Infection as a cause of irritable bowel syndrome

RC Spiller

The normal response to infection, such as vomiting and diarrhoea, is protective and beneficial. However, in about 10% of patients these protective changes persist and may contribute to the development of post-infective irritable bowel syndrome, which may persist for many years. New insights into the pathogenesis of this condition suggest novel, effective ways of treatment.

The gastrointestinal tract's main function is the digestion and absorption of food, but this means that it is exposed to a wide range of pathogens that attempt to subvert gut function for their own benefit. Therefore, the gut has evolved an extensive system of defences, both innate and acquired, to counteract this threat.

The innate defences consist of salivary lysozyme, gastric acid and small-intestinal defensins derived from Paneth cells. There is also a system of serotonin-containing entero-endocrine cells, which react to bacterial toxins and release serotonin. This leads to vomiting via stimulation of 5-hydroxytryptamine $(5\text{-HT})_3$ receptors on the vagus nerve, and also to profuse diarrhoea acting via intestinal secretory and propulsive reflexes, both local and distal. The profound watery diarrhoea characteristic of cholera is largely mediated by serotonin from entero-endocrine cells. This non-specific response flushes out organisms long before the development of any specific immune response.

As well as these immunological changes there are also behavioural changes. Nausea is associated with the development of a profound aversion to the offending food, thus avoiding repeated food poisoning. These behavioural adaptations may long outlast local intestinal responses.

Professor RC Spiller is Professor of Gastroenterology, Division of Gastroenterology, University Hospital, Nottingham NG7 2UH

TABLE 1.
Rome criteria for diagnosing irritable bowel syndrome*

Recurrent abdominal pain, occurring for 3 months out of the previous 12 months, associated with at least two of the following three features:
Relief by defecation
A change in stool consistency
A change in stool frequency

* From Thompson et al (1999)

IRRITABLE BOWEL SYNDROME

Recurrent abdominal pain associated with an irregular bowel habit is a common cause of consultation, which can often be diagnosed as irritable bowel syndrome (IBS) with some confidence on symptoms alone, provided certain precautions are taken. Diagnostic criteria for IBS were agreed at the Rome consensus meeting (Thompson et al, 1999) (*Table 1*), which make it clear that the pain originates in the colon. The earlier Rome diagnostic criteria for IBS (Drossman et al, 1990) required the presence of two or more of the following features for at least 25% of occasions or days:

- Altered stool frequency (more than three movements a day, or less than three a week)
- Altered stool form (lumpy and hard, or loose and watery)
- Altered stool passage (straining, urgency, sense of incomplete evacuation
- Passage of mucus through the rectum
- Bloating or feeling abnormal distension.

Although these features certainly support the diagnosis of IBS, they are not essential.

ALARM FEATURES

A careful history should be taken and a physical examination performed to consider other possible causes of abdominal pain, such as inflammatory bowel disease, peptic ulcer, gallstones, gastric, pancreatic and colonic cancer and diverticular disease. The alarm features listed in *Table 2* are useful clues to alternative diagnoses. Provided that these features are absent, the chances of a diagnosis other than IBS is small (Vanner et al, 1999). Once the diagnosis is made, few different diagnoses are subsequently suggested during follow-up (Harvey et al, 1987).

INCIDENCE OF IBS

Questionnaire surveys have been sent out to large numbers of the general population, and between 5 and 15% met these criteria (reviewed by Jones et al (2000)). The more stringent the criteria, the lower the frequency, but however defined, IBS is a common condition.

Thompson et al (2000) found that around 3% of all GP consultations were for IBS, but this leaves a large number of people who do not consult. The main factors distinguishing those who consult from those who do not are severity of symptoms (Koloski et al, 2001) and increased anxiety (Patrick et al, 1998). Individuals who do not consult but have symptoms of IBS (non-patients) have higher coping abilities (Drossman et al, 1988).

SUBTYPES OF IBS

Factor analysis of the symptoms of IBS leads to a division of patients into three main groups:

- Patients with mainly loose stools
- Patients with mainly hard stools
- An intermediate group with no predominant pattern (Ragnarsson and Bodemar, 1999).

