



Post-infectious Irritable Bowel Syndrome: A Narrative Review

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ABSTRACT

The Irritable bowel syndrome (IBS) is a functional disorder of alimentary system, which may be caused by infectious gastroenteritis determined as post infectious irritable bowel syndrome (PI-IBS). The prevalence of PI-IBS is reported to be 4-36% in patients with infectious gastroenteritis. The exact mechanism leading to PI-IBS is not fully understood and some factors pertaining to infectious agent and host response may have a role. Rome IV diagnostic criteria provided new definition for PI-IBS. Though it is now considered a well-defined functional disorder of gastrointestinal system, no specific treatment is yet available for PI-IBS. This article reviews the latest issues on these heading about PI-IBS.

KEYWORDS:

Irritable Bowel Syndrome, Infectious gastroenteritis, Prevalence

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INTRODUCTION

The Irritable bowel syndrome (IBS) is a functional disorder of alimentary system, which is recently considered as an erroneous gut-brain interaction.¹ It is a very common diagnosis in gastroenterology practice affecting up to 22% of general population.^{2,3} IBS symptoms are quite variable and troublesome for patients with a great impact on their quality of life, while there is seldom any abnormalities in the structure of gastrointestinal tract or in the laboratory results.⁴ The vague pathophysiology of IBS has now been more elucidated including mucosal irritability, intestinal dysmotility, and dysbiosis in intestinal microbiome as well as psychosocial factors.⁵

Despite the ambiguous and indolent development of IBS symptoms, 6-17% of these patients attribute onset of their symptoms to a recent gastrointestinal infection.^{6,7} This so called post-infectious IBS (PI-IBS) represents the persistence of symptoms like diarrhea and abdominal discomfort well after resolution of the culprit infection,⁸⁻¹⁰ which is confirmed in a systematic review that showed up to 6-fold increased risk of PI-IBS after GI infections.¹¹

PI-IBS has some similar features with diarrhea dominant IBS cases, though distinct pathophysiologic alterations are recognized in the former. Various factors such as genetic predisposition, psychologic

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background, host defense and behavior of infecting pathogens determine the clinical history and outcome of patients with PI-IBS. It is likely that exposure to infectious organism results in immunologic and inflammatory reactions sustaining IBS symptoms.¹²

Understanding basic mechanisms in PI-IBS may be helpful in clarifying other forms of IBS. This article will review epidemiology, pathophysiology and risk factors as well as symptoms, diagnosis and management of PI-IBS.

Epidemiology

Records about PI-IBS date back to the Second World War with numerous cases of abdominal discomfort happening in British troops.¹³ Later in 1962, a published case series of so-called 'irritable colon syndrome' described some of them as "post dysenteric irritable bowel syndrome".¹⁴ Hence, many articles have reported new onset IBS symptoms developing 6-18 months after an infectious episode of gastroenteritis.¹⁵⁻¹⁷

The prevalence of PI-IBS is reported to be 4-36% in patients with infectious gastroenteritis.¹⁸ Considering the high frequency of GI infections and the possibility of these patients not remembering minor or remote infections, it is postulated that the prevalence must be higher. In a large nationwide case control study in United Kingdom, the incidence of IBS was 11.9 times higher in patients with previous infection than uninfected controls (relative risk, RR = 11.9 [95% confidence interval [CI], 6.7-21]).¹⁹

PI-IBS is more prevalent after bacterial than viral infections.²⁰ Most common bacteria are *Campylobacter*, *Shigella*, *E. coli* and *Salmonella*. Recent studies reported cases of PI-IBS after *Clostridium difficile* infection or even *Vibrio* species.²¹⁻²³ Amebic GI infection followed by symptoms suggestive of IBS were also reported.²⁴

Pathophysiologic Changes

Patients with PI-IBS show some changes in their gastrointestinal tract that are different from sporadic IBS cases. Inflammation and mucosal injury is a significant response observed in patients with previous infection (e.g. *Campylobacter jejuni*)

which is reported in a study confirming presence of increased number of macrophages and T lymphocytes in serial intestinal biopsies.²⁵ Elevated IL-6 serum levels are evident in IBS patients, as a systematic review reported.²⁶ Increased IL-1 expression in rectal samples of PI-IBS patients is another evidence for the pathophysiologic role of inflammation in developing PI-IBS.²⁷⁻²⁹

Altered intestinal permeability leading to sub-mucosal exposure to foreign antigens may also facilitate inflammation due to troubled sensation or motility in gastrointestinal tract. A study managed to show increased intestinal permeability by using lactulose-mannitol excretion ratio.²⁸ Similar result was reported in another study but longer follow-up revealed that these changes might resolve in remote futures but not in PI-IBS patients.²⁵

Serotonin and enterochromaffin cells have a great role in maintaining healthy gastrointestinal function. Alterations in serotonin production and metabolism have also been noted in PI-IBS patients,^{25,30} though increased serum serotonin level is also observed in some sporadic IBS patients.³¹

