

Evolving Issues in the Diagnosis, Evaluation, and Management of Irritable Bowel Syndrome

a report by

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Irritable bowel syndrome (IBS) is a highly prevalent gastrointestinal motility disorder associated with decreased quality of life¹ and significant economic burden to both the individual patient and society.² For these reasons IBS has remained an area of active clinical research. This article will provide a summary of recent changes in the Rome criteria, discuss how brain imaging broadens our understanding of the brain–gut axis in IBS, and review new data on serotonergic agents, bacterial overgrowth, probiotics, and IBS.

Defining Irritable Bowel Syndrome

The definition of IBS has evolved significantly over the past several decades. The first set of symptom-based criteria was proposed in 1978 by Manning and colleagues, who identified four symptoms that occurred more frequently in IBS.³ These symptoms included looser stools at the onset of pain, increased frequency of bowel movements after the onset of pain, relief of abdominal pain after a bowel movement, and abdominal distension. The Manning criteria had a sensitivity and specificity of 42–90% and 70–100%, respectively, but concerns soon arose about their validity. The 1984 Kruis criteria placed more emphasis on symptom duration; however, these criteria were quite cumbersome to use in clinical practice and rapidly fell out of favor. In 1988 a group of experts met in Rome to discuss functional gastrointestinal disorders (FGIDs). This culminated in the publication of the Rome criteria in 1992. The criteria for IBS were used in research studies but proved unwieldy in clinical practice. In 2000 the Rome criteria were revised to the Rome II criteria, which also proved somewhat cumbersome in clinical practice.

The 2006 Rome III criteria contain several important changes, including a more concise and inclusive symptomatic time-frame for all FGIDs.⁴ One of the most significant revisions concerns the classification of IBS subtypes. Subtypes are now based on stool consistency rather than stool frequency, and include IBS-C (constipation), IBS-D (diarrhea), IBS-M (mixed), and IBS-U (unsubtyped). Validation studies have yet to be published, but the clinical utility of the Rome III criteria is promising.

Brain Imaging

Functional brain imaging evaluates central nervous system activity in patients with IBS. The most common techniques employed in IBS brain imaging are positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG). PET uses radiolabeled isotopes to capture changes in neuronal metabolism or cerebral blood flow, fMRI assesses changes in the concentration of oxygenated hemoglobin, and MEG enables more detailed temporal resolution by mapping the magnetic fields generated by brain activity. As these techniques measure different parameters, they may yield divergent results.

The first IBS imaging study used PET to investigate the brain's response to painful visceral stimuli, namely rectal distention. Altered levels of activation of various brain regions were noted in IBS patients relative to controls.⁵ Later studies employed fMRI or MEG, and tested neural responses to sham, subliminal, and non-painful rectal distension, as well as auditory and heterotopic stimuli. For example, a study by Andresen and colleagues noted hyper-reactivity to auditory and visceral stimuli in IBS patients.⁶ Gender differences in brain activation in IBS were noted,⁷ as were differences between IBS subtypes.⁸ Other studies identified several regions, including the insula, anterior cingulate and somatosensory cortices, thalamus, and limbic regions, which displayed unusual activation patterns in IBS patients. Study results were often in conflict, which is not surprising given the complicated pathophysiology that underlies IBS and the different methodologies employed. However, taken together, brain imaging studies have consistently demonstrated significant differences in activation patterns of IBS patients compared with controls. Future hypothesis-driven (rather than descriptive) studies and the concurrent use of imaging techniques may provide more information about the pathophysiology of IBS. Additionally, new developments in imaging, such as PET tracers that allow assessment of 5-hydroxytryptamine (5-HT) serotonin synthesis within the brain, will enable researchers to track the effects of IBS treatments.

Serotonergic Agents

Multiple serotonergic agents have been used to treat IBS. Selective serotonin re-uptake inhibitors (SSRIs) may improve visceral hypersensitivity, particularly in constipation-predominant IBS.^{9,10} Furthermore, SSRIs have been shown to improve patients' sense of wellbeing, even when not depressed.¹¹ Tegaserod, a 5-HT₄ receptor-selective agonist, is the only agent within the class of medications approved for IBS-C. Four randomized controlled trials demonstrated statistically significant improvement in global IBS symptoms.¹² Diarrhea was the most common side effect, but rarely required withdrawal of the medication.¹³ Concerns over possible cardiovascular adverse events resulted in the withdrawal of tegaserod from the general market in March 2007.

For diarrhea-predominant IBS, alosetron, a 5-HT₃ receptor antagonist, has been shown to improve control of urgency over placebo in women.¹⁴ Alosetron was taken off the market after reports of ischemic colitis and serious complications of constipation were observed. Since its removal from the market, patients with IBS have been shown to have a two- to four-fold increased risk of ischemic colitis.¹⁵ A recent review of clinical trial report forms and the US Food and Drug Administration (FDA)

MedWatch forms showed that the rate of ischemic colitis was extremely low (1.1 per 1,000 patient-years), and no patients with ischemic colitis had long-term sequelae.¹⁶ Cilansetron is another 5HT-3 receptor antagonist that has been shown to have similar efficacy in both men and women with IBS-D. In April 2005 cilansetron was reviewed by the FDA but was not approved, and further clinical trials were requested.