The latest Rome consensus (Thompson et al, 1999) agreed the subdivision of IBS into:

- Diarrhoea-predominant (D-IBS)
- Constipated-predominant (C-IBS)
- Those with an alternating stool pattern (alt-IBS) (*Table 3*).

These subtypes are important because they probably indicate different underlying pathogenesis and respond differently to treatments that alter colonic transit.

POST-INFECTIVE IBS

Most patients with IBS describe an insidious onset of symptoms, but a small subgroup describe an acute onset with a history of a previously completely normal bowel habit; these patients have post-infective IBS (PI-IBS). The criteria for PI-IBS are acute onset of IBS symptoms after an acute episode, characterized by at least two of the following:

- Fever
- Vomiting
- Diarrhoea, with or without a positive stool culture.

The proportion of people with IBS who have PI-IBS varies by country and setting; it is 17% in UK general practice, but only 6% in tertiary care in the USA (Longstreth et al, 2000).

TABLE 2.
Alarm features that suggest alternative diagnoses should be excluded

Documented weight loss
Nocturnal symptoms
Blood mixed with stool
Recent antibiotic use
Family medical history of colon cancer
Abnormalities on physical examination

INCIDENCE OF PI-IBS

Several studies have indicated that following infective bacterial gastroenteritis, between 7 and 17% of people with a previously normal bowel habit develop PI-IBS (Gwee et al, 1996; Neal et al, 1997; Parry et al, 2001). However, this figure is probably larger, as 8–18% of people who have increased bowel frequency and looser stools after infection do not meet the threshold for a diagnosis of IBS according to the Rome criteria (>25% of occasions or days) (Neal et al, 1997).

A recorded episode of food poisoning was the strongest single factor predicting the onset of IBS over the next year in a large, general practice-based study, which reported an increased risk of 11.9 of developing IBS compared with controls (Rodriguez and Ruigomez, 1999).

The main features of PI-IBS are:

- An increased bowel frequency with urgency 2–3 days a week
- Loose stools 3–4 days a week
- Abdominal pain 2–3 days a week (Neal et al, 1997).

Physiological studies demonstrate increased visceral sensitivity and accelerated colonic transit in people with PI-IBS (Gwee et al, 1999).

DIFFERENTIAL DIAGNOSIS OF PI-IBS

An infection may activate previously occult conditions, which must be excluded before the diagnosis of PI-IBS can be made (*Table 4*).

- Carcinoma of the colon should always be considered with a change in bowel habit, especially if the patient is >40 years of age, or even younger if there is a family history of colonic cancer.
- Diverticular disease should be considered in the elderly.

TABLE 3.
Features of the different subtypes of irritable bowel syndrome

	C-IBS	D-IBS	Alt-IBS
Stools	Hard, pellety	Loose, watery	Variable
Frequency of bowel movement	Less than three times a week	More than three times a day	Variable
Defecation	Straining	Urgency	Variable

Alt-IBS=alternating stool pattern in irritable bowel syndrome (IBS); C-IBS=constipated-predominant IBS; D-IBS=diarrhoea-predominant IBS.

- About 3% of patients presenting with IBS symptoms have coeliac disease, which can be screened for with an endomysial antibody test.
- Another diagnosis easily mistaken for PI-IBS is Crohn's disease in its early stages, which should be suspected if there is anaemia, an elevated erythrocyte sedimentation rate and/or nocturnal diarrhoea and pain.
- Lactose intolerance is only relevant if subjects consume substantial amounts of milk, and can be readily tested by means of a lactose breath test.
- Microscopic colitis can be triggered by an acute infection, but can be excluded by flexible sigmoidoscopy and mucosal biopsy.
- Small-bowel contamination should be considered in older patients, particularly those who have had small-bowel resections or irradiation, or who have achlorhydria.
- Drug-induced diarrhoea should be considered, including antibiotics, magnesium-containing antacids, proton pump inhibitors, angiotensin-converting enzyme inhibitors and statins.

