

State-of-the-art of irritable bowel syndrome and inflammatory bowel disease research in 2008

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Abstract

Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) are two of the leading causes of chronic intestinal conditions in the world. This issue of *World Journal of Gastroenterology (WJG)* presents a series of papers from world experts who discuss the current knowledge and opinions on these important conditions. Although great strides have been made in the diagnosis, treatment and pathology of IBS and IBD; much has yet to be explained. The etiologies and risk factors of these multifactorial conditions remain elusive. Specific diagnostic biomarkers need to be developed and safer treatments developed. The burden of IBS and IBD on the healthcare system is felt with repeated medical care visits and high costs. IBS and IBD patients can account for 30%-50% of office visits at gastroenterology services/clinics. Over one million people have IBD in the United States, with 30000 new cases being diagnosed every year. One-quarter million people in the UK are afflicted with IBD. The cost of medical care in the United States for IBD is estimated to be \$1.8 billion/year.

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IRRITABLE BOWEL SYNDROME (IBS)

Incidence of IBS

IBS is a global problem and is more common in women than men. In developed countries, the prevalence of IBS ranges from 3%-25% of adults^[1-4] and in the United States, IBS affects 15 million adults^[5]. In the United Kingdom, IBS affects 10%-15% of the adult population^[6]. The cost of direct and indirect medical care for IBS reached over \$200 billion dollars in the United States^[5,7].

Diagnosis of IBS

As there are no biologic markers for IBS, the diagnosis is usually based on symptoms and exclusion of other known causes of intestinal distress^[6]. Unlike IBD, IBS does not cause severe inflammation, ulcers or other structural damage that aids the diagnosis of IBD. IBS is a functional disorder characterized by abdominal bloating, flatulence, abdominal pain and bowel dysfunction. The varying nature of symptoms and lack of structural abnormalities presents a diagnostic challenge. There are three main types of disease phenotypes: diarrhea-predominant (IBS-D), constipation-predominant (IBS-C) or alternating diarrhea-constipation (IBS-A). The diarrhea-predominant type is more common (48%) in males, whereas constipation-predominant (39%) or alternating types (48%) are more common in women^[1]. Several tools (for example, Rome III, Manning criteria) have been developed to standardize the diagnosis of IBS. Most of the historic research has been focused on the pathophysiology of diarrhea, but constipation has not been as well described. The review by McCrea and colleagues in this issue summarizes our current knowledge about the physiology and pathology of constipation^[8]. The prevalence of constipation ranges from 15%-25% in the general population and is more common in women than men and in ages over 70 years old^[9]. The typical definition of constipation (less than three stools/week) may not be a sensitive measure for this condition, as individuals vary widely in their own bowel habits. An interesting finding in this review is that physicians and patients define constipation differently. Neurotransmitters are important in the pathophysiology of IBS and this paper reviews how neurotransmitters are involved in the normal and abnormal

function, and anatomy of the gastrointestinal tract. Age-related anatomical changes seem to have minimal impact on normal colonic function, which might help to explain why increasing age is not a significant risk factor for IBS. McCrea *et al* then describe the association of dysmotility on the pathology of IBS-C. This review of constipation highlights the need to conduct further research into the etiologies and functional causes of constipation, especially as it relates to disease conditions such as IBS.

Consequences of IBS

Patients with IBS report a significant reduction in quality of life and sexual function and have increased suicide ideation, absenteeism, have higher rates of depression and are heavy users of medical care^[6,10].

Pathogenesis

IBS is a multifactorial condition and the pathophysiology may involve a triad of factors: altered intestinal motility, psychosocial factors and heightened sensory function. Risk factors include genetic factors, food allergies and microbial dysbiosis^[11]. The low grade mucosal inflammation, altered motility and altered bowel microflora give rise to the characteristic clinical symptoms of IBS.

