communities, or "dysbiosis", leads to activation of the gut immune system and potential low-grade inflammation in IBS. Alterations in gut microbiota have been observed in IBS patients, and are also seen in post-infectious IBS, which in turn is postulated to be a trigger for IBD.[13]

***Impaired epithelial barrier***

- A defective mucosal barrier may result in increased intestinal permeability which promotes the exposition to luminal content and triggers an immunological response that promotes intestinal inflammation
- IBD patients display several defects in the mucosal barrier, from the mucus layer composition to the adhesion molecules that regulate paracellular permeability. This have been reported to represent primary dysfunction in Crohn's disease and also perpetuate chronic mucosal inflammation in ulcerative colitis.[14]
- Similarly, in IBS elevation of miRNA-29a which plays a significant role in down-regulating glutamine synthetase causes increased gut permeabilityand subsequent injury.[15]

## Extrapolating the differences

***FecalCalprotectin***

- Fecalcalprotectin (FC) is a non-invasive marker in distinguishing IBD from functional disorders as its expression is driven by the presence of intestinal inflammation
- High calprotectin levels are almost always due to ongoing inflammation related to chronic IBD. It has been proposed that a level below 40 mg/g is an indicator of no inflammation, whereas a level above 100 mg/g indicates significant inflammation, suggesting IBD
- A level of fecalcalproteinin-between 40–100 mg/g remains nonspecific for low level of IBD or IBS, or pre-IBD IBS.[16]

***Degree of inflammation***

- In IBD, mucosal inflammation is usually ongoing and slow to resolve, even in clinically asymptomatic patients. In contrast, IBS patients tend to exhibit low grade, variable, or even absent mucosal inflammation.[1]

***Symptoms versus inflammation mismatch***

- IBD is an organic disease, as evidenced by mucosal inflammation, whereas IBS lies more in the spectrum of a functional disorder, with no evidence of organic disease.[1]

***Visceral hypersensitivity***

- Visceral hypersensitivity is an important hallmark feature of IBS and strongly associated with abdominal pain in affected patients
- Patients with IBS usually present with persistent pain despite minimal inflammation and visceral hypersensitivity is the likely explanation for the symptoms and brain responses in IBS
- At peripheral level, visceral sensitivity in IBS is attributed to several mechanisms. Immune cells in the mucosal wall, such as mast cells, and enterochromaffin cells may sensitize afferent nerves by release of their mediators. Furthermore, increased mucosal permeability, altered intestinal microflora and dietary habits may contribute to this feature
- At central level, an increased prevalence of psychiatric comorbidities in IBS patients, alongside alterations in the hormonal brain-gut axis, increased vigilance towards intestinal stimuli and functional and structural changes in the brain tend to augment visceral hypersensitivity in IBS
- However, in IBD, the hallmark of the disease is mucosal inflammatory change that correlates with disease severity, and is the treatment target
- Visceral hypersensitivity is more apparent in IBD patients in remission, further strengthening the argument for IBS as a pre-IBD state (Table 1).[1,17,18]

**Table 1: Similarities and differences in IBS and IBD[1,4,5,8-10,14-16]**

| Similarities | Differences |
|---|---|
| Brain-gut axis has a bidirectional interaction between both IBS and IBD | Fecal calprotectin, a non-invasive marker distinguishs IBD from functional disorders |
| Genetic factors such as tumor necrosis factor superfamily member 15 (TNFSF15) results in dysregulated immune response and chronic inflammation common to both IBS and IBD | Degree of inflammation is more pronounced in IBD |
| Altered intestinal microbiota is present in patients with IBD and IBS | Symptoms versus inflammation mismatch in both IBS and IBD |
| Impaired epithelial barrier promotes intestinal inflammation both in IBS and IBD | Visceral hypersensitivity is strongly associated with abdominal pain in IBS patients |