PROGNOSIS IN PI-IBS

Earlier studies suggested that patients with a history of infection had a much better prognosis than those with other subtypes of IBS (Chaudhary and Truelove, 1962). However, a more recent prospective study indicated the prognosis to be less good (Neal et al, 2002); only 43% of patients with PI-IBS recovered after 6 years, which was a figure not significantly different from the 31% of people without PI-IBS who recovered over the same period.

RISK FACTORS FOR DEVELOPING PI-IBS

Several studies have indicated that the severity of the initial illness strongly influences the risk of developing PI-IBS. Neal et al (1997) showed that patients whose initial diarrhoeal illness lasted >3 weeks had an increased relative risk (RR) of developing new PI-IBS compared with those whose illness lasted <7 days (mean RR=11.4, 95% confidence intervals (CI) =2.2–58).

The other main risk factor of PI-IBS is being female (mean RR=2.9, 95% CI=1.6–5.1). Interestingly, older people have a lower RR of symptoms, with those >60 years having an RR of 0.46 (95% CI=0.2–0.9).

TABLE 4.
Conditions that may present as post-infective irritable bowel syndrome

Carcinoma of colon
Diverticular disease
Drug-induced diarrhoea
Coeliac disease
Small-bowel contamination
Crohn's disease
Lactose intolerance
Microscopic colitis
Giardiasis

ROLE OF PSYCHOLOGICAL FACTORS IN PI-IBS

Gwee et al (1996) found that the risk of developing PI-IBS was increased for patients with greater anxiety, depression or hypochondriasis. Fifty per cent of patients with PI-IBS had moderate anxiety, compared with only 9% of those who did not develop PI-IBS. However, when this is translated into RR, the value of RR=2.0 (95% CI=1.75–2.45) of developing PI-IBS is much less than that associated with other factors such as female sex and duration of illness (Gwee et al, 1999). Indeed, Dunlop et al (2001) found in an outpatient setting a significantly lower lifetime incidence of treatment for anxiety or depression in patients with PI-IBS (26%) than in IBS patinets without an infectious onset (54%), suggesting that such factors play a much smaller part in PI-IBS compared with in other IBS subtypes.

ROLE OF BACTERIAL PATHOGENICITY IN THE DEVELOPMENT OF PI-IBS

Neal et al (1997) suggest that the initial mucosal injury, which is the main determinant of the length of the original illness, is the most important predictor of developing PI-IBS. This probably explains why PI-IBS is much more common after *Campylobacter* and *Shigella* infections, which both induce extensive mucosal ulceration and bloody diarrhoea, as compared with *Salmonella* infection. The most common *Salmonella* species found in the UK, *S. enteridis* and *S. typhimurium,* often produce a much less severe mucosal injury.

Further evidence of the importance of bacterial pathogenicity is the strong relationship between the in-vitro toxicity of the infecting organism and development of PI-IBS (Thornley et al, 2001). Thus, Thornley et al (2001) found that the RR for developing PI-IBS in people infected with *Campylobacter* spp. that produced the most severe effect on cultured cells in vitro was 12.8 (95% CI=1.6–101).

LOCAL MUCOSAL RESPONSE

Few studies have examined the acute injury in patients with PI-IBS, but 2 weeks after infection

there is no polymorph infiltrate and the mucosa looks relatively normal (Spiller et al, 2000). However, quantitative histology shows evidence of continuing inflammation, with elevated T-lymphocytes and increased serotonin-containing entero-endocrine cells (Spiller et al, 2000; *Figure 1)*. These changes gradually resolve over the next 3 months, but still remain abnormal in some individuals even at 1 year. Strikingly, those patients attending the clinic with a history of PI-IBS showed markedly elevated serotonin-containing entero-endocrine cells as well as modest elevations of mucosal T-lymphocytes, even though their initial illness was some years previously (*Figure 2*).