Microbiota

Infectious diarrheal episodes are connected with significant loss of symbiotic bacteria in gastrointestinal lumen. The consequence is transformation of microbial signature due to lack of inhibiting products such as fatty acids. The mentioned proposition is well confirmed in animal studies.³²⁻³⁴ Reports of bacterial overgrowth in IBS patients are mostly relied on breath hydrogen tests with high rate of false positive results.¹⁸

PI-IBS patients have dysbiosis, yet with different scheme from patients with sporadic IBS.³⁵ Predisposition to gastrointestinal infections is also related to gut's microbial structure. For example, Bacteroides load is lower in patients who acquire traveler's diarrhea and PI-IBS risk is also lower in these patients.^{29,36} Figure 1 shows the proposed mechanism of dysbiosis by Barbara et al.²⁰

Genetic Factors

Data regarding genetic risk factors for PI-IBS is

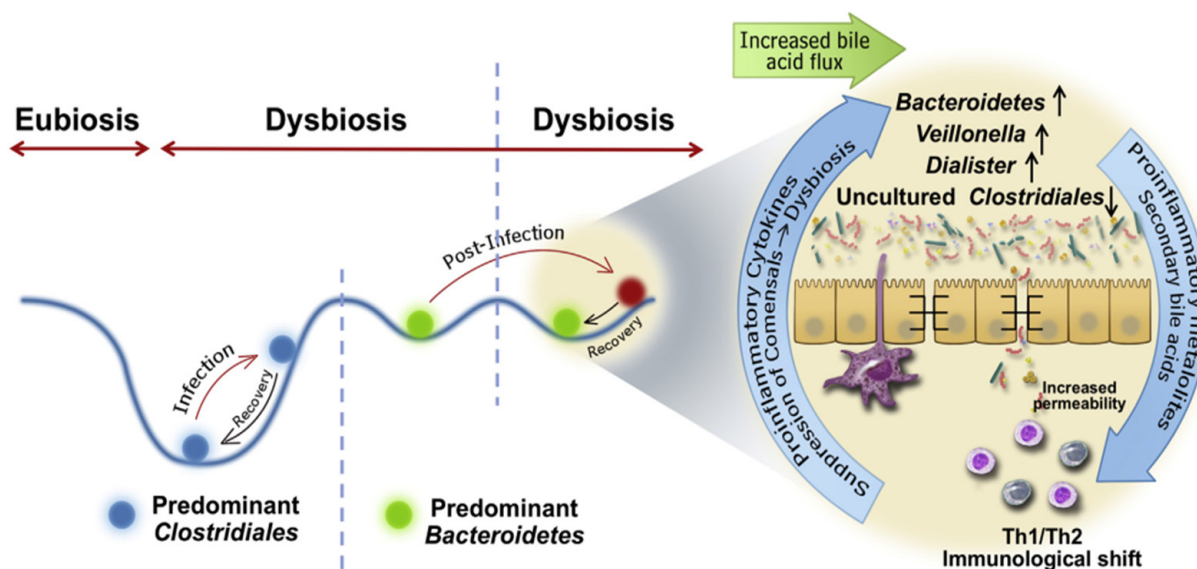


Fig. 1: Role of infection-associated shifts in microbiota in PI-IBS. A host with a Clostridiales predominant microbiota type is likely to remain in the eubiosis state after infection, whereas, presence of a Bacteroides predominant community may predispose to development of long-term dysbiosis upon infection. Adapted from Barbara et al.²⁰

limited. Although evidence show that genetics may have a role in development of PI-IBS, no confirmed genes are identified. Previous studies revealed the likely role of gene polymorphism resulting in high levels of TNF- α for development of post infectious IBS and lower expression of IL-10 in these patients compared to controls.^{37,38}

One of the best researches studying genetic predisposition to PI-IBS was held at Walkerton after an outbreak of infectious gastroenteritis. This study could find an association between toll-like receptor 9, (TLR9), IL-6 and CDH1 gene variants with PI-IBS. Although this relationship was not confirmed after considering total number of single nucleotide polymorphisms, it was independent from known clinical risk factors.³⁹ More powerful studies are required to elucidate the role of genetic variants in PI-IBS.

Mucosal abnormalities

Introduction of pathogenic bacteria into the gastrointestinal lumen causes structural and or functional alterations. This may also induce epithelial and enterocyte injury due to toxin exposure. Mucosal hallmarks of inflammation such as edema, erythema

or trivial hemorrhage might also be apparent in the acute phase.^{31,40} More virulent pathogens are associated with more inflammatory damage including lymphocyte infiltration and villous reduction.