Treatment for IBS

Current treatments for IBS target the patient's predominant symptoms at the time of the acute episode and the efficacy of these treatments vary widely^[4]. Hammerle and Surawicz review the challenges of treating patients with IBS^[12]. The effectiveness of conventional therapy for IBS varies due to the need to treat different types of symptoms (IBS-D, IBS-C or IBS-A) and the need to limit underlying etiologic triggers, which are commonly unknown. The authors point out the need for individualized treatment regimes, as symptoms and treatment responses vary widely. The chronic nature of IBS necessitates life-long treatments that may need adjustments reflective of shifting clinical presentations. Hammerle and Surawicz also review the role that serotonin has on the function of the intestinal tract and how decreased levels of neurotransmitters are involved in the pathology of IBS. Pharmacotherapy directed at modulating neural transmitters offer a promising class of treatments for IBS. 5-HT₄ antagonists may be an effective choice for IBS-D as they slow intestinal transit, increase stool firmness and reduce intestinal secretion. In contrast, 5-HT agonists (such as tegaserod) are more effective for IBS-C. Octreotide has been tested in human volunteers and slows diarrheal symptoms, but is only available intravenously, limiting its usefulness. Other types of antagonists are reviewed, but clearly more randomized clinical trials are needed. Other types of treatments (including antidepressants, antispasmodics, antibiotics, fiber, probiotics and dietary changes) are reviewed and may be effective in some patients, but more research is needed for these types of treatments as well.

As patients with IBS have been shown to have disrupted intestinal microflora and some episodes of IBS are triggered by gastroenteritis, a treatment strategy that involves microbial replacement is attractive^[13]. Probiotics are beneficial microbes that are given to restore normal microflora and have

been shown to be effective for other types of diarrhea (antibiotic-associated diarrhea, *Clostridium difficile* disease, traveler's diarrhea and pediatric diarrhea)^[14,15]. The meta-analysis by McFarland and Dublin explores the efficacy of various probiotics for the treatment of IBS^[16]. The results from 20 randomized clinical trials with 23 different probiotic treatment arms were compared to controls. Generally, probiotics were found to significantly reduce IBS symptoms globally [pooled odds ratio (OR), 0.78; 95% confidence interval (95% CI), 0.62-0.94]. However, no one type of probiotic had sufficient numbers of confirmatory trials to conclude one type of probiotic was more effective than another probiotic. Probiotic trials in the past have been directed by other types of diarrheal disease, but probiotic treatment for IBD and IBS is receiving renewed attention. This review is a call to arms for researchers interested in this area. Larger clinical trials are needed in the future in order to have sufficient power to detect significant differences between the treatment groups, multiple confirmatory trials using the same strain of probiotic are needed and a consensus on a common outcome measure is needed. Many of the trials of IBS used different outcome measures, some measuring a global response (no relapses of disease), some measuring a reduction in symptom scores and some creating their own individual outcome measures. Obviously, this makes comparing different study results challenging. Despite these limitations, probiotics may offer a safe and effective strategy for patients with IBS. More clinical trials are needed.

IBD

Incidence

Several intestinal conditions are under the umbrella of "Inflammatory Bowel Disease (IBD)", including Crohn's disease, ulcerative colitis and pouchitis. IBD, once considered a disease of industrialized countries, is now reported globally. The highest incidences (8-66/100 000 population) of Crohn's are found in Wales, New Zealand, Canada, Scotland, France, the Netherlands and Scandinavia^[17]. Other industrial countries such as in the United Kingdom, the United States and in Europe have intermediate rates ranging from 4-7/100 000^[17,18]. Historically, IBD was infrequently reported in developing countries, but currently low incidence rates are reported (0.2-3/100 000) in such countries like Brazil, China, Korea, Greece, Japan, Malta and Slovakia^[19]. The incidence in these countries has increased in recent years, whether it is due to an actual increase in the number of cases or better diagnostic and detection methods is not known^[18]. Interestingly, there is a north-south gradient in Europe, with more severe disease in northern European countries^[17]. Recent studies have found that Crohn's disease is more common in young patients. Most (74%) of in one study were under 30 years old and the typical age of onset is usually 15-30 years of age^[18]. Gender differences are not consistent across the country. More men than women are diagnosed with Crohn's disease in China, in contrast to the United States, where more women than men have Crohn's^[18].