This evidence of ongoing local inflammatory changes is mirrored by abnormal gut permeability (Spiller et al, 2000). The significance of entero-endocrine cell hyperplasia lies in the fact that these cells act as transducers of luminal stimuli, converting them via the release of serotonin to neural discharge. Locally, the release of serotonin stimulates enteric secretions, both intestinal and pancreatic. In addition, it activates visceral afferents and is responsible for nausea and altered gastric emptying. Finally, it acts through 5-HT_3 and 5-HT_4 receptors to mediate peristalsis, and when given intravenously to normal volunteers induces diarrhoea. Whether the increased entero-endocrine cell numbers are responsible for persisting symptoms in PI-IBS or whether they are just a marker of previous infection remains uncertain.

BILE SALT MALABSORPTION

Enteric infection with organisms such as *Salmonella* and *Campylobacter* produce an acute terminal ileitis, which may be associated with bile salt malabsorption. Sudden onset of severe, idiopathic bile salt malabsorption (retention of bile acids of <5%) may well be the result of an infection. Such patients respond well to cholestyramine, suggesting that bile salt colonic irritation is the main driver of the diarrhoea (Niaz et al, 1997).

TREATMENT OF PI-IBS

Dietary measures

Patients with urgency and loose stools should obviously avoid dietary laxatives, particularly bran, green vegetables and fruits high in unabsorbable sugars (e.g. plums, prunes) (Parker et al, 1995). Mucosal injury reduces brush-border enzymes, of which lactase is present in least quantities in the adult mucosa. Transient hypolactasia and milk intolerance is therefore not uncommon, but is rarely responsible for PI-IBS. Where doubt exists, a challenge with a quantity of skimmed milk or a lactose hydrogen breath test should help.

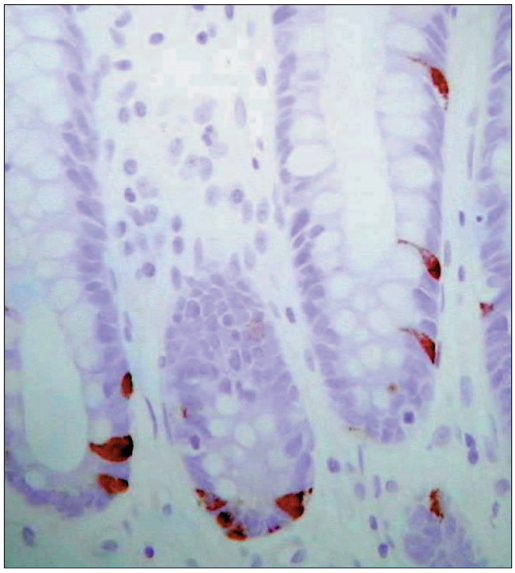


Figure 1. Entero-endocrine cells stained for serotonin lying at the base of mucosal crypts in a rectal biopsy from a patient with post-infective irritable bowel syndrome. Note the prolongation of the cell body to allow microvilli to sample the lumen. These cells respond to pressure, nutrients and bacterial toxins by releasing serotonin into the lamina propria where it activates submucosal nerves, initiating peristalsis and secretion.

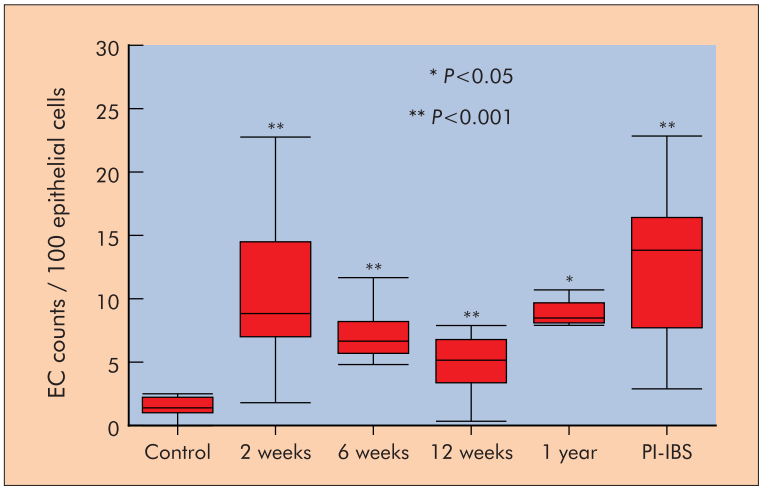
Loperamide

Loperamide is a peripherally acting μ-receptor agonist, especially effective in improving stool consistency, but slightly less effective in controlling pain in patients with IBS (Lavo et al, 1987). Loperamide should be given as 2 mg after each loose stool, up to a maximum of 12 mg daily. However, although this may cure the diarrhoea, some patients develop unacceptable bloating and discomfort, and may therefore abandon treatment.

