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Irritable bowel syndrome following *Clostridium difficile* infection

Dayananda P, Wilcox MH.

Microbiology, Leeds Teaching Hospitals NHS Trust and University of Leeds, Leeds, UK.

Corresponding author:

Professor Mark H. Wilcox

Microbiology,
Old Medical School,
Leeds General Infirmary,
Leeds LS1 3EX,
W. Yorks., UK.

mark.wilcox@nhs.net

Tel +44 113 392 6818
Fax +44 113 392 2696

Abstract

Purpose of review: The aim of this review was to provide an overview of the current understanding of the diagnosis, pathophysiology and the role of the gut microbiome in *C. difficile* infection (CDI) related post-infectious irritable bowel syndrome (PI-IBS).

Recent findings: PI-IBS is a recognised pathological entity and was estimated to affect 1 in 10 patients with infectious enteritis. CDI remains a major health care burden world wide with a 1 in 4 chance of recurrence of symptoms following treatment. While there is growing interest in functional gastrointestinal disorders including PI-IBS, studies examining the prevalence and risk factors of CDI related PI-IBS remain scarce. One of many proposed mechanisms for PI-IBS is related to dysbiosis of the gut microbiota, which is the hallmark of CDI pathogenesis. Therefore, restoration of the gut microbiota, which is associated with successful outcomes in CDI, may be a potential treatment option for PI-IBS. However, two randomised controlled trails exploring the restoration of the gut microbiota using faecal microbiota transplant came to differing conclusions.

Summary: PI-IBS, particularly CDI related PI-IBS, remains an understudied area. A better understanding of the pathophysiology of PI-IBS is essential to developing more specific and effective management strategies.

Keywords: Post-infectious irritable bowel syndrome, *C. difficile* infection, gut microbiota

Key points:

- CDI and PI-IBS are both pathological entities associated with gut dysbiosis.
- Published studies to date examining the incidence of CDI related PI-IBS suffer from methodological and diagnostic limitations for the diagnosis of both IBS and CDI
- A better understanding of PI-IBS is necessary to develop more targeted and effective therapies

Introduction

Clostridium difficile infection (CDI) is a significant cause of morbidity, mortality and is a major health care burden worldwide. In the UK, over 13,000 cases of CDI have been reported by NHS Trusts between April 2017 and the end of March 2018. Whilst there has been a marked reduction in CDI reports since the peak incidence in the UK in 2007/08, the latest data represent a 3.4% increase compared with the number of cases between 2016/17. [1] The hallmark of CDI is profuse diarrhoea, with a ~25% chance of recurrent symptoms following treatment. There has been considerable interest in developing new therapies for CDI, in particular focussed on reducing the risk of recurrence of infection. However, it is important to note that such studies typically define diarrhoea as >3 episodes of loose stools per day for at least 2 days, and they usually follow patients for 4 weeks after the end of therapy. This primary concern about recurrence risk, coupled with a short-term follow up, means that there has been a lack of focus on the possibility of post-infectious (PI) irritable bowel syndrome (IBS) in patients following CDI.

IBS is highly prevalent disorder characterised by persistent or intermittent abdominal discomfort, distension and changes in stool patterns. [2] The prevalence of IBS is around 12%. [3] Infectious enteritis is a recognised risk factor for the development of IBS and was first described in 1962 by Chaudhary and Truelove.[4] Since then, there has been a rapidly growing recognition of post-infectious IBS. [5-7]. In a recent meta-analysis by Klem et al. examining over 20,000 individual patients with infectious enteritis, 10.1% of patients developed IBS by 12 months after the episode. This rate is 4.2-fold higher in comparison with patients who did not have infectious enteritis. [8] Examining these data in more detail, *Clostridium difficile* was not been examined as an enteric pathogen in any of the included studies. Therefore, the relationship between CDI and PI-IBS cannot be established based on this meta-analysis.

To date, studies examining the prevalence and risk factors associated with the development of PI-IBS following CDI are scarce and all suffer from significant methodological and diagnostic limitations; these include a lack of use of an acceptable gold-standard to define the presence of IBS, such as the Rome Criteria, and more importantly use of optimised

methods for CDI diagnosis (with failure to follow the 2-step approach recommended originally in European guidelines). [9, 10]

