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# Infection, inflammation, and the irritable bowel syndrome

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ABSTRACT

Gastrointestinal infection is ubiquitous worldwide though the pattern of infection varies widely. Poor hygiene and lack of piped water is associated with a high incidence of childhood infection, both viral and bacterial. However in developed countries bacterial infection is commoner in young adults. Studies of bacterial infections in developed countries suggest 75% of adults fully recover, however around 25% have long lasting changes in bowel habit and a smaller number develop the irritable bowel syndrome (IBS). Whether the incidence is similar in developing countries is unknown. Post-infective IBS (PI-IBS) shares many features with unselected IBS but by having a defined onset allows better definition of risk factors. These are in order of importance: severity of initial illness, smoking, female gender and adverse psychological factors. Symptoms may last many years for reasons which are unclear. They are likely to include genetic factors controlling the immune response, alterations in serotonin signaling, low grade mucosal inflammation maintained by psychological stressors and alterations in gut microbiota. As yet there are no proven specific treatments, though $5HT_3$ receptor antagonists, anti-inflammatory agents and probiotics are all logical treatments which should be examined in large well-designed randomised placebo controlled trials.



## 1. Introduction

Infectious diarrhea is one of the commonest afflictions of mankind. Worldwide most of the burden, about 1 billion cases a year, is seen in children <5 years old [1], the vast majority in the developing world in communities where access to clean water and adequate sanitation is restricted. Here a child can expect to have 6–7 episodes per year compared to 1–2 in the developed world [2]. Following recovery from an episode of gastroenteritis (GE) the vast majority of healthy adults and children develop some degree of immunity to the organism responsible and return to normal functioning. However 7–31% develop post-infectious irritable bowel syndrome (PI-IBS). The proportion of unselected IBS that is post-infectious varies from 6 to 17% in the USA and Europe [3] but whether this differs in the developing world is unknown, though previous enteric infection is a known risk factor for IBS in Southern China [4].

This review will compare the epidemiology of infectious diarrhea in the developing and developed world and the link between mucosal inflammation and the development of IBS symptoms. The available evidence suggests that the acquisition of immunity in early childhood reduces the severity of subsequent gastroenteritis in adulthood. Since these are known risk factor for developing PI-IBS we hypothesize that this may underlie some of the regional differences in the incidence of both infection and IBS.

## 2. Epidemiology of IBS worldwide

There are three key questions. Firstly is the incidence of IBS less in the developing world, secondly is the incidence increasing with the adoption of a western urban life style and finally is the disease itself different? The answer to all three is probably yes though interpretation of cross-cultural surveys is fraught with problems relating to the imprecise translation of questions into different cultures. Initial reports from small uncontrolled studies suggested that IBS was very uncommon and predominantly affected a subpopulation who pursued a "western life style" [5]. More recent and robust work gives a range of values for prevalence from very low in Iran and India with just 5.8 and 4.2% respectively [6,7], to values in developed Asian countries that are generally lower but not dissimilar to those seen in the west [4,8,9]. The key factors associated with rapid westernization that underlie this increase in numbers is unclear but could include the effect of improved hygiene, increased overcrowding, stress and changes in diet. The best evidence comes from studies in which the same populations have been studied over a number of years as has been done in Singapore where after a decade of steady industrial growth the prevalence of IBS has risen from 2.3% [10] to 8.6% [8]. While female preponderance is the norm

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the recent Indian Society of Gastroenterology Task Force Survey of IBS reported a male/female ratio of 3/2 even in patients who had not sought medical help, thus controlling for the increased use of medical services by men [7]. This may reflect an overlap with dyspepsia with its male predominance since over half the Indian IBS patients reported epigastric pain, while the overlap with dyspepsia in the USA is only approximately 1/3 [11].

Finally there is a most important fourth question, why should these differences occur? It is clear that major differences in the epidemiology of gut infection exist between the west and the developing world. This is illustrated by *Campylobacter jejuni* enteritis, which causes a shorter, less severe illness in childhood than in adulthood, which is when most Europeans and North Americans are infected. The greater degree of inflammation which adults experience may increase the risk of developing subsequent PI-IBS which might partly account for the higher prevalence of IBS in the westernized nations.

## 3. Infectious diarrhea

Worldwide the average number of episodes of infection annually per person is 3 [1]. A poorly nourished child living in cramped conditions without access to sewerage and running water will have 8 or more infections in the first year of life, most frequently with enteric bacteria and parasites [12] whereas a child in better sanitary conditions would have less infections and these would be more likely to be viral in origin. Even in England an estimated 1 in 5 people per year have an episode of diarrhea in the community adding up to 9.4 million cases in total a year, largely unreported since only 1 in 30 present to their doctor [13]. It seems here that viral infections predominate in the very young, with bacterial infection particularly *Campylobacter* spp. being most common in adolescence and early adulthood. PCR analysis of stool in the same study showed that Norovirus and Rotavirus were the commonest pathogens detected across all age groups. *Campylobacter* spp. were most commonly found in age group 30–39 (16% compared to 6.7% of those aged 1–4) [14].