Tricyclic antidepressants

When anxiety is prominent, tricyclic antidepressants have multiple benefits provided that low doses are used (10–20 mg, three times a day), as patients with IBS are often intolerant of drug side effects generally. The antimuscarinic and antisero-

Figure 2. Increased entero-endocrine cell (EC) counts 2, 6 and 12 weeks following Campylobacter infection. A small number of patients with persisting symptoms came back at 1 year and still had elevated levels, as did eight individuals with post-infective irritable bowel syndrome (PI-IBS) attending the outpatient clinic. From Spiller et al (2000).



tonergic effects reduce diarrhoea, while antihistaminic effects provide sedation, which is useful for insomnia if given last thing at night. Tricyclic antidepressants also reduce pain (Myren et al, 1984), probably by enhancing antinociception.

Serotonin antagonists

Given the known increase in serotonin-containing entero-endocrine cells, it would seem logical that there may be excess serotonin released locally into the gut mucosa. A pilot study measuring 5-HT_3 in peripheral blood supported this concept (Bearcroft et al, 1998), but more definitive studies are awaited. Certainly, 5-HT_3 antagonists slow colonic transit in patients with D-IBS (Houghton et al, 2000). This translates into improvement in stool consistency and relief of IBS symptoms in D-IBS (Camilleri et al, 1999). Whether patients with PI-IBS are specifically benefited by 5-HT_3 antagonists remains to be proven.

CONCLUSION

Patients who develop symptoms of IBS characterized by diarrhoea, urgency and loose stool following gastrointestinal infection should have other diagnoses excluded before PI-IBS is diagnosed. Once this has been established, they should be reassured that PI-IBS is essentially a benign condition, and that 50% of patients recover within 6 years. Specific therapies are still awaited, but symptomatic treatments are usually quite effective when combined with dietary measures. HM

Figure 2 *is reproduced by kind permission of the BMJ Publishing Group.*

Conflict of interest: Professor Spiller has received educational grants from AstraZeneca Pharmaceuticals and Novartis Pharmaceuticals to study the irritable bowel syndrome and its pathogenesis.

Bearcroft CP, Perrett D, Farthing MJ (1998) Postprandial plasma 5-hydroxytryptamine in diarrhoea-predominant irritable bowel syndrome: a pilot study. *Gut* **42**: 42–6

Camilleri M, Mayer EA, Drossman DA et al (1999) Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5-HT_3 receptor antagonist. *Aliment Pharmacol Ther* **13**: 1149–59

Chaudhary NA, Truelove SC (1962) The irritable colon syndrome. *Q J Med* **123:** 307–22

Drossman DA, McKee DC, Sandler RS et al (1988) Psychosocial factors in the irritable bowel syndrome. A multivariate study of patients and nonpatients with irritable bowel syndrome. *Gastroenterology* **95**: 701–8

KEY POINTS

- Post-infective irritable bowel syndrome is characterized by persistent diarrhoea, urgency, loose stools and abdominal pain following infection.
- Depending on the patient's age and family history, coeliac disease, Crohn's disease, lactose intolerance, microscopic colitis, giardiasis, carcinoma of the colon and diverticular disease should be excluded by appropriate tests.
- Prognosis is benign with 50% recovering within 6 years.
- Symptomatic treatment with loperamide, tricyclic antidepressants and serotonin antagonists my be beneficial.

