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MECHANISMS OF GASTROINTESTINAL, PANCREATIC AND LIVER DISEASE

Bugs and irritable bowel syndrome: The good, the bad and the ugly

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Abstract

Recently, there has been strong interest in the therapeutic potential of probiotics for irritable bowel syndrome (IBS). At the same time, there is a rapidly growing body of evidence to support an etiological role for gastrointestinal infection and the associated immune activation in the development of post-infectious IBS. In a more controversial area, small intestinal bacterial overgrowth has been associated with a subset of patients with IBS; the issue of whether it is appropriate to treat a subset of IBS patients with antibiotics and probiotics is currently a matter for debate. Thus, it appears that the gastrointestinal microbial flora may exert beneficial effects for symptoms of IBS under some circumstances, while in other situations gut microbes could give rise to symptoms of IBS. How do we make sense of the apparently diverse roles that 'bugs' may play in IBS? To address this question, we have conducted an in-depth review, attempting where possible to draw lessons from Asian studies.

Introduction

The gut contains a vast and complex microbial ecosystem, comprising mainly bacteria, of which most are strict anaerobes; it also includes fungi and viruses.[1,2] The human gastrointestinal (GI) tract contains more than 500–1000 species of bacteria.[3] The bacterial population increases in number and diversity in the more distal parts of the gut; human large intestine contains as many as 10^{11-12} organisms per gram of fecal material.[4] Recently, there has been increased interest in the role of qualitative and quantitative changes in gut flora in health and in GI diseases. Irritable bowel syndrome (IBS), a common gastrointestinal disorder of unknown pathogenesis, is one such condition which might be related to changes in the gut flora.

Recent published reports on post-infectious IBS (PI-IBS),[5] small intestinal bacterial overgrowth (SIBO) in IBS,[6] relationships between the gut flora and sensorimotor functions of the GI tract,[3] and the role of probiotics[7,8] and antibiotics[9] in altering the symptoms of IBS provide evidence supporting this issue. Food hygiene, the nature and frequency of GI infections and infestations and the composition of the gut flora are expected to differ in some Asian countries compared with North America, Europe and Australia/New Zealand. Hence, we sought to review the relationship between gut flora, GI infections and IBS, with particular attention to the Asian published reports.

Gut flora and IBS

The intestinal microflora may influence the structure (including maturation of blood vessels), physiology, biochemistry, immunology, and gene expression of the host; these effects may contribute to the development and maintenance of gut digestive and defensive functions.[3] Evidence to confirm the role of altered gut flora in IBS has been scanty to date. However, there are reasons to believe that quantitative and qualitative changes in gut flora may contribute to this disorder. The evidence supporting this proposal is as follows: (i) the intestinal microflora of patients with IBS differs from that of healthy subjects;[10–12] (ii) colonic gas production, which is related to bacterial fermentation of unabsorbed food substances, is greater in patients with IBS than healthy subjects;[10,13] (iii) small intestinal bacterial overgrowth (SIBO) has been reported in some patients with IBS;[14] (iv) symptoms of SIBO closely resemble those of IBS;[15] (v) recently, methane produced by *Methanobrevibacter smithii*, has been shown to be associated with constipation;[16] methane reduces gastrointestinal motility[17] and post-prandial serotonin;[18] (vi) IBS can develop following acute gastrointestinal infection, a condition known as post-infectious IBS (PI-IBS);[19] and (vii) therapeutic manipulation of gut flora, either with antibiotics[9] or probiotics,[7,8] improves symptoms of IBS.

Intestinal microflora in patients with IBS may differ from that in healthy subjects. In a study on 20 patients with IBS, Balsari *et al*. showed that there was considerable homogeneity in the fecal flora, and that there was a decrease of Coliforms, Lactobacilli, and Bifidobacteria in patients compared with healthy individuals.[10] Lactobacilli are less gas producing than some other bacteria, such as Clostridia and Enterobacteriaceae.[11] Patients with IBS also have greater colonic gas production, particularly of hydrogen, than do controls.[13] Administration and colonization of the gut with Lactobacilli of patients with IBS has been associated with reduced

gas-related symptoms.[20] This might be related to inhibition of colonization and enterocyte adherence of pathogenic bacteria due to increased secretion of defensins, decreased interleukin (IL)-8, and abrogation of nuclear factor kB activation.[8]

