

Irritable bowel syndrome; update on pathophysiology and management

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The description of the de novo development of irritable bowel syndrome following an episode of bacterial gastroenteritis (post-infectious irritable bowel syndrome) illustrated the potential for a luminal factor (a bacterial pathogen) to cause this common gastrointestinal ailment. As a consequence of these and other observations, as well as results of experiments involving animal models, the enteric flora and the immune response that it generates in the host have, somewhat surprisingly, come centre-stage in irritable bowel syndrome research, given their potential to induce the pathophysiological changes that are associated with irritable bowel syndrome. While evidence for immune dysfunction both in the mucosa and systemically continues to accumulate, methodological limitations have hampered a full delineation of the nature of the microbiota in irritable bowel syndrome. The latter is eagerly awaited and may yet provide a firm rationale for the use of certain probiotics and antibiotics in irritable bowel syndrome, whose benefits have now been described with some consistency. Despite its prevalence, there is a striking lack of effective therapeutic options for irritable bowel syndrome. While there is reason for optimism in the management of irritable bowel syndrome with several promising new agents currently undergoing clinical trials, confirmation of the efficacy and safety of these agents in wider patient populations is awaited. A clearer understanding of the physiopathologic mechanisms underlying irritable bowel syndrome, as well as of interrelationships between irritable bowel syndrome and other gastrointestinal and non-gastrointestinal disorders, will likely be required before effective drug therapies can be found.

Key words: Irritable bowel syndrome, pathophysiology, management, post-infectious IBS

İrritabl barsak sendromu; patofizyolojisi ve tedavisi hakkında güncelleme

İrritabl barsak sendromunun bakteriyel gastroenterit atağı ertesinde de novo olarak gelişebildiğinin gösterilmesi (post-enfeksiyöz irritabl barsak sendromu) bu sık karşılaşılan kalıcı gastrointestinal bozukluğun nedeni olarak luminal bir faktörün (bakteriyel patojen) potansiyel etken olabileceğini ortaya koymuştur. Bu gözlemlerin ve hayvan modellerini de içeren deneylerin sonucunda, enterik flora ve şaşırtıcı olarak bunun konakta oluşturduğu irritabl barsak sendromu ile ilişkili patofizyolojik değişiklikleri indükleyebilen immün yanıt konusu, irritabl barsak sendromu araştırmalarının merkezine oturmuştur. Mukozal ve sistemik immün disfonksiyon hakkındaki kanıtlar çoğalmaya devam ederken, metodolojik yetersizlikler irritabl barsak sendromunda floranın rolünün tam olarak ortaya konulmasının önünde engel oluşturmaktadır. Bu ikinci noktanın aydınlatılması; irritabl barsak sendromu tedavisinde yararları gösterilmiş olan belirli probiyotiklerin ve antibiyotiklerin kullanımı için gerekçeyi ortaya koyacağı için, merakla beklenmektedir. Sık görülmesinin aksine, irritabl barsak sendromunda etkin tedavi seçenekleri dikkat çekici şekilde azdır. Halen klinik araştırmaları süren birçok yeni ajan irritabl barsak sendromunun tedavisinde umut vadetmekle beraber, bunların geniş hasta gruplarındaki etkinliğinin ve güvenilirliğinin gösterilmesi gerekmektedir. Etkin ilaçların bulunabilmesi için öncelikle, irritabl barsak sendromunun altında yatan patofizyolojik mekanizmaların ve irritabl barsak sendromu ile diğer gastrointestinal ve gastrointestinal sistem dışı bozukluklar arasındaki ilişkinin aydınlatılması gerekmektedir.

Anahtar kelimeler: İrritabl barsak sendromu, patofizyoloji, tedavi, post-enfeksiyöz IBS

The functional gastrointestinal disorders (FGID) are symptom-based disorders that cannot be currently explained by definable structural or biochemical causes (1). These disorders are common: the presence of at least one functional GI disorder was identified in 70% of participants in a large US ho-

useholder survey (2). An associated co-morbid psychiatric condition such as anxiety, mood or panic disorder is seen in up to 60% of those attending gastroenterology outpatient clinics with a functional compliant (3). Functional GI disorders are associated with significant impairment of quality of

life and considerable economic burden on the healthcare system (4-6).

