An Update on Post-infectious Irritable Bowel Syndrome: Role of Genetics, Immune Activation, Serotonin and Altered Microbiome

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The literature on post-infectious irritable bowel syndrome (IBS) is reviewed with special emphasis on recent new data. Further accounts of this phenomenon continue to be reported following a range of infections including giardiasis as well as viral and bacterial gastroenteritis. Risk factors such as severity of initial illness, female gender together with adverse psychological factors have been confirmed. Recent evidence of a genetic predisposition needs replication. Animal studies suggest activation of mast cells and inflammation driven impairment of serotonin transporter may be important, which are findings supported by some recent human studies in IBS with diarrhoea. Experimentally induced inflammation leads to damage and remodelling of enteric nerves. Similar changes have been reported in IBS patients with increase in nerves expressing transient receptor potential cation channel V1. While changes in microbiota are very likely this area has yet to be explored using modern techniques. Since the prognosis is for slow improvement, treatments should currently target the key symptoms of diarrhoea and abdominal pain. Future therapies aimed at correcting underlying mechanisms including immune activation and serotonin excess are currently being explored and may provide better treatments in the future.
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Key Words
Genetics; Infection; Irritable bowel syndrome; Serotonin

Introduction

Approximately 6%-17% of patients with irritable bowel syndrome (IBS) believe their symptoms began following a bout of gastroenteritis.[1] One of the first accounts of this phenomenon was by Chaudhary and Truelove[2] who described a series of patients with the IBS and its association with psychological problems. A subgroup who had developed IBS following a bout of gastro-

enteritis had a more a favourable prognosis than those without an infectious precipitant.[2] More recent studies have used a more rigorous definition of post-infectious IBS (PI-IBS), namely new IBS developing after an episode of acute infectious gastroenteritis[3] which is characterised by an acute illness with $\geq$ 2 of the following clinical features: fever, vomiting, diarrhea and a positive stool culture.[4] Although a positive stool culture is desirable this is often not available, as many cases occur while travelling when the patient may not have ready access to a doctor. One

of the commonest causes of PI-IBS in the United Kingdom (UK) is *Camplylobacter jejuni* enteritis. A survey of 840 cases of *C. jejuni* enteritis reported 103 cases who had developed PI-IBS meeting Rome I criteria, 63% of whom were classified as diarrhea predominant.[3] The original description by Chaudhary and Truelove[2] suggested that PI-IBS had less psychiatric illness than IBS patients with no infectious precipitant,[2] a feature confirmed in a series of outpatients with IBS.[4]

Epidemiology

The incidence of infective gastroenteritis in the UK is 19/1,000/year resulting in a high burden of consultation to primary care. However less than 1% of episodes of gastrointestinal infections in the community are reported to national surveillance systems so national statistics grossly underestimate the true incidence.[5] A more recent large community survey in the UK involving over 6,800 participants showed that the overall rate of infective diarrhea was 274 cases/1,000 persons/year. Viral gastroenteritis was the commonest cause, norovirus being the most frequent organism isolated, with an incidence of 47/1,000 persons/year. The commonest bacteria was *Campylobacter* spp. with incidence rate of 11/1,000 persons/year which gave an estimate of > 500,000 cases in the UK in 2009.[6] Other common bacterial intestinal infections were *Salmonella* spp. and *Escherichia coli*. It is worth noting that given the marked underreporting of infectious gastroenteritis the true incidence of PI-IBS may well be greater than is currently believed.

Epidemiological studies suggest that enteric infection is one of the most important risk factors for developing IBS, equal to anxiety and greater than depression, sleep disorders, smoking, body mass index and alcohol excess.[7] The proportion of patients developing IBS following intestinal infections varies in different series from as low as 3.7%[8] to as high as 36%.[9] The highest figure was reported from the Walkerton outbreak, when the municipal water supply was simultaneously contaminated by both *C. jejuni* and *E. coli* O147. The commonest bacteria causing PI-IBS in the UK are *C. jejuni*, *Salmonella enteritidis* and *Shigella flexneri*. The IBS symptoms which develop are often regarded by the patient as a continuation of the initial illness, most meeting the Rome criteria for IBS with diarrhea (IBS-D) or IBS with mixed bowel habit.[10-12] The similarities between PI-IBS and these other subtypes of IBS suggest that studying PI-IBS patients may provide insight into the pathophysiology of all IBS. Thus PI-IBS has been studied by many authors,[9-15] possibly because the clearly defined onset makes it easier to define what is the cause and what the effect, something which could often be difficult in other subtypes of IBS.