Post-infectious IBS

As early as 1962, Chaudhary and Truelove first reported that 25% of IBS patients date the onset of their IBS to an episode of bacillary or amoebic dysentery.[21] In a study by Gwee *et al*. 20 of 75 (27%) patients with acute gastroenteritis had persistent symptoms of IBS even 6 months after the episode of diarrheal disease.[22] Subsequently, many other studies have reported that between 6 and 17% of patients with IBS, symptoms began after an acute infective gastroenteritis.[23]

Post-infectious IBS has been defined as the acute onset of new IBS symptoms (by Rome criteria for IBS) in an individual who has not previously met the Rome criteria, following an acute illness characterized by two or more of the following: fever, vomiting, diarrhea, or a positive bacterial stool culture.[24] Several studies on PI-IBS were initially reported from the UK,[22,25–27] and, subsequently, studies from USA and Canada have reported development of PI-IBS after bacterial and viral infection.[28,29] However, there are scanty data on PI-IBS in Asia, where gastrointestinal infection is more common than in developed countries.

Table 1 summarizes the studies on PI-IBS from Asia. In several studies from China, a history of dysentery was reported to be a significant independent risk factor (Beijing odds ratio [OR] 3.0, Guangzhou OR 1.63).[30,31] In a prospective cohort study in a major Beijing hospital on 293 patients who recovered from bacillary dysentery and 243 controls, IBS diagnosed using Rome II criteria developed in 8.1% patients with dysentery, as compared with 0.8% of controls.[32] As with the non-Asian studies, a longer duration of diarrhea (> 7 days) was associated with a higher risk. However, unlike the studies from the UK, where 77% of women developed IBS compared with only 36% of men, similar risks were observed for men and women in China.[22,32] The authors showed that both the immune and nervous system may play important roles in the pathogenesis of PI-IBS.[32]

Korea is the only other Asian country that has reported the development of PI-IBS. In December 2001, 181 healthcare workers in a major hospital were involved in an outbreak of Shigella dysentery.[19] One-hundred and one patients with bacillary dysentery and 102 controls were interviewed during follow-up at 3, 6, and 12-months. Fifteen patients and six controls developed IBS.[19] In this study, the OR of developing IBS was 2.9 at 12 months; similar to that of the Beijing study; the length of diarrhea during the acute illness was an independent risk factor, and the risk of developing post-infectious IBS was the same for men as for women.[19] The comparable gender frequency of occurrence of PI-IBS in both the Asian studies contrasts to that of Western studies in which women were more often affected. However, this is in accordance with epidemiology of IBS from Asian countries where female preponderance of IBS is not observed, in contrast to that in other developed countries.[33]

A long-term follow-up study from the Korean group showed that about half of PI-IBS and previous IBS patients with or without infection recovered over 5 years. Previous IBS and functional bowel disorders are risk factors of PI-IBS after 5 years.[34] In another study from Korea, routine colonoscopy was carried out as part of a general health screening.[35] Random colonic biopsies taken from 42 patients with IBS diagnosed using Rome II criteria revealed significantly more non-specific inflammatory findings (mucosal hyperplasia, lymphocyte aggregation and eosinophilia) than those taken from asymptomatic subjects. Similar colonic and small intestinal mucosal changes have been reported from India but have been termed 'tropical enteropathy'.[36]

Special issues in diagnosis of post-infectious IBS in Asia

Long ago, an entity in which malabsorption syndrome developed following acute gastroenteritis, also called 'epidemic tropical sprue' or 'post-infective tropical malabsorption' was described from southern India.[37–39] Epidemics of this condition were also reported in soldiers and prisoners of war in the Indo-Burma region during the Second World War,[40] in American military personnel serving in the Philippines,[41] and in Bangladesh.[42] This condition was also reported from temperate countries where it was named 'temperate sprue'.[43] Tropical sprue is often accompanied by colonization and overgrowth of bacteria in the small bowel,[44,45] as has been recently reported in association with IBS.[14,46]

Tropical sprue is characterized by prolonged diarrhea; similarly, PI-IBS is usually diarrhea-predominant type.[24] Diarrhea-predominant disease is more often associated with SIBO than other type of IBS.[47] Patients with tropical sprue had abnormal excretion of urinary D-xylose and steatorrhea.[44] Would one diagnose this condition as PI-IBS if it occurs today, particularly if malabsorption of nutrients is not carefully excluded by appropriate investigations?