To date, only four studies have been conducted to determine the frequency of PI-IBS post CDI; these reported markedly variable prevalence rates of PI-IBS between 3 to $\geq$ 6 months after infection (4%-25%).[11-14] Most of these studies, as mentioned above, suffer from significant limitations. For example, a retrospective cohort study of 891 military personnel, identified cases according to disease coding, which likely included case heterogeneity, given the variance in diagnostic approaches to CDI. [12] It is now clear that some *C. difficile* detection methods have poor predictive value for CDI. [15] Of relevance here, a retrospective survey of PI-IBS post CDI, only used the presence of toxin genes in faeces, as opposed to direct detection of faecal toxin, to define cases. Consequently, this study likely included patients colonised by *C. difficile* who had diarrhoea not related to CDI. In this study, the authors found that 52 out of 205 patients (25.4%) surveyed between 6 - 9 months after CDI, developed IBS based on the Rome III criteria. [11] One small study with 23 patients did include cases diagnosed by a positive stool culture and *C. difficile* toxin detection; interestingly, this reported that only 4% of patients had symptoms compatible with IBS 3 months after the infection, but clearly the small sample size here means there is considerable variance around such a rate. [13] Also, the study did not meet the minimum 6 months required to meet the Rome III criteria for diagnosing IBS. [16] These issues may account for the significantly lower percentages of PI-IBS compared with those reported in the other three studies (12-25%). [11, 12, 14] Notably, only one study, which was also methodologically and diagnostically flawed, has comprehensively examined the risk factors associated with the development of PI-IBS following CDI; CDI duration, anxiety and higher BMI were associated with an increased risk of PI-IBS. [11] In a prospective, observational, cohort study of 41 patients with CDI and matched controls, 5 cases (12.2%) developed PI-IBS versus 0 from the control group at 6 months after CDI diagnosis. It is worth nothing, however, that the method of CDI diagnosis was not specified. [14] Thus, the validity of the results should be interpreted with caution.

***C. difficile* infection**

CDI is classically an infection secondary to disturbances of the gut microbiota, particularly after antibiotic use. CDI is mediated by the production and release of toxins, namely large glycosylating exotoxins A (TcdA) and B (TcdB). Both TcdA and TcdB disrupt the epithelial tight junction causing epithelial cell death resulting in a direct injury to the colonic epithelial cells. In addition, the toxins stimulate the affected colonic epithelial cells to release proinflammatory cytokines and neutrophil chemoattractants, which promote recruitment of neutrophils via the innate immune response pathway. This is a key characteristic of CDI pathophysiology. [17] More recently, *C. difficile* strains producing a third toxin, *C. difficile* transferase (CDT) toxin or binary toxin has been increasingly observed. [18] CDT intoxication leads to a loss of actin based cytoskeleton of the host cell, formation of microtubule based cell protrusions, which increases pathogen adherence as well as enhancing proinflammatory cytokines and suppression of the innate immunity response. [17]

Diagnosis and Pathophysiology of Post infectious IBS

IBS is a diagnosis of exclusion and is based on the presence of symptoms based on the Rome Criteria. [19, 20] Since the Rome Criteria were first described in 1988, revisions have occurred to incorporate new information and evidence; the latest revision (Rome IV) was published in 2016. [9] For a diagnosis of PI-IBS to be made, there is an additional caveat that the onset of symptoms meeting the Rome IV Criteria for IBS follows an episode of acute infectious gastroenteritis characterised by two or more of: fever, vomiting, diarrhoea and positive stool culture result. [21]

IBS is a disorder with a number of clinical phenotypes and a range of different pathogenesis. As such, new research is constantly challenging our understanding of the pathophysiology of IBS. [3] Holtman and Ford et al. proposed that IBS is likely to consist of multiple aetiologies. These different aetiologies share similar pathways that explain the phenotypic similarity and variability in symptoms, including the alteration of predominant bowel patterns. In the context of PI-IBS, one of the proposed pathway is that individuals who are genetically predisposed and have a susceptible microbiome, any insult, such as infectious or other environmental factors, can readily alter the microbiome resulting in an increase intestinal permeability. As a natural response, the antigens in the mucosa triggers a T-helper-2 cell

response, which promotes inflammatory infiltrate and loss of immune homeostasis. In some cases, this can lead to mast cell degranulation and induce visceral hypersensitivity and secondary motor abnormalities. [22] This represents the current conceptual framework regarding the pathogenic mechanisms for PI-IBS. [23]

Several studies have examined the mechanisms underlying PI-IBS related to specific infectious agents including *Giardia*, *Campylobacter* and *Shigella*. [20] However, further research is required to elaborate the mechanisms underlying CDI related PI-IBS.

Gut microbiota

The gut microbiota likely has an important role in pathogenesis of IBS. [24] The human gastrointestinal microbiota consists of more than a trillion bacteria, viruses, fungi, archaea and eukaryotic organisms. The role of the gut microbiome in health and disease has generated great research interest and there is growing evidence that the gut microbiome affects virtually all aspects of human health. [25] Many gastrointestinal diseases including IBS and PI-IBS are associated with alterations of the gut microbiome or dysbiosis. Although whether gut dysbiosis is a cause or effect in most cases has not been established. [26]

In the context of PI-IBS, a study by Carroll et al. has shown that patients with D-irritable bowel syndrome had significantly higher levels of enterobacteriaceae and lower levels of faecalibacterium compared with healthy controls. [27] Another study by Tana et al. found that patients with irritable bowel syndrome have significantly higher numbers of Veillonella and Lactobacillus compared with healthy controls. [28] More recently, a systematic review by Liu et al. in 2017 supports the earlier findings and added that Lactobacillus and Bifidobacterium were also found in significantly lower quantities in patients affected with IBS. [29, 30] Notably, it remains unknown whether such changes are characteristic of IBS post CDI.