Drossman DA, Thompson WG, Talley NJ, Funch-Jensen P, Janssens J, Whitehead WE (1990) Identification of subgroups of functional gastrointestinal disorders. *Gastroent Int* **3**: 159–72

Dunlop SP, Jenkins D, Spiller RC (2001) Distinctive clinical and histological features of post-infectious IBS. *Gut* **48**: A44

Gwee KA, Graham JC, McKendrick MW et al (1996) Psychometric scores and persistence of irritable bowel after infectious diarrhoea. *Lancet* **347**: 150–3

Gwee KA, Leong YL, Graham C et al (1999) The role of psychological and biological factors in postinfective gut dysfunction. *Gut* **44**: 400–6

Harvey RF, Mauad EC, Brown AM (1987) Prognosis in the irritable bowel syndrome: a 5-year prospective study. *Lancet* **i**: 963–5

Houghton LA, Foster JM, Whorwell PJ (2000) Alosetron, a 5-HT_3 receptor antagonist, delays colonic transit in patients with irritable bowel syndrome and healthy volunteers. *Aliment Pharmacol Ther* **14**: 775–82

Jones J, Boorman J, Cann P et al (2000) British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome. *Gut* **47**(suppl 2): II1–II19

Koloski NA, Talley NJ, Boyce PM (2001) Predictors of health-care-seeking for irritable bowel syndrome and non-ulcer dyspepsia: a critical review of the literature on symptom and psychosocial factors. *Am J Gastroenterol* **96**: 1340–9

Lavo B, Stenstam M, Nielsen A-L (1987) Loperamide in treatment of irritable bowel syndrome — a double-blind, placebo-controlled study. *Scand J Gastroenterol* **22**(suppl): 77–80

Longstreth GF, Hawkey CJ, Ham J et al (2000) Demographic and clinical characteristics of patients with irritable bowel syndrome from three practice settings. *Gastroenterology* **118**: A146

Myren J, Lovland B, Larssen S-E, Larsen S (1984) A double-blind study of the effect of trimipramine in patients with the irritable bowel syndrome. *Scand J Gastroenterol* **19**: 835–43

Neal KR, Hebden J, Spiller R (1997) Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. *BMJ* **314**: 779–82

Neal KR, Barker L, Spiller RC (2002) Prognosis in post-infective irritable bowel syndrome: a six-year follow-up study. *Gut* **51**: 410–13

Niaz SK, Sandrasegaran K, Renny FH, Jones BJ (1997) Postinfective diarrhoea and bile acid malabsorption. *J Roy Coll Phys Lond* **31**: 53–6

Parker TJ, Naylor SJ, Riordan AM, Hunter JO (1995) Management of patients with food intolerance in irritable bowel syndrome: the development and use of an exclusion diet. *J Hum Nutr Diet* **8**: 159–66

Parry SD, Barton R, Welfare MR (2001) Prevalence of pre-existing functional gastrointestinal disorders in infectious diarrhoea subjects compared to a matched community control group. *Gastroenterology* **120**: A–633

Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL (1998) Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. *Dig Dis Sci* **43**: 400–11

Ragnarsson G, Bodemar G (1999) Division of the irritable bowel syndrome into subgroups on the basis of daily recorded symptoms in two outpatients samples. *Scand J Gastroenterol* **34**: 993–1000

Rodriguez LA, Ruigomez A (1999) Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study. *BMJ* **318**: 565–6

Spiller RC, Jenkins D, Thornley JP et al (2000) Increased rectal mucosal enteroendocrine cells, T lymphocytes and increased gut permeability following acute *Campylobacter* enteritis and in post-dysenteric irritable bowel syndrome. *Gut* **47**: 804–11

Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA (1999) Functional bowel disorders and functional abdominal pain. *Gut* **45**(suppl 2): II43–II47

Thompson WG, Heaton KW, Smyth GT, Smyth C (2000) Irritable bowel syndrome in general practice: prevalence, characteristics and referral. *Gut* **46**: 78–82

Thornley JP, Jenkins D, Neal K, Wright T, Brough J, Spiller RC (2001) Relationship of *Campylobacter* toxigenicity in vitro to the development of post-infectious irritable bowel syndrome. *J Infect Dis* **184**: 606–9

Vanner SJ, Depew WT, Paterson WG et al (1999) Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome. *Am J Gastroenterol* **94**: 2912–17