Recently, there have been increasing numbers of published reports of PI-IBS in association with decreasing numbers of publications about post-infective malabsorption syndromes. In most studies on PI-IBS, post-infective malabsorption syndrome has not

Table 1 Studies on post-infectious irritable bowel syndrome (IBS) in Asia

Country	No. patients	No. controls	No. infection	Frequency of IBS development among patients	Frequency of IBS development among controls	Follow-up	Reference
China	295	243	Shigellosis	8.1%	0.8%	1–2 years	32
Korea	101	102	Shigellosis	14.9%	5.9%	1 year	19
Korea	53	49	Shigellosis	20.8%	12.2%	5 years	34

Table 2 Studies on small intestinal bacterial overgrowth in irritable bowel syndrome (IBS) and controls in Asia

Country	No. patients	No. controls	Method of diagnosis of SIBO	Percentage of SIBO in IBS	Percentage of SIBO in controls	Reference
Korea	39	49	Lactulose HBT†	49%	26.5%	54
India	225	100	GHBT	11%	1%	14
India	69	–	GHBT	13%	–	46
India	148	40	GHBT	7.4%	0%	47

†Criteria for diagnosis of small intestinal bacterial overgrowth (SIBO) by lactulose hydrogen breath test (HBT): either double peak or a peak of > 20 parts per million hydrogen above basal within 90 min of lactulose ingestion. Thirteen patients with IBS and 20 controls also underwent glucose hydrogen breath test (GHBT). Frequency of positive GHBT in patients with IBS (7%) and controls (20%) was not significantly different statistically.

been carefully excluded using tests for mucosal malabsorption like D-xylose or fecal fat estimation. Seven to 31% of people experiencing an attack of acute gastroenteritis develop PI-IBS;[48] while the attack rate of tropical sprue among soldiers in the tropical countries was rather similar at 8–10%.[42] Abnormal small intestinal permeability, which is also a feature of malabsorption syndrome including tropical sprue,[49] has been described in patients with PI-IBS.[50] Since IBS is a symptom-based diagnosis, a patient with mild malabsorption syndrome can easily be diagnosed as IBS, particularly of diarrhea-predominant type, unless malabsorption is carefully excluded by appropriate investigations. Recent reports of celiac disease and SIBO misdiagnosed and reported as IBS support this contention.[15,51–53]

Small intestinal bacterial overgrowth in IBS

Recent studies have suggested that a proportion of patients with IBS could have SIBO.[14,46,54] This is not unexpected as symptoms of IBS and symptoms of SIBO are the same.[15] Hence, patients with SIBO would be expected conform to the diagnosis of IBS because the latter is established by symptom-based criteria.

Initial studies on SIBO in IBS from the USA by Pimentel *et al.* reported that as many as 78% of 202 patients with IBS diagnosed using Rome I criteria, had SIBO using a lactulose hydrogen breath test (lactulose HBT).[55] Eradication of the overgrowth by open label antibiotic treatment resolved symptoms to the extent of Rome I criteria turning negative in 48% of patients.[55] Such a high frequency of SIBO, however, has not been reproduced in subsequent studies, including those from Asia.[14,46,54] The unusually high frequency of SIBO in the initial studies might be related to the criteria used to diagnose SIBO.[55] In the earlier studies, rise in breath hydrogen 20 parts per million (PPM) above basal levels within 90 min after ingestion of lactulose was considered diagnostic of SIBO.[55] This criterion has not been validated. Moreover, it presumes that mouth-to-cecum transit time is always greater than 90 min, so that a peak in breath hydrogen within 90 min after lactulose ingestion must be due to bacterial fermentation in the small bowel. However, such a presumption may not be correct. Mouth-to-cecum transit time in Asian populations is often shorter than 90 min. For example, median mouth-to-cecum transit time in 12 healthy Indian subjects was 65 min (range 40–110 min).[44] In a study of 45 healthy Taiwanese, mean mouth-to-cecum transit time was 85 min (SD 37).[56] Therefore, a large proportion of these healthy subjects would have been diagnosed having SIBO if the lactulose HBT criterion had been used. Conventionally, diagnosis of SIBO by lactulose HBT is based on the occurrence of two peaks in lactulose HBT.[57] However, using such criteria, sensitivity of lactulose HBT for diagnosis of SIBO is 31%, while specificity is 86%.[57] It is concluded that lactulose HBT may not be appropriate for the diagnosis of SIBO, at least in Asia.