Although several classification systems exist for defining functional gastrointestinal disorders, the Rome criteria are the most commonly used for research purposes. The most recent iteration, the Rome III diagnostic criteria was released in 2006 (7). It defines 28 distinct functional gastrointestinal disorders in 6 major domains. A Canadian household survey using Rome II criteria found that functional bowel syndromes including irritable bowel syndrome (IBS), the focus of this review, were the most prevalent, diagnosed in 41% of responders, followed by functional oesophageal syndromes, including functional heartburn, which were found in 28% (8). In addition, considerable overlap exists between the FGIDs, with 30% of those with irritable bowel syndrome and 60% of those with functional heartburn also fulfilling criteria for the diagnosis of functional dyspepsia (9, 10). These findings have considerable implications for the assessment of the patient presenting with irritable bowel syndrome.

The Rome III guidelines emphasize the importance of the therapeutic relationship in the management of functional gastrointestinal disorders. A non-judgmental interview, together with an explanation of why symptoms occur, reassurance that the condition is not life-threatening and education regarding healthy lifestyle behaviours, may be important therapeutic tools. While invasive investigations to rule out organic pathology will be required in some, for many, a positive diagnosis based on symptom patterns can be made and the much more extensive and invasive “diagnosis by exclusion” route avoided. Indeed, inappropriate or repeated tests suggest physician uncertainty to the patient and may lead to fear on the part of the patient and a cycle of ineffective management (11).

IBS Pathophysiology

Approximately 10-20% of adults in the West have symptoms consistent with IBS (12, 13). A combination of visceral hypersensitivity, smooth muscle spasm and impairment of central pain processing (14, 15) likely contribute to the pain associated with IBS, while altered intestinal motility underlies the disordered defecation experienced by some patients (16).

Over the decades, various theories have been advanced to explain the pathogenesis symptoms in the IBS patient, including dysmotility, visceral

hypersensitivity and the psyche. The concept of the gut brain axis, emphasizing the interactivity at sensory, motor and neuro-endocrine levels, between the brain and the gut has provided a useful paradigm to encompass these diverse factors. This axis has been extended, by some, to include interaction between the gut flora (or microbiota), the immune system (both mucosal and systemic), the gut and the brain (the gut-brain-immune-microbial axis). In this scenario, interactions between the flora (be it normal and disturbed) and the mucosal immune system (gut-, or mucosa-associated lymphoid tissue, GALT or MALT) lead to the release of peptides and other neuro-active substances which generate, both locally and systemically, the neuro-muscular events that typify IBS and lead to the patient’s symptoms. The advancement of this concept in IBS occurs at a time when considerable emphasis and research effort is being expended with considerable success at understanding the role of the microbiota in health and disease (17) and in unlocking its therapeutic potential (18).

1. Post-infectious IBS

We are now beginning to see real data to directly support the concept of post-infectious IBS (19). First reported in detail by McKendrick and Read, (20) the occurrence of IBS following episodes of bacteriologically-confirmed gastroenteritis has now been documented in several studies (21–31). Thabane and colleagues concluded that the overall risk for the development of IBS was increased six-fold following an episode of bacterial gastroenteritis; with younger subjects, those who have prolonged fever during the episode of gastroenteritis and those who suffer from anxiety or depression being at greatest risk (32). These symptoms are not transient; in a Scandinavian study in which 12% of their subjects had IBS within 3 months of gastroenteritis, 9% still had symptoms five years later (28). Neal and colleagues documented similar recovery rates for post-infectious and non-post-infectious IBS in a six-year follow-up study (33).

One study went on to establish a direct link between prior exposure to an infectious agent, persisting low grade inflammation and IBS (23). In this study, an increase in the number of chronic inflammatory cells in the rectal mucosa was seen only among those exposed patients who had developed IBS. Others have demonstrated a persisting increase in rectal mucosal enteroendocrine cells, T lymphocytes and gut permeability in patients with

post-dysenteric IBS (24,25). These observations are important as they indicate a relationship between perturbations of the microbiota, mucosal inflammation and IBS, an hypothesis that is amply supported by data from studies in experimental animal models. The development of IBS has, recently, been linked with non-GI infections (34), again, perhaps, invoking a role for a systemic inflammatory response in the mediation of symptoms.