Risk Factors

Genetic

IBS shows a familial tendency and an early study[16] on monozygotic and dizygotic twins in Australia reported a heritability of 57% but later studies have suggested a weaker effect.[17,18] Thus although the large twin study in Virginia[18] showed concordance for IBS was greater in monozygotic twins (17%) than dizygotic twins (8%), it also showed the importance of social conditioning, since having a mother with IBS was a stronger predictor than having a dizygotic twin with IBS. Studies of single nucleotide polymorphisms (SNPs) also support a genetic influence. A greater proportion of IBS patients compared to control (46% vs 26%) are heterozygous for the -308 (G/A) SNP which a high producer of TNF-α.[19] Possession of both the high producer TNF-α SNP -308 A and low producer of IL-10 -1082 A allele was also more prevalent in IBS patients (9%) versus controls (3%). More recently the G allele of SNP rs4263839 in the *TNFSF15* gene, which has been associated with Crohn's disease, has been demonstrated to increase the risk of IBS in a cohort of 1992 IBS patients from both Sweden and the USA (OR, 1.37).[20] A closely related SNP in the *TNFSF15* gene has also been shown to increase the risk of IBS-D but not IBS with constipation (IBS-C).[21] The same study also found an increased prevalence of the TNF-α SNP rs1800629 genotype GA compared with GG in PI-IBS, confirming findings in an earlier study of PI-IBS patients.[19] Further SNPs associated with PI-IBS have recently been reported from the Walkerton outbreak in 2007[22] which identified 3 gene regions where SNPs increased the risk of PI-IBS, namely Cadherin 1, IL-6 and Toll-like receptor 9. Cadherin 1, coding for E-cadherin, is a tight junction glycoprotein which influences intestinal barrier function.[23] Toll-like receptor-9 is the receptor for unmethylated CpG dinucleotides which are a marker of bacterial DNA and represent the pathway whereby bacteria activate innate immunity, while IL-6 is an inflammatory cytokine activated by infection. One limitation of this study is that the significance of these associations did not withstand corrections for multiple testing possibly owing to small sample size (228 PI-IBS and 581 controls) so these associations need to be reproduced in a separate cohort.
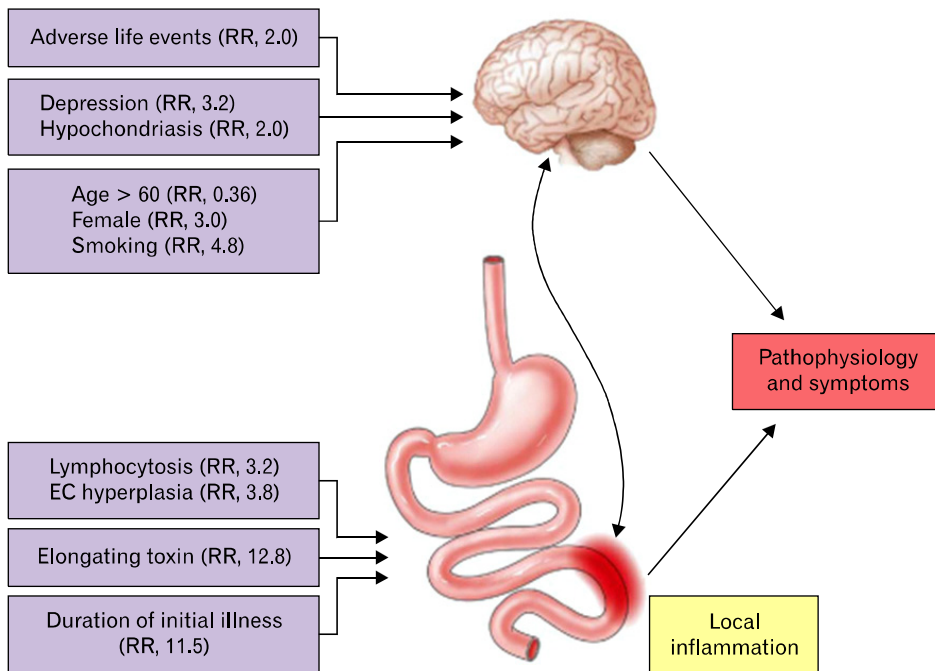
Figure. Host and bacterial factors influencing risk of developing post infectious irritable bowel syndrome. Reproduced from Spiller and Garsed[24] with kind permission of the editor of Gastroenterology. RR, relative risk; EC, enterochromaffin.