In some studies, glucose hydrogen breath test (GHBT) has been used for diagnosis of SIBO. In one study, sensitivity and specificity were 44% and 80%, respectively.[57] However, in that study, methane was not estimated, resulting in low sensitivity of the test. Since 14–35% of the population harbor methanogenic flora in their gut,[58] estimation of methane is expected to increase the sensitivity of the test to detect SIBO. In a study from India, nine of 69 (13%) patients had SIBO using GHBT without estimation of methane.[46] In another study, 25 of 225 (11%) patients with IBS had SIBO using GHBT as compared with 1/100 controls.[14] Considering the fact that GHBT has a sensitivity of 44% only, both these studies could have underestimated the frequency of SIBO. In a study from Korea on 39 patients with IBS and 49 healthy controls, frequency of SIBO using lactulose HBT (SIBO diagnosed by an early peak within 90-min or a double peak) 49% versus 26%, respectively; the frequency using GHBT among IBS and controls was comparable.[54]

Table 2 summarizes the studies on SIBO in patients with IBS from Asia. Most used GHBT and found a frequency of SIBO among patients with IBS to be consistently around 10%; in contrast, SIBO was absent in most controls. A common observation by Indian clinicians has been that response of patients with IBS to metronidazole, recently documented scientifically,[59,60] might be related to treatment of SIBO rather than any effect on suspected chronic amoebiasis.[61] What is now needed are studies addressing the pathogenesis of SIBO that is found in a proportion of patients with IBS, clinical parameters that predict its occurrence and efficacy of treatment of SIBO in relieving symptoms or curing IBS.

We believe that the Western criteria of the peak in breath hydrogen value of 20 ppm above basal within 90 min of ingestion of lactulose during lactulose HBT for diagnosis of SIBO in Asia is inappropriate; available data from the region show that mouth-to-cecum transit time is often shorter than 90-min. Glucose hydrogen breath test with estimation of methane may be used instead. Post-infective malabsorption syndrome should be excluded by appropriate investigations before a diagnosis of PI-IBS is made, because symptom-based criteria may be fallacious in such situations. Particular attention should be given to diagnose malabsorption syndrome and SIBO in patients with diarrhea-predominant IBS in Asia.

Parasites and IBS

Studies from non-Asian countries showed that *Giardia lamblia* infection could lead to development of functional bowel disease, including IBS.[62] In a study from Norway, structured interview and questionnaires given 12–30 months after the onset of Giardia infection revealed that 66 of 82 (81%) patients had symptoms of IBS according to Rome II criteria.[62] Diarrhea-predominant IBS was the commonest subtype (47%).[62] A few other studies from non-Asian countries showed similar findings.[63–65] In a study from Thailand, however, the frequency of detection of parasites among 59 patients with IBS diagnosed by Rome II criteria was comparable with the frequency among the control group.[66] However, this study had a case-control design with a small sample size, which might have resulted in type II statistical error. In general, persistent infection with Giardia is expected to cause chronic diarrhea, irregular bowel movement and abdominal discomfort, which may be diagnosed as IBS by a symptom-based criterion. However, there are scanty data from Asian countries where this infection is expected to be more common. For example, a study on 78 members from 15 families from rural India revealed that all except two (97%) shed parasites in the stool as detected by microscopy on alternate days for one month, and 42 (54%) showed Giardia.[67] Hence, more studies evaluating the role of *Giardia lamblia* in Asia are needed.