A number of parasites, such as *Dientamoeba fragilis*, *Blastocystis hominis* and giardia have been associated with the development of chronic gastrointestinal symptoms which may mimic IBS (35,36); whether parasitic infections can trigger IBS, per se, is unknown. Very recently, an outbreak of viral gastroenteritis was associated with the new onset of an IBS-type syndrome in 24% of affected subjects when interviewed three months later; subsequent follow up suggested that post-viral IBS was more transient than its bacterial counterpart (36).

Post-infectious IBS may explain only a minority of cases of IBS [1-6.7% in one recent study (38)] but it does represent a clear link between exposure to an environmental agent, inflammation and IBS in predisposed individuals.

2. Inflammation and IBS

Direct and compelling evidence for a role for mucosal inflammation in IBS was first provided by Chadwick and colleagues among 77 IBS patients: 31 demonstrated microscopic inflammation and eight fulfilled criteria for lymphocytic colitis. However, among the group with 'normal' histology, immunohistology revealed increased intraepithelial lymphocytes, as well as an increase in CD3+ and CD25+ cells in the lamina propria; all, therefore, showed evidence of immune activation (39). Subsequent studies have provided further evidence of T-lymphocyte (40,41) and mast cell activation (42-45) in the mucosa in IBS; others have demonstrated an extension of inflammation into the myo-neural compartments (46) and others still cytokine profiles in peripheral blood mononuclear cells (47,48) and serum (49) compatible with a pro-inflammatory state.

It is attractive to suggest that these immunological changes could result from exposure to an exogenous (such as bacterial) antigen challenge (50,51). That IBS patients may be predisposed to an, albeit contained, inflammatory response to lu-

minal triggers is, indeed, supported by the finding of polymorphisms in genes that encode for the production of anti-inflammatory cytokines among IBS patients (52,53) and by the very recent description of high titers of anti-flagellin antibodies in serum derived from IBS patients (54,55). Further, more direct support for this hypothesis comes from the demonstration of elevated levels of defensins in fecal fluid (56) and of upregulation of Toll-like receptor 4 (TLR-4; which binds lipopolysaccharide from Gram-negative organisms) (57), in IBS.

While the idea that IBS patients may truly harbor inflammatory changes in the colonic mucosa is increasingly gaining credence (58), many important questions remain to be answered and it is clear that this is going to be an area of active investigation for some time to come.

3. Qualitative or quantitative changes in the enteric flora (microbiota)

For some time, various studies have suggested the presence of qualitative changes in the colonic flora in IBS patients; a relative decrease in the population of bifidobacteria being the most consistent finding (59-64). It should be noted, however, that these findings have not always been reproduced and the methods employed have been subject to question. Nevertheless, qualitative changes in the colonic flora, be they primary or secondary, could lead to the proliferation of species that produce more gas (63,64) and short chain fatty acids and are more avid in the deconjugation of bile acids. With regard to the former, the relative dominance of gas-forming species could result in local changes in gas production, a development which may be poorly tolerated by IBS subjects who seem to have difficulties with the transport of gas along the intestine and to be overly sensitive to gas-induced distension. The latter could, in turn, lead to clinically significant changes in water and electrolyte transport in the colon and affect colonic motility and/or sensitivity. Similarly, a repopulation of the flora with the deficient commensal(s) could restore homeostasis. Attractive as this concept may be, it belies the challenges posed by attempts at a comprehensive description of the flora in IBS, or in any condition.

Several factors limit the interpretability of prior studies, including the unrepresentative nature of the fecal flora, a failure to describe those bacterial populations that may be adherent to the mucosal

surface and, above all, the recognition that a very significant proportion of the colonic microbiota are not identified by conventional culture methods. Molecular methods are now being applied to this complex issue and have, indeed, confirmed that IBS patients, regardless of sub-type, do exhibit a fecal flora that is clearly different from control subjects (61,62,65-67). The precise nature of these differences and their potential to disturb mucosal or myo-neural function, in the gut wall, or induce local or systemic immune responses, remains to be defined.