Physical and Psychosocial

Both central psychological factors and local gut injury influence the risk of developing PI-IBS (Figure).[24] Several studies confirm that high stress and anxiety levels,[25] hypochondriasis (relative risk [RR], 2.0), adverse life events in the preceding 3 months (RR, 2.0)[14] and depression (RR, 3.2),[26] all increase the risk of developing PI-IBS. Mucosal factors are also significant and each 1 standard deviation rise in T lymphocyte and enterochromaffin (EC) cell numbers increases the risk of PI-IBS by 3.2- and 3.8-fold, respectively. Other host factors include age and smoking. Being older than 60 years protects against PI-IBS (RR, 0.36), possibly because of declining immune response with ageing, while smoking increases the risk 4.8-fold, through an as yet unclear mechanism.[24] The underlying mechanisms whereby these psychological factors increase the risk of PI-IBS are unclear. Animal studies show corticotrophin releasing factor (CRF) is an important mediator of the stress response, acting via the hypothalamic-pituitary-adrenal axis in animal models of PI-IBS.[27,28] CRF acting via CRF1 receptors mediates the stimulation of colonic motility by various stressors[29,30] and CRF and stress enhance abdominal pain via the central CRF pathway and activation of mast cells in rats.[31] CRF may also be proinflamatory, stimulating lymphocyte proliferation by increasing IL-2 receptor expression and enhancing production of both IL-1 and IL-2[32] as well as enhancing cytokine release (TNF-α, IL-1 and IL-6) in

response to endotoxin.[33] Stress also aggravates chemically induced colitis.[34] Thus by enhancing the local inflammatory response to infection, stress may increase the risk of PI-IBS. This has been examined in more detail recently using an animal model of PI-IBS. Rats infected with *Citrobacter rodentium* who were subsequently exposed to chronic water avoidance stress showed increased level of corticosterone and epinephrine levels and an increase peripheral nociceptive signalling from rectal distension, assessed both by recordings from afferent nerves, as well as visceromotor responses in intact animals. They also found increased tissue proteases in homogenates of the colon of *C. rodentium*-infected mice, most likely from activated mast cells, which induced hyperexcitability in colonic dorsal root ganglia cells.[35] Human studies have also shown activation of mast cells induced by immersion of hand into cold water which causes pain and sympathetic activation with raised pulse and blood pressure. This lead to the release of mast cell products such as histamine and tryptase into the lumen of the small bowel[36] providing a possible mechanism for how stress could increase human small bowel secretion and motility, leading to the accelerated transit which is a characteristic of IBS-D. The same group have also shown evidence of increased numbers of mast cells in anxious IBS-D patients associated with increased release of tryptase from jejunal biopsies, a finding recently replicated by Foley et al.[37]

Bacterial Factors

Bacterial toxins play important part in development of intestinal inflammation during infection. *C. jejuni* infection is one of the commonest causes of infectious gastroenteritis, leading to PI-IBS in 9%-13% of cases.[26,38] Patients infected with a strain that secret toxin which causes elongation of human epithelial (HEp-2) cells have an increased risk of developing a long term change of bowel habit with a RR of 12.8 (Figure).[38] Other bacterial pathogens that cause marked gut inflammation and have been associated with PI-IBS include enterotoxigenic *E. coli*,[39] the shiga-toxin producing *E. coli* O147 especially when combined with *C. jejuni*,[22] *Shigella* spp.[11] and *S. enteritidis*.[40] A surrogate marker for bacterial toxicity is the duration of initial illness; initial episodes lasting more than 21 days had a RR of 11.37 (95% CI, 2.2-5.8) for PI-IBS[10] compared to illness lasting less than a week. Vomiting as part of the initial illness may be protective,[10] perhaps because it reduces the infecting dose.