Association of Giardia infection and IBS would be of importance even in non-Asian countries due to the high frequency of giardiasis (5.3 of 100 000) in travelers returning from endemic areas.[68] Highest frequencies have been noted among travelers returning from the Indian Subcontinent (628 of 100 000), East Africa (358 of 100 000), and West Africa (169 of 100 000).[68] In a study including 328 travelers and foreign residents in Nepal, protozoal parasites were found quite commonly (Giardia in 12%, Cryptosporidium and *Entamoeba histolytica* each in 5%, *Blastocystis hominis* in 33% and mixed infestations in 17%).[69] Since as high as 80% of patients contracting Giardia infection may develop chronicity and symptoms of IBS,[62] the role of travel-acquired infection with Giardia may be of major importance.

Initial studies suggested that *E. histolytica* may also play a role in IBS.[21] However, two Indian studies have contradicted this hypothesis.[61,70] In one study, there were comparable frequencies of *E. histolytica* among 144 patients with symptoms of IBS and 100 symptom-free controls, whether detected in stool (18% *vs.* 18%), serological evidence of infection (42% *vs.* 41%), colonoscopic (7% *vs.* 3%) or histological abnormalities (49% *vs.* 30%).[70] In another study of 154 inmates of a leprosy rehabilitation home, 22 (14%) had IBS. Amoeba was detected more frequently among subjects with IBS than those without it (50% *vs.* 16%). Amoebae were characterized by polyacrylamide gel electrophoresis for hexokinase isoenzyme in four patients with IBS; all of these amoebae showed a slow moving band suggesting the non-pathogenic nature of the protozoa. During one year follow-up, spontaneous disappearance of amoebic cysts in the stool was not associated with a reduction in IBS symptoms.[61] Both of these studies suggested that amoeba carriage had no relationship with IBS. The discordance between older and the more recent studies might be related to the fact that whereas older studies recruited patients with invasive amoebic dysentery, the more recent Indian studies recruited chronic carriers of amoebic cysts. Since the former patients developed colonic amoebic ulcers, they might develop protracted inflammation more commonly than the latter patients. Also, patients with invasive disease are infected with pathogenic strains of amoeba as compared with chronic carriers, who usually harbor non-pathogenic strains.

Blastocystis hominis, a common intestinal parasite, has also been studied in patients with IBS. In a study from Pakistan, *Blastocystis hominis* was more commonly detected among 95 patients with IBS (32% and 46% by stool microscopy and culture, respectively) than 55 controls (7% both by microscopy and culture).[71] In another study from Pakistan, serological evidence of past infection (immunoglobulin G [IgG] antibody against *Blastocystis hominis*), was higher in stool culture-positive as well as culture-negative IBS than controls.[72] Another finding, the significance of which is yet to be determined, was that IgG2 subclass antibodies were significantly increased in IBS patients compared with asymptomatic controls.

In a study from Turkey, among 69 patients infected with Blastocystis, diarrhea was common in men, whereas dyspepsia was common among women.[73] In a study from Thailand, however, the frequency of parasites, including *Blastocystis hominis*, was not different among 59 patients with IBS (diagnosed using Rome II criteria) as compared with controls.[66] However, such apparently diverse literature can be explained, at least partly, by knowledge of the biology of Blastocystis. In a study using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) of the entire small-subunit rRNA (ssrRNA) revealed significant genetic variation of Blastocystis among 30 randomly selected human isolates.[74,75] These PCR-RFLP profiles (riboprints) could be grouped into seven distinct genotypes (ribodemes).[74,75] It is important to note that while some of these genotypes are potentially pathogenic, others are not.[76] In general, most studies suggest that subtype 1 is associated with disease, while subtypes 2 and 3 may be non-pathogenic.[76] However, morphologically these genotypes look quite similar.[76] Furthermore, the density of the infective organism and presence of mixed infections with different subtypes and even with other protozoa may influence the clinical outcome.[76] It follows that the contradictory findings in different studies based on isolation of Blastocystis by stool microscopy might be related to variation in pathogenic potential of the individual protozoan parasites present.

The impact of intestinal helminthic infestation on IBS is another interesting issue that has not been addressed in the published reports. Intestinal helminthes shift the immune system towards a Th2 response, which may be associated with reduced chance of protracted GI inflammation.[77,78] Low grade inflammation has been proposed as a putative pathogenic mechanism in recent models of IBS.[79,80] Hence, a high frequency of helminthic infestation[67] may explain the low frequency of IBS in tropical countries, such as India, Bangladesh and Thailand,[33] despite a high frequency of bacterial GI infections. For example, 48 of 78 (62%) subjects from rural India had hookworm infestation.[67] Despite a high frequency of bacterial GI infection, the frequency of IBS in Indian populations is 4.2%.[59] In contrast, 2% of 533 refugees from Santa Clara County, California had hookworm infestation.[81] Despite a low frequency of bacterial gastrointestinal infection, the frequency of IBS in US populations is as high as 20%.[82] Though this might suggest that helminthes can protect against PI-IBS, studies to prove such a hypothesis are not available in published reports.