Dysbiosis of the intestinal mucosa in IBS occurs at different levels. The overall community is less diverse with more variation between different patients and over time. This potentially reduces the microbiome's resilience to external stressors and may be responsible for triggering and maintaining the dysbiosis. Furthermore, it is worth noting that several groups of bacteria are commonly elevated (Lactobacillus, Veillonella, Ruminococcus,

Enterobacteriaceae, aerobes group, *S aureus*) or reduced (Bifidobacterium, B catenulatum and Bacteroides) in patients with IBS. [23]

Interestingly the dysbiosis noted in patients with IBS is different from patients with CDI as shown in a study by Sangster et al. examining the difference in the gut microbiome between patients with CDI with non-CDI diarrhoea. The authors showed that *Peptostreptococcaceae* matching closely to the infecting *C. difficile* strain, *Akkermansia muciniphila* and an unknown Enterobacteriaceae were more abundant compared with the control group. In addition, a relative depletion of anaerobes from the *Bacteroidales* and *Clostridiales* group was noted. Upon clinical resolution of CDI, there was a shift towards repletion of *Bacteroides* and butyrogenic bacteria (*Lachnospiraceae* and *Ruminococcaceae*), matching that of the non-CDI cohort. [31]

Treatment

There is no widely accepted management strategy for PI-IBS. Treatment is directed towards symptomatic relief rather than curative. Drug therapy is the mainstay of management options for symptomatic management for PI-IBS and has recently been summarised elsewhere. [23]

Faecal microbiota transplantation (FMT)

In patients with disease related to gut dysbiosis such as CDI, restoring the normal gut microbiome is essential for resolution of the disease. [32] Faecal microbiota transplantation is one of the options to achieve this. While there is increasing evidence to support the role of FMT in CDIs, there is limited and differing evidence around the use of FMT for IBS. [33]

The very first randomised controlled trial investigating the use of faecal microbiota transplantation versus placebo for moderate – severe IBS was conducted and reported by Johnsen et al. Ninety participants were randomised receive treatment or placebo using a 2:1 block randomisation. The patients had to have either IBS with diarrhoea being the predominant symptom or mixed IBS where constipation is not the predominant symptom. None of the patients included was diagnosed with PI-IBS. The authors found that 36/55 (65%) of patients in the FMT group showed a response of a decrease in IBS-SSS (severity scoring system) of more than 75 points at 3 months after FMT versus 12/28 from the

placebo group, but this effect was not maintained at 12 months compared with the placebo group. This supports the notion that the pathophysiology of IBS is closely related to the composition and function of the gut microbiota, and so restoring the gut microbiota is a potential treatment strategy for IBS. [34]

Halkjær et al. published another randomised, double-blind, randomised, controlled study examining the role of FMTs in IBS. Fifty-two patients were randomised to receive either placebo or FMT capsules. None of the patients included was diagnosed with PI-IBS. The authors found that patients with IBS have a lower stool microbial diversity compared with healthy donors. The authors also observed an overall reduction in IBS symptoms in both the FMT and placebo group. Surprisingly, the placebo group demonstrated a significant reduction in of IBS symptoms and improved quality of life. This is despite the fact that the microbiotas of patients with IBS resembled donors' microbiotas closely following FMT treatment. [35] These findings do not support a role for FMT in providing symptomatic benefit in patients with IBS.

Conclusion

IBS is a heterogenous and common condition. The pathophysiology of the different subtypes of IBS is yet to be understood and the causes are likely to be multifactorial in origin. There are several proposed theories but none appear to be specific to CDI related PI-IBS. As CDI is associated with gut dysbiosis, this may be the predominant pathway responsible for PI-IBS.

There is no widely accepted curative treatment option for IBS and symptomatic management is generally employed. There are increasing numbers of studies examining the role of faecal microbiota transplant in IBS. However, the only two double-blind, randomised, controlled trial results published to date showed conflicting evidence regarding its efficacy, and did not include patients with CDI related PI-IBS.

The true impact of post-CDI IBS is poorly described. CDI treatments that can best prevent or ameliorate such complications should be identified. Further research on the pathophysiology of CDI related PI-IBS, and the potential benefits of upcoming treatments are warranted.

Conflict of interest

MHW has received: consulting fees from Actelion, Astellas, bioMerieux, Cambimune, Da Volterra, Ferring, MedImmune, Menarini, Merck, Meridian, Pfizer, Qiagen, Sanofi-Pasteur, Seres, Spero, Summit, Synthetic Biologics and Valneva; lecture fees from Alere, Astellas, Merck & Pfizer; and grant support from Actelion, Astellas, bioMerieux, Da Volterra, Merck, Motif Biosciences, Nabriva, Paratek, Pfizer, Sanofi-Pasteur, Seres and Summit.

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