Mechanism

Inflammation

There is limited data on the morphological and functional changes in human gastrointestinal mucosa during an outbreak of gastroenteritis. Enteric bacterial pathogens adhere to the intestinal epithelium and deliver enterotoxins or cytotoxins which may cause marked secretion or inflammation and enterocyte damage associated with symptoms of diarrhea.[41,42] During the acute phase of gastroenteritis, macroscopic changes may mimic features of inflammatory bowel disease. Macroscopic features seen during colonoscopy include erythema, oedema, haemorrhagic spots, friable mucosae, ulcers and mucopus.[43-45] A marked increase in gut permeability is commonly seen, possibly reflecting damage to the enterocytes.[10] During the acute phase of viral gastroenteritis, there is reduction in villous surface area and villous height along with increased intraepithelial lymphocytes and gut permeability. However this rapidly resolves with little inflammatory damage,[46] which may explain why PI-IBS after viral gastroenteritis is short-lived.[47] Other studies following protozoan infection such as giardiasis, which is associated with PI-IBS, have confirmed inflammatory changes including villous shortening and increase of plasma cells and leucocytes in the lamina propria.[48] Detailed prospective studies in men are difficult to perform so studies on animal models have been used to assess the

pathophysiology of PI-IBS. Mice infected with *Trichinella spiralis* show transient acute mucosal inflammation with increase in mast cells and T lymphocytes which resolves as the worm migrates from the gut to encyst in muscle tissue. However although acute inflammation resolves and the mucosa heals there is persistent T lymphocyte-dependent EC cell hyperplasia,[49-51] increased expression of tachykinins,[52] prolonged motility dysfunction and visceral hypersensitivity that lasts for many weeks following clearance of the infection.[51,53-56]

Several studies have shown similar evidence of low grade "immune activation" in IBS patients.[12,14,57,58] A prospective study using serial rectal biopsies on patients following *C. jejuni* gastroenteritis has shown raised serotonin (5-hydroxytryptamine, 5-HT)-containing EC cells, intra-epithelial lymphocytes (IELs; CD8) and T lymphocytes (CD3, CD4 and CD8) which could last up to 4 years.[12,26] Increased EC cells are an independent predictor of developing PI-IBS[25,26] with each standard deviation rise in EC counts being associated with a RR of 3.8. Immune activation with increased level of CD3, CD4 and CD8 are also found in unselected IBS patients.[59] This "immune activation" is subtle compared with changes seen in inflammatory bowel disease or microscopic colitis and does not include neutrophil infiltration.[58,59]

Serotonin

EC cells are an important subgroup of enteroendocrine cells which act as "taste buds" of the intestine, responding to luminal pressure and contents including nutrients and bacterial products, transducing these to neural responses by secreting peptides and amines which activate enteric nerves. EC cell granules contain 5-HT which activates enteric reflexes via the 5-HT_{1p}, 5-HT_3, 5-HT_4 and 5-HT_7 receptors to stimulate secretion and propulsion of the gut.[60,61] 5-HT plays an important role in the motility and secretion of the gut, particularly in response to toxins such as cholera toxin which causes profuse intestinal secretion.[62] Mice infected with *Trichuris muris* develop T-cell mediated immune activation in the gut leading to an increase in EC cells and 5-HT content.[49-51] EC hyperplasia is associated with increased serotonin release, which can lead to increase motility and secretion, features which may explain diarrheal symptoms in IBS-D patients.[63,64] As discussed above mice infected with *T. spiralis*, which showed similarities with PI-IBS in human, exhibit hyperplasia of EC in most sections of the bowel (except colon) and reduced serotonin transporter (SERT).[49-51] 5-HT's action is terminated by degradation by intracellular enzymes, monamino-oxi-

dases. Being a polar molecule, 5-HT is excluded from cells and requires SERT to transport it across the cell membrane before it can be degraded. It follows that reduction in SERT leads to impaired intracellular uptake and degradation and hence increased availability of serotonin within the mucosa.[56,65] This may be relevant to IBS since patients with IBS-D show similar findings including increased IELs and mast cells and reduced SERT mRNA in duodenal biopsies.[37] The raised IELs are inversely correlated with level of SERT messenger RNA, in keeping with experimental data showing inflammatory cytokines, possibly from lymphocytes and macrophages, reduced SERT mRNA.[66] Impairment of SERT function will increase mucosal 5-HT availability, stimulating secretion and motility which may contribute to the diarrheal symptom in IBS-D.[37,63] This concept is supported by the clinical effectiveness of 5-HT$_3$ receptor antagonists which are amongst the most potent treatments for IBS-D.[67]