Diagnosis

As there are no standard biomarkers for IBD, the diag-

nosis of Crohn's disease and UC are typically made based on clinical symptoms, endoscopic and histologic findings. Variances in symptom types and frequency and a lack of structural abnormalities observed upon endoscopic examination typically may delay the diagnosis of IBD for 6 mo to 1 year^[18]. The clinical presentation of Crohn's disease is abdominal pain, diarrhea and weight loss, while patients with UC most often complain of abdominal pain, bloody diarrhea and stool mucus^[18,20]. Crohn's disease results in inflammation, deep fistulas or abscesses anywhere along the gastrointestinal tract, but most commonly along the ileocolon. Colonoscopic examination of patients with ulcerative colitis shows pathology is limited to the large colon with surface inflammation and left-sided colitis, proctitis and proctosigmoiditis being most common^[20]. Recent innovations in diagnostic techniques including noninvasive imaging techniques and more sensitive endoscopic equipment may improve the diagnosis of IBD.

Consequences of IBD

Complications for Crohn's disease are frequent (40%) and include lower gastrointestinal bleeding, intestinal obstruction, perforation and the need for surgery^[18]. Mortality in IBD patients is generally low (about 6%) with some studies finding IBD significantly increases the risk of mortality (OR, 1.4; 95% CI, 1.2-1.6) compared to non-IBD patients. The risk of mortality is higher for patients with Crohn's are compared with patients with UC^[21]. In studies that have followed large numbers of UC patients for at least ten years, 70%-100% suffered at least one relapse of UC^[22]. In patients enrolled in clinical trials and randomized to placebo, relapse rates for Crohn's disease ranged from 10%-60% and 11%-90% of UC patients relapsed^[23].

Another important consequence of UC may be a higher risk of colorectal cancer. Whether precancerous lesions are an etiologic factor for IBD or whether chronic intestinal inflammation increases the risk of colon cancer has been debated. Zisman and Rubin review the epidemiology of cancer and dysplasia in IBD patients^[24]. Using historical data, the cumulative incidence of colorectal cancer increased by the duration of UC, with highest rates present after 30-40 years of UC. However, this increase may be an example of a period-cohort bias, as increased colonoscopy in the younger patients (with shorter durations) may have reduced cancer rates. The authors explore the possible risk factors for colorectal cancer in UC patients. The degree of inflammation seems to correlate with increased risk of colorectal cancer. Further research may be needed to prospectively document inflammatory biomarkers and then follow patients for the development of cancer. Other risk factors are discussed, including family history of colon cancer, primary sclerosing cholangitis and strictures, but the weight of evidence is weak for these factors. The link between colorectal cancer and Crohn's disease is less clear, as many have no colonic involvement. Despite this, the incidence and risk factors for Crohn's disease patients and colon cancer are remarkably similar to UC. The importance of colonoscopy surveillance is highlighted. Dysplasia, thought to be an intermediate step between chronic inflammation and carcinoma, is also reviewed by these authors. The unpredictable course of not

only dysplasia, but IBD itself, complicates the determination of the role of molecular markers and mutations. It becomes more paramount that methods for prevention are pressed into clinical use. Evidence that prophylactic chemotherapy is effective in reducing colorectal cancer is not conclusive. Colonoscopy remains the most recommended preventive method for preventing colorectal cancer and its use should be encouraged. Innovations in novel imaging technology may increase the detection of early stages of cancer in IBD patients. Despite the scarcity of research in some areas in this field, it seems likely that the chronic inflammation insult to the colon present in IBD patients may increase the risk of colorectal cancer.