Previous studies revealed that post infectious changes are almost temporary and resolves within 2 weeks to 3 months, though they may be above normal limits even in longer periods. Immunohistochemical assessments with synaptophysin also showed elevated level of this cell marker in PI-IBS patients.²⁵

Host factors

Older age (> 60 years) was described to be protective against developing symptoms of PI-IBS (RR = 0.36; 95% CI 0.3 - 0.9) which is believed to be due to alterations in immunologic response in this age group.¹⁹ Other studies though revealed no effect for age.⁴¹

Most of studies to date are congruent that female sex is an established risk factor for developing PI-IBS. Relative risk reported are in range of 1.5 to 3. It is evident from larger studies such as Walkerton study that there might be some confounding factors for this association.^{39,42,43}

Table 1: Rome IV Criteria for Diagnosing IBS*

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- Recurrent abdominal pain, on average, at least 1 day/week in the last 3 months, associated with two or more of the following criteria:
- Related to defecation
 - Associated with a change in frequency of stool
 - Associated with a change in form (appearance) of stool.
-

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.
Adapted from Lacey et al.⁴⁷

Table 2: Diagnostic Criteria for Post-infection Irritable Bowel Syndrome (Based on Rome IV)

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1. Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, with symptom onset at least 6 months before diagnosis, associated with two of the following:
 - a) defecation
 - b) a change in frequency of stool
 - c) a change in form (appearance) of stool
 2. Symptom development immediately after resolution of acute infectious gastroenteritis
 3. Infectious gastroenteritis defined by positive stool culture in a symptomatic individual or presence of two of the following acute symptoms (when stool culture not available)^a:
 - a) fever
 - b) vomiting
 - c) diarrhea
 4. Should not meet criteria for IBS before onset of acute illness^b
-

a A recollection of the precise date of onset of IBS symptoms can also be suggestive of PI-IBS.

b Some patients may experience irregular bowel movements before onset of acute illness (but not associated with the frequent pain characteristic of IBS) that can still be defined as developing PI-IBS.
Adapted from Barbara et al.²⁰

It seems that greater prevalence of psychologic disorders in women may induce this effect. However, Moss-Morris et al. showed that female gender is an independent factor for PI-IBS with RR of 2.36 (95% CI, 1.23 - 3.98).⁴¹ This study also showed a RR of 1.82 (95% CI, 1.05 - 1.22) for anxiety and there is a body of evidence for association of psychologic problems with IBS in general.^{18,43,44}

Clinical Features

Diagnosis

Although there is several symptom-based IBS diagnostic criteria, the diagnosis of IBS is still challenging due to several reasons.⁴⁵ The Manning symptoms-based criteria, the first global IBS diagnostic criteria was proposed in 1978.⁴⁶ Rome IV as the last diagnostic criteria defines IBS as an abdominal pain that is associated with defecation or a change in bowel habit (table 1).⁴⁷

There is no validated definition of PI-IBS. The new diagnostic criteria defined PI-IBS as new onset of IBS after an episode of acute gastroenteritis in individuals who did not have IBS previously²⁰ (table 2). Overall, PI-IBS patients have greater stool frequency and looser stools compared to spo-

radic IBS.⁴⁸ The frequency of PI-IBS phenotypes is reported as mixed IBS (IBS-M) as the most common PI-IBS phenotype (46%), diarrhea predominant IBS (IBS-D) (40%) and constipation predominant IBS (IBS-C) (15%).⁴⁹

The diagnostic approach for patients with PI-IBS proposed recently has emphasis on excluding alarm signs, obtaining stool culture and limited testing such as complete blood count, C reactive protein (CRP).²⁰ The most common differential diagnoses are acute acquired hypolactasia following gastroenteritis, bile acid malabsorption, inflammatory bowel disease (IBD) and lymphocytic colitis.⁵⁰⁻⁵²

Management

To date, there is no specific practice guideline or treatment strategies for PI-IBS. Meanwhile, patient education and providing reassurance is the key element in dealing with these patients. It is evident that troublesome and disturbing symptoms in PI-IBS patients still need to be addressed accordingly.

Different drug classes can be used for treating PI-IBS similar to patients with IBS in general. Opiates provide transit time increase with reduction in secretions and may help IBS-D like symptoms.⁵³

Controlling pain and tenesmus is of great importance in all IBS phenotypes, hence we may use antispasmodics as well as tricyclic antidepressant with accurate patient selection since these drugs might have unpleasant side effects.^{54,55}

As discussed earlier, serotonin (5-HT) has a potential role in pathophysiology of IBS. 5-HT₃ agonists are well studied in IBS-D patients with favorable results⁵⁶ while 5-HT₄ agonists such as prucalopride are beneficial in managing constipation.⁵⁷ After an episode of gastroenteritis, bile acid malabsorption may ensue. It is confirmed that cholestyramine can alleviate symptoms in PI-IBS patients especially with diarrhea.^{58,59}

Though it is shown that antibiotics or probiotics may have a role in controlling symptoms in other functional gastrointestinal disorders (e.g. bacterial overgrowth),⁶⁰⁻⁶³ their value for treatment of PI-IBS is still not accepted and more well designed researches are needed in this area.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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