More recently, the role of the gut flora in IBS has been taken a stage further with the suggestion that some IBS patients may harbour quantitative changes in the indigenous flora in the small intestine: small intestinal bacterial overgrowth (SIBO) (68-72). The occurrence of SIBO has been associated with abnormalities in small intestinal motor function (73) and its eradication with symptomatic relief (68,69,72,74-77). These striking results have been the target of much criticism on several grounds (78-85). First, IBS symptoms are non-specific and may be mimicked by SIBO, regardless of aetiology; patient selection is therefore an issue. Second, the hydrogen breath test, which has been the test most widely used to make the diagnosis of SIBO in this context, is subject to considerable error, especially in relation to altered small bowel transit (86,87) and, third, others have failed to confirm these findings (88-91).

In terms of pathophysiology, and somewhat surprisingly, the enteric flora and the immune response that it generates have come centre-stage in IBS research with their potential to induce the pathophysiological changes that are associated with IBS being most vividly illustrated by post-infectious IBS. While evidence for immune dysfunction, both in the mucosa and systemically, continues to accumulate, methodological limitations have hampered a full delineation of the nature of the microbiota in IBS. The latter is eagerly awaited and may yet provide a firm rationale for the use of probiotics and antibiotics in IBS.

IBS Management

1. Symptomatic management

Traditionally, those with irritable bowel syndrome were advised to increase their intake of dietary fibre to improve stool consistency and were prescribed one of a variety of antispasmodic agents to ameliorate the associated pain and bloating. A re-

cent meta-analysis and systematic review looked at the efficacy of fibre, antispasmodics and peppermint oil in the treatment of IBS (92). It found that fibre in the form of psyllium (ipsaghula husk) is moderately effective in the treatment of global symptoms of IBS; however, wheat bran was no more effective than placebo. Antispasmodics were also shown to be of benefit. Hyoscine was the individual compound with the best evidence to support its use and is a reasonable first line treatment option for practitioners who wish to begin a trial of an antispasmodic agent. Data was limited, however, for many of the antispasmodics commonly used in the United Kingdom and elsewhere in Europe, such as mebeverine, dicloverine and alverine. Peppermint oil, which is known to have antispasmodic properties (93) was superior to placebo in the treatment of IBS. It is worthwhile taking into account that bulking agents such as ipsaghula may cause bloating, abdominal pain and flatulence (94,95). A gradual titration of the dose is, therefore, recommended particularly in those with predominant bloating or who have previously included relatively little fibre in their diet. In addition, as antispasmodics are useful in relieving postprandial pain, they are best used proactively approximately 30 minutes before meals. It must also be remembered that peppermint preparation can precipitate or aggravate heartburn, an issue that may be relevant to a number of patients, given the frequency of overlap between functional heartburn and IBS.

Disordered defecation in IBS is often treated with either laxatives or anti-diarrhoeal agents, as required. The American College of Gastroenterology (ACG) IBS task force recently looked at the role of both of these agents in a systematic review on the Management of Irritable Bowel Syndrome (96). Laxatives have mostly been studied in patients with chronic constipation but not in randomized control trials in adults with IBS. Polyethylene glycol is generally well tolerated and safe. It can easily be titrated by the patient under physician supervision.

The anti-diarrhoeal loperamide is an effective agent for the treatment of diarrhoea, improving both stool frequency and consistency. However it is not more effective than placebo at reducing pain or global symptoms of IBS. Anti-diarrhoeals may be used prophylactically on an as needed basis. Treatment should begin with a low dose to avoid constipation, however up to 2 tablets q.i.d. may be used to treat those with more severe diarr-

hoea. One must caution that high volume diarrhoea should alert the physician to the possibility that they are not dealing with IBS and should consider alternative diagnoses.