Mast Cells

As shown in the Table increased mucosa mast cells have been found in many series of both PI-IBS[11] and IBS-D patients.[57,68] Mast cells products can activate enteric nerves within the lamina propria which may be relevant to IBS symptoms since the number of mast cells < 5 μm from an enteric nerve correlates with the severity of visceral pain in IBS.[76,77] Increased amounts of mast cell mediators such as tryptase and histamine are found in supernatants from IBS patients' mucosal biopsies and have been shown to activate human enteric afferent nerves.[78-80] The release of these mediators from mast cells may contribute to visceral hypersensitivity by activating enteric afferents.[76,80] One study showed an increase in mast cells in the terminal ileum, ascending colon and rectum of IBS patients compared to healthy volunteers and higher mast cell counts in those with rectal hypersensitivity.[71] Interestingly after infection, regardless of symptoms, the numbers of mast cell in close proximity to enteric nerves were increased, presumably as part of the remodeling of the mucosa after the initial injury when regenerating nerves sought out their targets.[81]

Cytokines

IL-1β is a key pro-inflammatory marker which is released by activated macrophages and stimulates lymphocyte proliferation. IL-1β mRNA has been shown to be increased in the terminal ileum and recto-sigmoid colon of PI-IBS patients[11] and in rectal biopsies in patients who had PI-IBS, both during the acute infection and after 3 months.[82] It is more convenient to assess immune activation in peripheral blood mononuclear cells (PBMCs) which have been shown to release more proinflammatory cytokines (TNF-α, IL-1β and IL-6) in response to lipopolysaccharide in patients with IBS-D but not IBS-C.[23] This study had only 5 out of 20 IBS-D patients with PI-IBS who appeared to exhibit particularly high cytokine levels but this difference was not significant, though the study was obviously underpowered to test this. The origin of this increased reactivity of PBMCs is unclear since psychological stress may also lead to immune activation and

Table. Evidence of Mast Cell Abnormalities in Irritable Bowel Syndrome

Site	Mast cell count	Subtype	IBS/HC (n)	References
Duodenum	↑	IBS-D	20/29	Foley et al,[37] 2011
	→	IBS-C & IBS-D	38/20	Wang et al,[50] 2007
Jejunum	↑	IBS-D	20/14	Guilarte et al,[68] 2007
	→	IBS-C & IBS-D	38/20	Wang et al,[69] 2007
Ileum	↑	IBS-D	20/15	Weston et al,[70] 1993
	↑	IBS-D & PI-IBS	29/27/30	Wang et al,[11] 2004
	↑	IBS-D	18/15	Park et al,[71] 2006
	↑	IBS-C & IBS-D	38/20	Wang et al,[69] 2007
Caecum	↑	IBS	14/7	O'Sullivan et al,[72] 2000
	↑	IBS-D	14/14	Park et al,[73] 2003
	↑	IBS-D/IBS-C	21/29/21	Piche et al,[74] 2008
	↑	IBS-D/IBS-C/IBS-M	13/10/11/15	Vivinus-Nebot et al,[75] 2011
Descending colon	↑	IBS	44/22	Barbara et al,[76] 2004
Rectum	↑ Non PI-IBS → PI-IBS	PI-IBS/non PI-IBS	23/52/36	Dunlop et al,[4] 2003

IBS, irritable bowel syndrome; HC, healthy controls; IBS-D, IBS with diarrhea; IBS-C, IBS with constipation; PI-IBS, post-infectious IBS; IBS-M, mixed IBS.

increased IL-1β in PBMCs.[83] IL-6, which is also increased by infection, has been shown to be increased in both IBS and depressed patients, showing the complex interaction between psychological and infectious factors.[84] More recently a group from Sweden has reported increased % of PBMCs from unselected IBS patients which were CD69+, Integrin β7+ and HLRD+, indicative of T-cell activation and gut homing respectively[85] though this report did not indicate if any were PI-IBS.

Changes in Enteric Nerves

The enteric nervous system plays an important role during enteric infections by orchestrating secretory action and activating motor patterns to expel the pathogens.[86] *T. spiralis* infected mice show higher levels of substance P in the myenteric plexus[52] associated with visceral hypersensitivity, muscle wall thickening and greater sensitivity to cholinergic stimuli. A more severe model of gut inflammation, the trinitrobenzenesulphonic acid colitis, shows that inflammation in the gut causes extensive remodelling of enteric nerves. This leads to changes in the neurochemical coding with increased expression of tachykinins, vasoactive polypeptide, galanin and pituitary adenylate cyclase activating polypeptide within the enteric nervous system.[87,88] Similar studies in patients with symptomatic diverticular disease, who often have had prior episodes of acute diverticulitis, showed that the symptomatic patients had increased expression of substance P.[89] This supports the idea that the pain in PI-IBS could be due to changes in the enteric nerves, whose slow rate of repair might explain why symptoms often remain for many years after the initial infection.