Probiotics

Probiotics are defined as organisms that, when administered in adequate amounts, exert a positive influence on the health of the host animal. While the precise therapeutic mechanism is unknown, it is theorized that probiotics may ameliorate IBS symptoms by stimulating an immune response, reducing inflammation, or altering the composition of gut flora. Although frequently used by IBS patients, objective data supporting their efficacy are limited. A preliminary report noted that *Bifidobacterium infantis* improved some IBS symptoms, although the sample size was small (n=75).¹⁷ A recent study evaluated the efficacy of *B. infantis* in a large group (n=362, all subtypes included) of IBS patients.¹⁸ Women between the ages of 18 and 65 years who met Rome II criteria were included. Subjects were randomized in a blinded fashion to placebo or one of three daily doses of *B. infantis* for the four-week trial period: 1x10⁶ colony-forming units (CFUs), 1 x10⁸ CFUs, or 1x10¹⁰ CFUs. The primary efficacy end-point was daily abdominal pain and discomfort; secondary end-points included individual symptoms of bloating, straining, bowel dysfunction, and incomplete evacuation. *B. infantis*, at a dose of 1x10⁸ CFUs, improved abdominal pain and discomfort significantly more than placebo (p=0.023), although the other two doses were not better than placebo. Analysis of secondary symptoms (bloating, passage of gas, straining, bowel satisfaction, and feelings of incomplete evacuation) demonstrated that *B. infantis* at 1x10⁸ CFUs daily was significantly better than placebo (p values all <0.05), although doses of 1x10⁶ and 1x10¹⁰ were not better than placebo. Of note, no dose was associated with a significant change in stool frequency. Adverse events were few in number and no different between *B. infantis* and placebo. *Post hoc* analysis found that the high-dose capsules (1x10¹⁰) coagulated, thus preventing adequate release of the bacterium. In summary, this well-designed multicenter study is the largest to date to evaluate the safety and efficacy of a probiotic for the treatment of IBS. Further studies are needed to better define the mechanism of action of probiotics and to identify which IBS patients might respond with the greatest efficacy.

Bacterial Overgrowth and Irritable Bowel Syndrome

The role of small intestine bacterial overgrowth (SIBO) in the pathogenesis of IBS remains controversial. Several studies have shown a

high prevalence of SIBO in IBS patients.¹⁹ As a natural consequence of this, antibiotics are now being evaluated as possible treatments for IBS. Rifaximin has generated significant interest because it has low systemic absorption (<0.4%). A recent study evaluated the efficacy of rifaximin in men and women who met Rome I criteria for IBS.²⁰ Patients were randomized to either placebo or rifaximin 400mg orally three times daily for 10 days and then followed for a total of 10 weeks. Patients randomized to rifaximin had an overall improvement in symptoms compared with placebo (p=0.020). Bloating was also better in the rifaximin group (p=0.01).

Scores for abdominal pain, diarrhea, and constipation were no different between the two treatment groups. This widely publicized study should be interpreted with caution for a number of reasons, however. First, the rifaximin group had a higher level of pain at baseline. Second, subject recruitment may have been biased. Third, the end-point for analysis was not typical for that used in IBS trials, and a treatment responder was not defined *a priori*. Finally, the authors did not report the results of the breath hydrogen tests that were performed in all of these patients.

Other research groups have not been able to replicate the high prevalence rates of SIBO in IBS patients reported by these authors. A retrospective chart review was performed at the Mayo Clinic of all patients who had a duodenal aspirate and culture over a one-year period.²¹ One hundred and fifty-one patients met the criteria for IBS after a comprehensive chart review. Abnormal aspirate counts were present in 6% of those patients with IBS and in 11% of those with complaints of bloating. The authors concluded that patients with IBS were not more likely to suffer from SIBO. Using the lactulose breath test, the test most commonly used by clinicians to evaluate a patient for SIBO, Bratten and colleagues also found that IBS patients were no more likely than healthy volunteers to have SIBO.²² Thus, the relationship between SIBO and IBS remains unclear and requires further study.

Conclusions

IBS is a highly prevalent gastrointestinal motility disorder that is being actively studied. In the last five years, new imaging techniques such as PET scans have provided important information on the brain-gut axis. Furthermore, several new therapies are now available to treat IBS and many of them target the serotonin system, which plays a critical role in normal gut pathophysiology. While novel research investigating the relationship between IBS and the gut flora is emerging, the role of antibiotics and probiotics in the treatment of IBS remains controversial and requires further investigation. ■

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