2. Anti-depressants

The severity of IBS-associated pain is highly predictive of related medical costs and quality of life impairment (97). Antidepressants have been used in the treatment of IBS-associated abdominal pain both for their potential modulation of pain perception (98) and for treatment of coexistent psychiatric illness. A recent meta-analysis examining the role of antidepressants in the management of IBS (99) demonstrated a benefit for both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) over placebo in the treatment of IBS. Both agents appeared to be equally effective. Data on the safety and tolerability of these agents in IBS is limited. TCAs are usually used at low doses in the treatment of IBS as the symptom improvement seen may be more related to their pain modulation and motility effects rather than treatment of psychological symptoms. The administration of the TCA imipramine prolonged both orocaecal and whole gut transit in a cohort of patients with IBS with diarrhoea (IBS-D) and healthy controls (100). This makes them an attractive option for the treatment of those with IBS-D, particularly, in those where pain is a predominant feature. In contrast, the SSRI, paroxetine, has been shown to accelerate gut transit time (101). SSRIs generally have a lower side effect profile than TCAs and should be considered in the treatment of IBS when psychological symptoms or coexistent somatic pain syndromes are present, or in those patients who have not responded to laxatives or antispasmodics. The same dose as that used for mood disorders is recommended (102). While citalopram and escitalopram generally have less side effects and drug interactions than the other SSRIs, paroxetine may be favoured in the treatment of IBS-C due to effects on gut transit. Data on the use of SNRIs in the treatment of irritable bowel syndrome is not currently available.

3. Antibiotics, probiotics and prebiotics

A number of studies have demonstrated some efficacy for antibiotic therapy in IBS. Whether these effects are mediated through an impact on the small intestinal or colonic flora, or through other mechanisms remains unclear; initial reports indicated symptomatic improvement with neomycin,

metronidazole and clarithromycin (103, 104). However, routine use of these drugs is limited by concerns about potentially serious adverse effects and the development of microbial resistance. Rifaximin is an oral non-absorbable antibiotic that is approved in the US for the treatment of travellers' diarrhoea and hepatic encephalopathy (105). Its localized action in the GI tract results in a low risk of adverse effects whilst providing targeted therapy against Gram-positive and Gram-negative aerobic and anaerobic enteric pathogens. Two smaller trials have demonstrated efficacy of rifaximin in relieving global symptoms of IBS, as well as bloating and diarrhoea (106, 107). More recent large multi-centre studies have confirmed these findings for rifaximin by demonstrating an approximately 10% therapeutic gain for the antibiotic over placebo (108-110).

Probiotics in clinical trials have varied widely in terms of species, strain and dose. This makes evaluation of the data in relation to IBS difficult. Like in other areas, effects of probiotics in IBS are highly strain specific; some species and strains can improve individual IBS symptoms, such as bloating or flatulence while few provide overall benefit. Thus, while one recent meta-analysis (111) concluded that probiotics as a whole appeared to be efficacious in IBS, in another, however, only *bifidobacterium infantis* improved global symptom relief in IBS (112). Further studies are needed to establish which species, strain and dose of probiotic will be of greatest benefit in the long term. Given the encouraging results with probiotics, some attention is now being focused on the use of prebiotics in the treatment of irritable bowel syndrome. Prebiotics are non-digestible but fermentable foods that selectively stimulate the growth of one or more species of bacteria in the gut and in doing so confer a health benefit to the host (113). A recent randomized controlled trial examined the effect of a prebiotic (galactooligosaccharide) in a small cohort of patients with IBS (114). It demonstrated that the prebiotic in question specifically stimulated gut bifidobacteria in IBS patients and was effective in relieving symptoms. Although larger studies are warranted, this points towards a possible future role for prebiotics in the management of IBS.

4. New agents

Lubiprostone is a highly selective activator of type 2 chloride channels in the gastrointestinal tract. It increases secretion of chloride-rich enteric fluid

without affecting serum chloride, sodium and potassium levels. The increase in intestinal fluid eases stool passage and, thereby, improves stool frequency and form (115). Lubiprostone was initially used in the treatment of chronic constipation. A dose of 24 micrograms twice daily was found to be efficacious in improving stool frequency, stool form and straining in both men and women with chronic constipation (116). An improvement in abdominal pain was seen in a subset of the patients in these trials and led to the evaluation of lubiprostone in subjects with IBS-C. Two large Phase III trials (117) have recently demonstrated that patients with IBS-C receiving lubiprostone at a dose of 8 micrograms b.i.d. were almost twice as likely to report an improvement in the global symptoms of IBS as those receiving placebo. Lubiprostone was generally well tolerated with nausea, vomiting and abdominal cramping being the most common side effects. As most of the subjects in clinical trials of lubiprostone were female, lubiprostone is approved by the FDA for the treatment of IBS-C in women at a dose of 8 micrograms b.i.d. It should be taken with meals to reduce nausea.