Following shigella enteritis, neuron specific enolase (paneuronal marker) and substance P were both increased in the terminal ileum and rectosigmoid tissue in PI-IBS. However this was also seen in non-infectious IBS patients suggesting there is more than one mechanism mediating these changes.[11] Animal studies showed that colonic mucosal injury induced by acetic acid was followed by increased expression of the transient receptor potential vallinoid 1 (TRPV1) receptor which caused increased visceral hypersensitivity in this model.[90] More recently human studies using rectal biopsies of unselected IBS patient have shown increased TRPV-1 positive neuronal fibres, whose numbers correlated with severity of abdominal pain.[91] The key nerves responsible for transmitting pain to the human brain lie not in the mucosa but within the myenteric plexus which not easily obtainable in IBS patients. However in a highly selected series of 10 IBS patients with very severe symptoms, full thickness biopsy of jejunum showed increased lymphocytes and neuronal degeneration in the myenteric plexus suggesting altered enteric nerves may be important.[92]

Altered Microbiome

The appearance of new non-culture based techniques for profiling of the bacteria in the gastrointestinal tract has revealed an immense complexity with as many as 1,500 separate species. Each individual's intestinal microbiota depends on many factors including genetics, age, diet, antibiotics and other environmental factors including infection. There is a symbiosis between the human host and the microbiota which helps to keep the environment in the colon stable, protecting the host from pathogens via production of a range of antibacterial products including short chain fatty acids (SCFA).[93] During an acute phase of bacterial enteritis, the inflammatory response inhibits the normal microbiota[94] and there is reduction in SCFA and increase in the faecal pH.[95] Subjects with infectious diarrhea showed decreased diversity and new strong bands which were seen using gel electrophoresis profiling indicating overgrowth of selected bacteria groups, features not seen in normal healthy controls.[96] Taking a bowel preparation for screening colonoscopy in some ways simulated an acute episode of diarrhea and in some patients this appeared to alter the gut microbiota, an effect which persisted for at least 8 weeks.[97]

Many studies have tried to characterise the changes in intestinal faecal microbiota in IBS patients. An earlier study using traditional culture-based techniques have shown reduction of bacteria such as coliforms, *Lactobacillus* spp. and *Bifidobacterium* spp. and increased number of Enterobacteriaceae in the gut flora of IBS patients.[98,99] More recently a study using DNA-based techniques showed increased numbers of Proteobacteria and Firmicutes and reduction in number of Actinobacteria and Bacteroidetes in patients with IBS-D when compared to healthy volunteers.[100] Another study found changes in the composition of bacteria according to subtypes of IBS. IBS-D has lower amount of *Lactobacillus* spp. whereas IBS-C patients had increased amount of *Veillonella* spp.[101] These findings vary between studies which may be due to different laboratory techniques and possibly due to the heterogeneity of IBS patients. Indeed it is unlikely that attempting to characterise all the bacteria will be helpful since it is the overall metabolic effect which is likely to determine bowel symptoms. Thus in the future it is likely that dividing into enterotypes, ie, clusters of associated bacteria will improve the link between microbiota and gut symptoms which at present are uncertain.

Prognosis

There is a slow decline in prevalence of PI-IBS in the years following initial diagnosis. A 5 year review following *Salmonella* spp. infection showed 7 out of 11 patients still had disturbed bowel function, but only 5 had diarrhea more than 1×/week.[102] A 6 year follow-up study in PI-IBS revealed 43% of PI-IBS patients had recovered[103] while a meta-analysis of PI-IBS reported steady reduction in IBS following infection, with odds ratio for those infected compared to noninfected controls of 7.6 at 3 months and 3.8 at 3 years.[15] The long term follow up of the outbreak of gastroenteritis in Walkerton showed a decline in the prevalence of PI-IBS from 28% to 15.4% after 8 years.[104] Risk factors for developing PI-IBS were similar to previous reports and included female gender, younger age and fever or weight loss during the acute enteric infection. A history of severe psychiatric illness that is untreated may impair recovery. These data show that the clinician can reassure the patients that the prognosis is one of improvement and the chances of developing a new condition like inflammatory bowel disease is very low.