Early studies of *Campylobacter* spp. enteritis in the UK described a double peak in incidence, the first in early childhood between ages 1–4 years and the second peak aged 15–24 [15]. By contrast in developing countries, infections occurs earlier in life with *Campylobacter* spp. the most commonly isolated bacterial pathogen from children [16] under the age of 2, with a rapidly falling incidence of symptomatic infection as immunity is acquired so that the disease is unimportant in the adult population [17].

## 4. Mechanisms of diarrhea

Infectious diarrhea results from either an increase in fluid and electrolyte secretion, predominantly in the small intestine, or a decrease in absorption which can involve both the small and large bowel. During a diarrheal illness these two mechanisms frequently co-exist. Enterotoxins from *Vibrio cholerae* or enterotoxigenic *E. coli* induce profuse secretion while decreased intestinal absorption can be induced by mucosal injury caused by enteroinvasive organisms (e.g., *Salmonella*, *Shigella*, and *Yersinia* spp.). These invasive infections injure cells and excite an immune response and activate enteric nerves and mast cells resulting in an acute inflammatory infiltrate with the release of pro-inflammatory mediators and stimulation of secretion. Clinically the patient will have an acutely inflamed mucosa with ulceration and bleeding.

Viral infection on the other hand most often results in short-lived watery diarrhea associated with remarkably little tissue damage. Norovirus infection causes increased enterocyte turnover and apoptosis leading to a 50% reduction of villous surface area, weakening of tight junction, increased permeability, all associated with an increase in intraepithelial lymphocytes but not polymorphs [18].

As will be discussed later, the development of post-infective functional gut disorders depends on the extent and distribution of inflammation, duration and timing of infection (be it childhood, as a young adulthood or in older age) as well as psychological and immunological factors. The relative importance of these factors is most easily described by looking in detail at a single agent. *C. jejuni* which is ubiquitous worldwide and has been the subject of frequently studies.

## 5. *Campylobacter jejuni*

This organism produces a range of toxins including cytolethal distending toxin [19], that first produces a secretory diarrhea in the small intestine in the early part of the illness after which there is invasion of the distal ileum and colon to produce an inflammatory ileocolitis, which can extend all the way to the rectum [20].

The disease is less severe in developing countries than in developed countries, with watery stool, fever, abdominal pain, vomiting and dehydration predominating as opposed to the severe abdominal pain, weight loss, fever and bloody stool that is seen more frequently in infections in the west [16]. Infants usually have milder disease with less fever and pain [21], which in some cases is due to immunity acquired during previous infection. The reasons for these differences between the developed and developing world are unclear. The organisms do not appear to be less virulent since travellers from Europe who acquire infection abroad have just as severe symptoms as those acquired at home [22]. The duration of diarrhea is greater in the developed world with more prolonged excretion of bacteria compared to developing world [23]. *C jejuni* infections in Sweden were in general only with a single serotype and were always symptomatic with re-infection being rare whereas in Mexico infections were frequently with mixed serotypes, and re-infection with new serotypes often resulted in no symptoms suggesting the development of immunity [24] which may also prevent bloody diarrhea [25].

## 6. Disturbances of gut microbiota in IBS

The composition of the resident intestinal microbiota is highly variable between individuals but relatively stable for each individual [26], though IBS patients show a more unstable microbiota. This instability may be due to antibiotic therapy [27] or alterations in diet, both of which are commoner in IBS. Patients given antibiotics are 4 times more likely than untreated controls to report bowel symptoms 4 months later [28], and antibiotic use is a risk factor for developing IBS with an adjusted OR of 3.70 (1.80–7.60) [29]. Antibiotic use increases the incidence of post-infective functional diseases following both *Salmonella enteritidis* [30,31] and travellers' diarrhea, in whom antibiotic treatment gave a relative risk of developing PI-IBS of 4.1 (1.1–15.3) compared with those not receiving treatment [32].

During acute infectious diarrhea there is a decrease in anaerobes [33,34]. Mice infected with *Citrobacter rodentium* or *C. jejuni* or subjected to a chemically induced colitis show significant reduction in the total numbers of microbiota, which is mainly due to activation of the host immune response and only to a much lesser degree by bacterial factors [35]. This loss of anaerobes is associated with a depletion in short chain fatty acids and an increase in the pH of the stool allowing overgrowth of other organisms which may contribute to disturbed bowel function.