## Understanding the disease pattern in IBS-IBD overlap

- **IBS as a prodrome of IBD: The initial transition**
  - » IBS symptoms represent sub-clinical inflammation and immune activation with increased mucosal barrier defects that progress in severity towards the expression of IBD. The initial or prodromal insult is enteric infection, resulting in postinfectious IBS, which is followed by a period of IBS like symptoms without obvious colonic inflammation and also known as "early or pre-IBD" period at which there is a low level or grade of colonic inflammation. This further lead to active IBD, followed by subclinical IBD with ongoing low-grade inflammation, although it is possible that irritable IBD occurs when the inflammation burns out.[1,19]

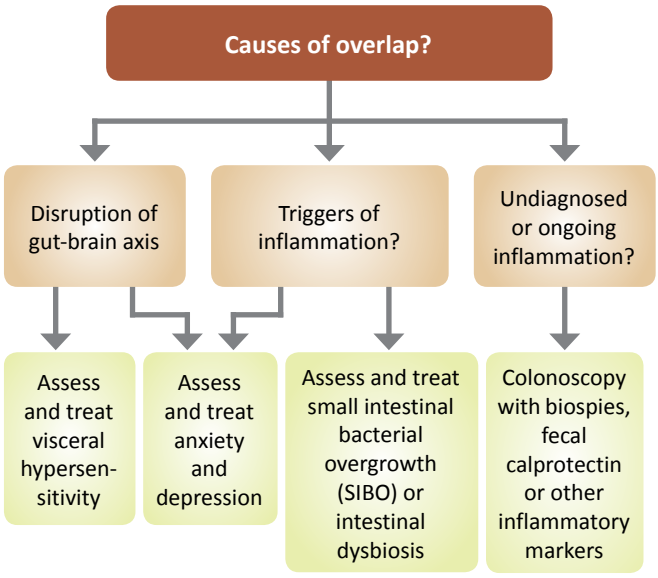
- **IBS as an 'inflammatory' disorder**
  - » Inflammation may play a pathogenic role in IBS. Studies have highlighted the persistence of mucosal inflammation at the microscopic and molecular level in IBS, with increased recruitment of enteroendocrine cells. Increased mast cell density and activity in the gut may correlate with symptoms of visceral hypersensitivity in IBS. Patients who develop postinfectious IBS, infective gastroenteritis could cause systemic inflammation and altered microbiome diversity, which in turn perpetuates a cycle of chronic, low-grade, subclinical inflammation. Apart from mucosal inflammation, neuroinflammation is probably involved in the pathophysiology of IBS via the "gut-brain" axis, resulting in altered neuroendocrine pathways and glucocorticoid receptor genes. This gives rise to an overall proinflammatory phenotype and dysregulated hypothalamic-pituitary-adrenal axis and serotonergic (5-HT) functioning.[20] Likewise, new triggers including new enteric infection in the form of small intestinal bacterial overgrowth (SIBO) or intestinal dysbiosis, that is often unsuspected in IBS or IBD, can also sustain the low-grade inflammation.[1]

## Diagnostic approach in IBS-IBD overlap

When considering progression or overlap of IBS-IBD, following points to be considered:[1]

- Undiagnosed or ongoing inflammation: Use of biomarkers including fecal calprotectin (or others, either existing or in development) and other inflammatory markers and pathological assessment
- Triggers for ongoing inflammation: Assess and treat small intestinal bacterial overgrowth (SIBO) or intestinal dysbiosis and psychological dysfunction
- Disruption of gut-brain axis: Assess and treat visceral hypersensitivity (Figure 2).[21]

**Figure 2: Diagnostic work up for a patient presenting with IBS-IBD overlap**




**Adapted from:** Abdul Rani R, Raja Ali RA, Lee YY. Irritable bowel syndrome and inflammatory bowel disease overlap syndrome: pieces of the puzzle are falling into place. *Intest Res.* 2016;14(4):297–304.