How could normal or abnormal gut flora affect GI sensorimotor functions?

Gut flora could affect the sensorimotor functions of the gut in three ways: (i) end products of bacterial fermentation and metabolism; (ii) neuroendocrine factors; and (iii) immune mediators.

Bacterial chemotactic peptides, such as formyl–methionyl–leucyl–phenylalanine, stimulate the enteric nervous system and afferent nerves, while endotoxin (lipopolysaccharide) may affect gut motility.[3] Short-chain fatty acids (SCFA), such as butyrate, acetate, and propionate have important roles in gut health and motility and may contribute to pathogenesis of gastrointestinal diseases.[83,84] SCFA are important nutrients to maintain healthy colonocytes.[83] They stimulate absorption of water and electrolytes and thereby prevent diarrhea.[83] Colonic acidification by SCFA may increase its motility.[85] In contrast, motility of proximal gut by SCFA is reduced due to induction of the ileal brake;[84] as a result, reduced proximal gut motility may predispose to SIBO. Bacteria in the small intestine in patients with SIBO produce SCFA and deconjugate bile acids.[86] These may contribute to diarrhea in patients with SIBO.

Bacterial fermentation and production of various gases may contribute to the pathogenesis IBS and its symptoms. A study by Pimentel *et al*. from the USA reported that 12 (39%) of 31 constipation-predominant IBS patients excreted methane, whereas none of 34 diarrhea-predominant patients were methane excreters.[87] This led to a hypothesis that methane gas produced by bacteria may contribute to the development of constipation in patients with IBS.[88] In dogs, luminal methane infusion compared with room air infusion significantly reduced intestinal transit.[17] Exposing tissues to methane also increased the force of contractions in response to mucosal stimulation; the authors therefore suggested that methane predisposes to constipation via promotion of segmental, non-propagating contractions.[17]

In a study in guinea pigs, the amplitude of peristaltic contraction was significantly decreased when hydrogen was infused, whereas it was significantly increased in the methane infusion group.[89] Further, peristaltic velocity was significantly delayed after methane infusion.[89] The area under curve of intra-luminal pressure was also markedly increased after infusion of methane. These results support the concept that methane promotes non-propagating or segmental contractions of the small bowel. This study provides an experimental basis for verifying that there is a significant correlation between methane producers and constipation-predominant IBS.[89] Some authors have hypothesized that methanogenic flora may reduce flatulence; as one molecule of carbon dioxide combines with four molecules of hydrogen to produce one molecule of methane, it may result in reduction of total volume of gas in the gut.[58] In an Indian study, predominant methanogenic flora (fasting methane concentration > 10 ppm) was present in 50/345 (14.5%) patients with IBS diagnosed by Rome II criteria as compared with 88/254 (34.6%) of healthy controls.[58] These studies suggest that the gut flora and the gas produced by it may play a role in the pathogenesis of IBS symptoms, but more studies are needed to resolve this issue.

Neuroendocrine factors are important mechanisms of control of sensorimotor functions by the gut flora. Ileal brake is a physiological phenomenon, in which the presence of fat or products of its digestion such as fatty acids reduces motility of proximal small intestine. Colonic flora produces SCFA, reflux of which into the ileum liberates peptide YY, neurotensin and glucagon-like peptide-1 that inhibits proximal gut motility (ileal brake).[90] SCFA produced by gut flora influences serotonin, motilin and somatostatin containing enteroendocrine cells in the colon and ileum;[91] these are key mediators of gut motility.