Management

Management of PI-IBS should be tailored according to patient's symptom severity. It is important to ensure that patient has realistic expectations of treatment and recognise that although they are likely to improve, symptoms may persist for some years. Meanwhile treatment should be given according to the predominant symptoms. Patient with abdominal pain and anxiety should try mild tranquilisers like low dose tricyclics agents such as amitriptyline 10-30 mg at night, a practice supported by consensus of experts but without high quality randomised controlled trials.[105] The only recent good quality study used desipramine 50 mg which is much less well tolerated, though if compliance is good it does lead to superior response rates compared to placebo.[106] The symptoms of diarrhea and urgency respond well to loperamide, 2 mg with each loose stool.[107,108] However this often induces bloating and distension, so many patients prefer to only use loperamide when they are travelling or on special occasions, when urgency would be very inconvenient.

Our increase in understanding of the underlying pathophysiology has opened more opportunities to target treatment to specific mechanisms that may cause PI-IBS/IBS. Given the underlying immune activation prednisolone was a logical choice but at a dose of 30 mg daily for 3 weeks proved to be ineffective in symptomatic relief of IBS despite reducing T-lymphocyte numbers in the rectal mucosa.[109] A proof of concept study concluded that ketotifen, a mast cell stabiliser, decreased visceral hypersensitivity and reduced IBS symptoms although there was poor correlation with mast cell activation assessed in biopsies.[110] More recently, mesalazine, an anti-inflammatory agent, has been used. Some pilot studies have shown reduction in mast cell numbers and improvement of overall well-being, abdominal discomfort and altered gut microbiota[111,112] but the studies were underpowered (n = 20 and n = 12, respectively). Another uncontrolled study using mesalazine in PI-IBS and IBS patients with predominantly diarrhea concluded that there was improvement in stool consistency, frequency and abdominal discomfort.[113] However given the high placebo response in IBS, a large double blind and placebo controlled study using mesalazine for treatment of IBS is now needed to convincingly confirm or refute these findings.

Given the data on the relationship between immune activation and increased availability of 5-HT in IBS-D, a 5-HT antagonist would be a logical treatment for PI-IBS. A 5-HT$_3$ antagonist, alosetron, was highly effective for unselected IBS-D patients with beneficial effect on abdominal pain and overall well being.[114] Unfortunately owing to its side effect of severe constipation and ischaemic colitis, this drug was initially withdrawn and is now only available under very restricted conditions. Other 5-HT$_3$ antagonists include ramosetron and ondansetron. Ramosetron is a potent 5-HT$_3$ antagonist, used at the very low dose of 5 μg daily, not available in Europe or America but available in Japan and Korea where it is approved for both males and females. Ischemic colitis has not been reported and the pivotal randomised controlled trial demonstrated 47% response rate compared to 27% on placebo, giving a number needed to treat of 5, suggesting it is one of the most potent IBS treatments for IBS-D.[115] Ondansetron, a 5-HT$_3$ antagonist may be another potential treatment of IBS-D patients. It has been widely used as an anti-emetic for over 2 decades with an excellent safety profile and no reports of ischemic colitis. Our recent randomised placebo controlled trial showed a responder rate, defined as a 50% reduction in days per week with loose stool of 70% on ondansetron versus 33% on placebo. This gives a number needed to treat of 2.7 making it one of the most potent drugs for IBS-D. The mode dose was very low at 4 mg on alternate days with a low incidence of constipation (9%), which virtually always responded to dose reduction.[116] An alternative approach is to inhibit serotonin synthesis and a tryptophan hydroxylase 1 inhibitor has been shown recently to benefit IBS-D.[117]

Conclusion

PI-IBS developing after viral, bacterial and protozoan infections continues to be reported. These recent studies have confirmed the importance of the previously established risk factors, namely severity of initial illness, female gender and adverse psychological factors. Recent evidence suggests a genetic predisposition involving excessive cytokine response. Mucosal immune activation involving mast cells and lymphocytes with secondary impairment of serotonin transporter have been demonstrated in IBS-D. While the prognosis is for slow improvement, treatments should currently target the key symptoms of diarrhea and abdominal pain. Loperamide is effective for diarrhea while tricyclic antidepressants benefit pain. Future disease modifying therapies aimed at correcting underlying mechanisms including immune activation and serotonin excess are currently being explored and may provide better treatments in the future.

Acknowledgements

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