## Therapeutic interventions for IBS or related disorders and IBD

| Therapy | Interventions |
|---|---|
| Diet | Low FODMAP; gluten-free diet (GFD) |
| Psychological therapy | Cognitive behavioral therapy, hypnotherapy, mindfulness therapy |
| Pharmacologic treatment for constipation | PEG, stimulant laxative, secretagogue, prokinetic |
| Pharmacologic treatment for diarrhea | Loperamide, 5-HT3 antagonist , bile acid sequestrant, mixed opioid agonist/antagonist |
| Pharmacologic treatment for pain, anxiety, depression | Antispasmodic, antidepressant (tricyclic antidepressant, SSRI) |
| Antibiotics | Rifaximin |
| Probiotics | Multiple agents |
| Pelvic floor therapy and exercise / Physical therapy | Biofeedback for dyssynergic Defecation/exercise |
| Complementary alternative medicine (CAM) | Herbal therapy, dietary supplements, acupuncture, moxibustion, yoga[21] |

## Use of antispasmodic in IBS-IBD overlap predominate with pain

Abdominal pain is the most bothersome symptom in patients of IBS who tend to seek medical care. A report by Indian Society of Gastroenterology Task Force revealed that as high as 70% of IBS patients have abdominal pain or discomfort significantly affecting the patient's quality of life. Likewise, IBD abdominal pain has a profound negative impact on patients' lives. There are growing data suggesting that pain is variably related to the

degree of active inflammation with other associated factors such as obstruction, psychological, psychosocial, neurobiological, and genetic factors. Antispasmodics have been mainstay therapy for pain management in gastrointestinal disorder. Antispasmodics, namely, hyoscyamine, dicyclomine, propantheline, and mebeverine are commonly used, but they are associated with lot of anticholenergic side effects, which often restricts there clinical usage. Drotaverine, an antispasmodic, has a good relaxing effect on intestinal smooth muscle, which helps in alleviating pain and is devoid of anticholinergic side-effects with well established efficacy in management of spasmodic pain in IBS and IBD patients.[22,23]

## Lactose Intolerance and IBS: An interesting intersection

Lactose Intolerance (LI) is characterised by digestive symptoms, including bloating, abdominal discomfort and diarrhoea, after ingestion of dairy products. In people with lactase deficiency, lactose is not digested and absorbed in the small bowel, but passes into the colon where bacterial fermentation produces gas and short-chain fatty acids and other products that can cause luminal distension and alter digestive function.[24] Almost 60-70% of people in India are lactose intolerant.[25] Patients with IBS are more likely to report intolerance to dairy products and other foods than healthy individuals. A study conducted among Indian patients reported that diarrheal type of IBS have a higher incidence of lactose intolerance.[26] Similarly, another study results revealed that the proportion of IBS-D patients report typical symptoms of lactose intolerance to be significantly higher at every dose.[27,28] Meanwhile, the findings also corroborated that IBS-D patients are more sensitive and hypervigilant than healthy controls to events of the gastrointestinal tract. This brings to light another aspect of the relationship between lactose intolerance and IBS, where IBS patients impose self avoidance of lactose rich products, an approach that has adverse nutritional consequences and rarely provides adequate symptom relief.[28] For IBS patients with proven lactase deficiency, a diet poor in lactose might be indicated. Notably, the use of oral lactases before the ingestion of lactose-containing foods is likely to be useful for alleviating or even abolishing the symptoms of lactose intolerance in these patients.[29]

## Conclusion

Gastroenterologists often encounter situations when the clinical and pathophysiological features that typically distinguish functional from organic disorders overlap. The idea of IBS and IBD being intimately interlinked seems gaining momentous based on the underlying evidence and research developments. Thus, the disease paradigm may have to be altered to consider both IBS and IBD as belonging on the same timeline, but with differing presentation and outlook, in order to devise a more comprehensive management plan to cater patients presenting with significant overlap of the two disease entities.

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