Guanylate cyclase C (GC-C) is a transmembrane protein located in intestinal epithelial cells. Activation of intestinal GC-C induces secretion of fluid, sodium and bicarbonate in the intestinal lumen (118). Linaclotide is a synthetic GC-C agonist. Initial studies, as well as a recent large multi-centre study (119), in subjects with chronic constipation and IBS-C have shown it to be an effective agent in terms of its effect on stool consistency and frequency and abdominal discomfort. In addition it appeared to be safe and well tolerated suggesting it may be a promising new agent in the treatment of IBS-C and chronic constipation (120).

Serotonin (5-HT) is an important neurotransmitter in both the brain and gastrointestinal tract and plays a key role in gut motility, secretion and sensitivity (121). Several drugs acting on the 5-HT receptor system have shown significant therapeutic benefit in the treatment of IBS. Tegaserod, a 5-HT₄ receptor partial agonist has shown significant benefit in improving abdominal discomfort, bowel habits and bloating in subjects with IBS-C (122). In contrast, alosetron, a 5HT₃ receptor antagonist, demonstrated sustained relief of abdominal pain and urgency in subjects with IBS-D (122). However despite their therapeutic benefit, both drugs were withdrawn from the US market in 2007 because of the association of tegaserod with

cardiac side effects and alosetron with ischemic colitis.

Three new 5-HT₄ receptor agonists, prucalopride, AT-7505 and velusetrag (TD-5108) have been evaluated in clinical trials involving subjects with chronic constipation; three multi-centre studies have shown efficacy for prucalopride in constipation (123-125). Ramosetron is a novel 5-HT₃ receptor antagonist. A global improvement in symptoms was seen in both men and women with IBS treated with ramosetron in two randomized control trials without serious adverse events (126, 127).

5. Non-pharmacological therapies

Postprandial worsening of symptoms (128) and a perceived intolerance to one or more food types (129) are frequently reported by patients with IBS, but is there evidence to support dietary manipulation in its management? Some patients find that fibre-containing foods actually worsen their symptoms. Foods rich in carbohydrates, or containing starch, lactose, fructose or sorbitol as well as fatty foods and food agents such as coffee, alcohol and spices were all reported to exacerbate IBS symptoms in one study (129). The precise contributions of specific food intolerances, the physiological response to food, the ability of food ingestion to potentiate pre-existing visceral hypersensitivity or dysmotility, interactions between the ingested food and the microbiota or psychological factors, to the genesis of food-related symptoms remains to be fully elucidated. What is clear is that there is little correlation between skin prick testing or serum IgE levels and reported food allergies in IBS patients (130,131). In addition, evidence to support the benefit of lactose, fructose and sorbitol exclusion diets is inconclusive at best (132). Although some evidence does exist to support both a role for food "allergy" testing based on IgG antibodies and some benefit for exclusion diets based on its results in IBS (133), methodological shortcomings in existing studies examining the role of food allergy and elimination diets in IBS led the ACG IBS task force to conclude that, at present, there is insufficient evidence to support the routine use of elimination diets outside of clinical trials (96).

Psychotherapeutic interventions used in the treatment of irritable bowel syndrome have included cognitive behavioural therapy (CBT), dynamic psychotherapy, hypnotherapy and relaxation therapy. Although high quality evidence evaluating

the role of psychological interventions in IBS is somewhat lacking, available evidence suggests that CBT, dynamic psychotherapy and hypnotherapy are beneficial in the treatment of IBS and indeed may be as effective as anti-depressants in this setting (99). One of the major obstacles to objective data in this field is the challenge of performing a

double-blind placebo-controlled trial. The best evidence is for CBT (96), which teaches patients to identify the relationship between thoughts and physical symptoms and to modify dysfunctional beliefs and sick role behaviour (134). There is insufficient evidence to support the role of relaxation therapy in the treatment of IBS (96).

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