Pathogenesis

While research has uncovered some of the risk factors for Crohn's and UC, much about the etiology of these two conditions remains unknown. The pathogenesis of IBD may involve four major areas: it appears to be immunologically mediated, microbial dysbiosis is usually present, environmental factors trigger symptoms and genetic predispositions may play an important role^[25]. Proinflammatory cytokines are produced during IBD episodes and altered immune response is common in both Crohn's disease and UC. Microbial dysbiosis has been documented in patients with IBD^[26]. The 'hygiene hypothesis' postulates that decreased exposure to environmental microbes due to increased disinfectant use in some industrialized cultures may alter the development of the immune system early in life^[27]. However, there is only indirect evidence for this correlation and this hypothesis remains unproven. Several bacterial candidates, including *Mycobacterium avium paratuberculosis* (MAP), have been investigated as potential etiologies for IBD, but the research has been inconclusive^[28]. It is thought that inappropriate or exaggerated mucosal immune response to enteric infections may be involved in the initial etiology of some cases of IBD. In infants less than one year old who developed IBD, 50% had a prior bacterial infection requiring antibiotic therapy^[29]. Although as intriguing as this finding is, more research is needed to determine if enteric infections cause IBD.

Environmental triggers for IBD may include smoking, diet, stress, gallstones, surgery and exposure to microbes. In one study, the risk of Crohn's disease was significantly elevated (OR, 35; $P < 0.05$) if the patient smoked, had a sibling with Crohn's and carried at least two CARD15 genes^[30]. In contrast, the average age of patients developing ulcerative colitis was older (mean 44 ± 15 years) and there are no large differences by gender^[20]. Other risk factors for UC include prior smoking history (but not current smoking), family history of UC and high body weight (elevated BMI)^[25].

The carriage of susceptibility genes such as CARD15/NOD2, IBD5, DLG5, IL23R and ATG16LI are associated with increased rates of Crohn's disease in developed countries, but interestingly are not associated with an increase in Crohn's in Asian countries^[17,30,31].

Treatment for IBD

Without an exact reason for the etiologies of Crohn's disease and UC, finding effective treatments are challenging. As a hyper-immune response plays an important part in

IBD, immunomodulators and immune-suppressives have been used as a standard treatment for IBD. Corticosteroids and 5-aminosalicylates have been the traditional treatments for IBD, although many patients do not respond to these treatments or develop serious adverse effects during prolonged use, including increases in serious infections, reactivation of tuberculosis, development of lymphoma or demyelinating disease^[20]. Currently, there are two main strategies for the treatment of Crohn's disease: the top-down or the step-up approach. Shergill and Terdiman review the controversies and suggest another approach to the treatment of Crohn's disease^[32]. The top-down approach starts patients with newly diagnosed disease with the newer immunomodulators and biologic agents. The step-up approach begins with more conventional treatments (5-aminosalicylates, mesalamine) and then steps up to steroids if those fail. Immunomodulators are started only after the other treatments have failed. Symptom abatement with the least toxic drug is the guiding principal of the step-up approach. Shergill and Terdiman reassess this paradigm and conclude using a more aggressive therapy earlier in the disease may limit irreversible damage to the bowel, preventing future hospitalizations, surgeries and disabilities. Challenges inherent in determining the most effective treatment strategy include the varying nature of the symptoms, the subjective nature of many of the outcome measures and the lack of correlation between mucosal healing and the Crohn's disease activity index (CDAI), commonly used to determine treatment response. The authors point out treatments that heal the mucosa are often only started after irreversible damage has been done. Steroids are effective in rapidly suppressing flares, but have no benefit on the underlying damage to the mucosa. In contrast, immunomodulators take longer to reduce symptoms, but are able to induce mucosal healing and are able to maintain remissions for a longer time. Both steroids and immunomodulators have side effects which complicates treatment. These authors propose a new hybrid approach described as an "accelerated step-up" approach. Patients presenting with mild symptoms should be treated with mesalamine, antibiotics or budesonide to quickly reduce symptoms. If symptoms do not resolve or if the patient relapses, immunomodulators are then started. Since these agents take 2-4 mo to heal the mucosa, short-term steroids are added in the early months of therapy (unless contra-indicated by fistula or perforations). Once remission is achieved, immunomodulators could be tapered off. If none of these are effective, biologics such as anti-TNF drugs can be tried. The bottom line is that treatment of Crohn's disease is not easy and must be tailored to the individual patient and be constantly adjusted if recurrences happen. The review by Shergill and Terdiman provides a thoughtful assessment of different therapeutic choices and a balanced discussion of the benefits and risks of each treatment choice.