Gut flora is also important in normal development of the intestinal immune system and lymphoid tissue.[3] The gut immune system, which includes the cytokine profile, determines the degree and duration of inflammation in response to microbial challenge of the intestine.[92] Since gut inflammation is an important determinant of its sensorimotor functions and development of functional bowel disease, the importance of the immune system in regulating gut sensorimotor function cannot be underestimated.[92]

A study in an animal model illustrated the role of inflammation induced by infection on gut motility, which could have a bearing on development of functional bowel disorders complicating to infection.[93] Authors developed an animal model of persistent gut hypercontractility following acute gastrointestinal infection and studied the mechanisms of persistent hypercontractility. NIH Swiss mice were infected with *Trichinella spiralis*. Jejunal longitudinal muscles from these mice were incubated with or without cytokines. Subsequently, muscle contraction and cytokine mRNA and cytokine expression were examined.[93] During acute infection, IL-4 or IL-13, transforming growth factor (TGF)-β1, and cyclooxygenase (COX)-2 expressions were increased in intestinal smooth muscle. Following infection, Th2 cytokine expression returned to normal, but TGF-β1 expression remained high in the muscle layer. Exposure of muscle cells to IL-4 or IL-13 increased TGF-β1, COX-2 protein, and prostaglandin (PG)E2. Exposure of muscle cells to TGF-β1 increased PGE2 and COX-2 protein. Incubation of tissue with IL-4, IL-13, TGF-β1, or PGE2 increased carbachol-induced muscle contractility. COX-2 inhibitor attenuated TGF-β1-induced hypercontractility of the muscles. The authors suggested that Th2 cytokines induce muscle hypercontractility during infection by a direct action on smooth muscle. The maintenance of hypercontractility results from Th2 cytokine-induced expression of TGF-β1 and the subsequent upregulation of COX-2 and PGE 2 at the level of the smooth muscle cell.

The Good bugs: Review of Asian studies of probiotics in IBS

Probiotics are live microorganisms, which, when administered in adequate amounts, confer a health benefit on the hosts. Several systematic reviews and meta-analyses have examined the effect of probiotics on patients with IBS.[7,94–97] A recent systematic review indicated that *Bifidobacterium infantis* 35624 has shown efficacy for improvement of IBS symptoms.[94] Several other authors have suggested that probiotics are effective in treatment of IBS.[96,97] However, the data available on the use of probiotics in IBS are still contradictory. This may be partly because studies have been carried out using different species, dosages, treatment durations and end-points to evaluate results.

Studies on the use of probiotics to treat IBS in Asia are scanty. In a single-blind follow-up study published from Japan,[68] patients with IBS were randomized to receive probiotics containing *Lactobacillus acidophilus*, *Lactobacillus helveticus*, and

Bifidobacterium or placebo. After 6 weeks of treatment, significant improvements in pain and bloating were reported in the treatment group compared with the control.[98] A study from Korea showed probiotics (*Bacillus subtilis* and *Streptococcus faecium*) were effective in reducing the severity and frequency of abdominal pain compared with placebo in diarrhea-predominant or alternating type of IBS.[99] Another recent Korean study showed composite probiotics containing *Bifidobacterium bifidum* BGN4, *Lactobacillus acidophilus* AD031, and other species were safe and effective in the treatment of patients with IBS.[100] A third Korean study using *Lactobacillus acidophilus* for a small number of patients of IBS also showed potential efficacy.[101] A Chinese study showed that treatment with a probiotic preparation was effective in reducing the symptoms of abdominal pain, bowel movement frequency, urgency and distension in IBS-like patients with chronic diarrhea.[102]

Conclusions

To many physicians, IBS is purely a psychosomatic disorder. The published reports on PI-IBS,[5] SIBO,[6] the relationship between gut flora and GI sensorimotor functions,[3] and the potential for probiotics[7,8] and antibiotics[9] to alter these functions and to improve some of the symptoms of IBS provide strong evidence in support of a major role for the gut flora in the pathogenesis of IBS. In this we see the beginning of a paradigm shift in our understanding of IBS. This is reminiscent of the evolution in our understanding of the pathogenesis of peptic ulcer disease, also once thought to be a psychosomatic disorder[103] before the advent of endoscopic capability and discovery of the *Helicobacter pylori* bacterium by Warren and Marshall, who were awarded the 2005 Nobel Prize in Physiology and Medicine.[104] Asia, the home of two-thirds of the world's population, with its diverse culture, socioeconomic profile, and food hygiene, is a fertile ground to study these exciting developments.

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