The development of antibiotic resistance presents an additional challenge in the treatment of patients with IBD. Beckler and co-authors describe a new PCR method to detect rifabutin and rifampicin resistance in *Mycobacterium avian paratuberculosis* (MAP) strains^[33]. As mentioned earlier, MAP is thought to be one of the etiologic agents of Crohn's disease. Proponents of this hypothesis cite

the lack of antibiotic response when patients are treated. However, the poor response may be due to antibiotic-resistance rather than the lack of an association between MAP and Crohn's disease. Beckler *et al* found mutations associated with increased antibiotic resistance were located on the *rpoB* gene of MAP. They developed a PCR tool to detect this antibiotic resistance and this tool provides a rapid method to detect MAP infection in IBD patients. Classic microbiologic methods of culturing MAP are slow and insensitive. The addition of this innovative tool may help to gather sufficient evidence to finally determine if MAP is associated with Crohn's disease or not.

If IBD persists and standard treatments fail or if the patient develops serious complications, surgery is often the only available option for the patient. The lifetime risk for colectomy surgery is 70%-80% for Crohn's disease patients and 20%-30% of UC patients^[2]. In UC patients with colectomy, as many as 50% will develop at least one episode of pouchitis post-operatively^[34]. The rationale, types of procedures, benefits and risks of surgery are reviewed by Hwang and Varma^[35]. The paper presents an extensive description of the available types of surgeries depending upon the site and type of disease. Colectomy is typically restorative, but has a high post-operative complication rate (23%-48%) of sepsis or pouchitis. Revision surgery is often required (19%-24%) and 21%-50% of patients suffer remissions even after surgery. Small bowel surgery for patients with Crohn's disease is usually needed due to repeated flares of disease or the development of extra-intestinal manifestations despite medical treatment. Indications for surgery of the colon include treatment failures, dysplasia or colorectal cancer and toxic colitis. Regardless of the site of surgery, recurrences are common (40%-70%). Surgery is unfortunately usually not curative and associated with significant morbidity. This highlights the need to focus research on effective treatments to manage IBD and IBS.

Other alternative therapies being tested include hypnotherapy, herbal medicines and probiotics^[36]. As prior enteric infections have been associated with the development of IBD, therapies that target or ameliorate the intestinal disruption brought on by antibiotic therapy seem a logical choice. In a survey of 86 children with IBD in Scotland, 44% reported that they used probiotics to control their IBD symptoms^[37]. The effectiveness of probiotics for IBD has shown mixed results, depending upon the type of probiotic and the condition treated. Evidence from clinical trials found *Saccharomyces cerevisiae boulardii* was effective for Crohn's disease, while *E. coli* Nissle, VSL#3 (a mixture of 8 bacterial strains) and *Lactobacillus rhamnosus* GG were not effective^[23,38]. Effective probiotics for UC include a mix of *Bifidobacterium* and *Lactobacillus acidophilus*, while other studied strains were not effective. More promising results were reported in five clinical trials when VSL#3 was tested to prevent pouchitis after colectomy surgery^[23].

This series of articles presents the challenges that face healthcare providers and patients with IBS and IBD. These chronic conditions place a heavy burden on healthcare institutions and contribute to significant morbidity. Newer treatment strategies may help patients remain in remission longer, but our efforts should be focused on unraveling the etiologies of these diseases so that preventive measures

can be developed that will stop irreversible damage from occurring in the first place, lofty goals, but well worth our efforts.

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