

## Recent Advances in the Diagnosis and Treatment of Irritable Bowel Syndrome

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### ABSTRACT

IBS remains a highly prevalent functional bowel disorder that is characterized by dysfunctional bowel movement. Current treatment approaches are mainly symptomatic. In the past years, a number of diagnostic criteria have been discovered that may provide further insights in the pathogenesis, potential triggers, and pathophysiology of IBS. With these newly available tools at hand, new treatment approaches may arise that provide targeted relief of IBS symptoms and may even help to treat the underlying disease itself. The editorial summarizes new treatment approaches and diagnostic tools and points to further developments that are necessary to advance patient care.

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**Key words:** Irritable Bowel Syndrome; Serotonin (5-HT); Inflammation; Drug development; Clinical trials

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### REVIEW

Irritable bowel syndrome (IBS) is a functional bowel disorder (FBD) with a high but variable prevalence of 2-20% in the general population<sup>[1]</sup>. Our lack of knowledge of the underlying pathophysiology and varying presentation of symptoms has made classification, differential diagnosis, and treatment of IBS a challenge for the medical community. IBS is often classified according to

the predominant symptoms of intestinal transit time (diarrhea, constipation, or mixed) and accompanying symptoms of abdominal pain or discomfort, bloating, and distension<sup>[2]</sup>. Several factors have been identified that may exaggerate symptoms such as menses in women, stress, gastrointestinal infections (especially post-infectious IBS), and diet<sup>[3]</sup>.

Since it appears that there are a number of factors involved in the development and symptom severity of IBS, diagnostic and treatment approaches have to be tailored to the needs of the patient. This often challenges the healthcare professional when evaluating and providing the best care for a patient with IBS since severity and alterations in symptom range can vary significantly with infrequent relapses that can involve opposite symptom representations<sup>[4]</sup>. It is therefore critical to have the best treatment options available and to be aware of emerging diagnostic criteria that aid in the process of identifying and distinguishing IBS patients from other FBD patients.

Recent advances in the diagnosis of IBS include the identification of potential biomarkers in the intestinal lumen as well as in serum<sup>[5]</sup>. One prominent hypothesis that has been supported by research is the involvement of low-grade intestinal inflammation in the development and symptom severity of IBS as demonstrated by several smaller studies that indicate an increase in mast cells, intraepithelial lymphocytes, and cytokines (mainly decreased levels of anti-inflammatory interleukin-10 and increased levels of several pro-inflammatory cytokines such as tumor necrosis factor alpha, interleukin-8, interleukin-6, and interleukin-1 beta)<sup>[6]</sup>. Although this has triggered new research especially in regards to the use of anti-inflammatory agents such as mesalazine for the treatment of IBS symptoms, there is considerable variability and inconsistency in regards to the validity of the above-mentioned biomarkers since they are non-specific for IBS.

Another interesting and established hypothesis for the underlying pathophysiology of IBS relates to a dysfunctional brain-gut axis represented in part by the enteric nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. It has been shown that several biomarkers are altered in IBS that relate to the HPA axis (increased cortisol levels in serum) and to the enteric nervous system (serotonin transporter gene and toll-like receptor gene polymorphisms)<sup>[4]</sup>. It has recently been demonstrated that IBS patients present with an altered tryptophan metabolism that is mediated via toll-like receptor activation<sup>[7]</sup>. Despite these correlations, these biomarkers provide limited use in the diagnosis of IBS since they are

similarly non-specific like the intestinal biomarkers. However, altered tryptophan metabolism appears to be an evolving biomarker for the differential diagnosis of IBS.

In contrast to patients with no prior history of intestinal infections, the subpopulation of post-infectious IBS (PI-IBS) patients shows a more consistent pattern for diagnosis and treatment if patient history is carefully evaluated<sup>[8]</sup>. Since there is evidence of an imbalance in the intestinal microflora in IBS patients<sup>[9]</sup>, certain supplement treatments containing probiotic bacterial strains may provide benefits in alleviating symptoms. Furthermore, it has been shown that certain bacterial strains are more prevalent in IBS and IBD populations<sup>[10]</sup> which can be utilized as a general diagnostic tool.

The current diagnostic criteria of choice remain symptom-based evaluation and patient history with exclusion of other FBDs for the differential diagnosis of IBS. There are attempts to restructure the evaluation of IBS as a positive and not an exclusion-based diagnosis<sup>[11]</sup> although most physicians still conduct a battery of tests to minimize missing another diagnosis.

Based on research focusing on the pathophysiology of IBS, a number of new treatment approaches are being evaluated in preclinical and clinical stages. The most common treatment approaches remain symptomatic with anti-diarrheals (opioid agonists, high fiber supplements), anti-spasmodics (anticholinergic agents), and motility-altering drugs (5-HT<sub>3</sub> receptor antagonists for IBS-D and 5-HT<sub>4</sub> receptor agonists for IBS-C)<sup>[6]</sup>. Visceral pain reduction is mainly accomplished through administration of the  $\gamma$ -aminobutyric acid (GABA) receptor modulator drug class of the benzodiazepines<sup>[6]</sup>. In recent years, there have been a number of drug introductions that are more targeted in reducing symptoms specific to IBS, such as the chlorine channel agonists (lubiprostone and linaclotide) that reduce intestinal transit time and the neurokinin receptor antagonists (aprepitant and nepadutant)<sup>[6]</sup>. In addition, asimadoline, a  $\kappa$ -opioid receptor agonist, has shown some effectiveness in reducing pain sensation and discomfort.

A number of new treatments are currently in development for both visceral pain reduction and intestinal motility in IBS. A glucagon-like peptide, ROSE-010, showed some promising results in patients with IBS-C in reducing pain sensation and discomfort<sup>[12]</sup> but further studies are necessary to support the effectiveness of the drug. Another drug, the neurokinin receptor 1 antagonist AV608, decreased pain sensitivity and increased mood in a pilot study including women with IBS-D<sup>[13]</sup>. This further provides evidence for the involvement of neurokinin receptors and related signaling pathways in the pain sensation associated with IBS. An interesting development has been the use of a spherical carbon adsorbent, AST-120, to reduce pain and bloating in IBS-D patients<sup>[14]</sup>. The effect of this adsorbent to reduce IBS-D symptoms at least temporarily has been postulated to be mediated through adsorption of histamine and serotonin from the intestinal lumen and thereby prevent these mediators from triggering hypersensitivity and increased motility in the intestinal tract.

The clinical data so far for these new treatment approaches is limited to only a few studies, in many cases small clinical trials. All novel treatment approaches are symptom-based and therefore can only provide limited relief of the underlying condition. It has been proposed to consider fecal microbiota transplantation for patients with severe IBS as it has shown good success rates in eradicating *Clostridium difficile* infections in the past<sup>[15]</sup>. This points to common supportive treatment approaches that consider lifestyle changes, elimination diets, and the supplementation with probiotic bacterial strains to support a normalized intestinal microbiota<sup>[16]</sup>. Because of the ineffectiveness of pharmacological treatment approaches for many IBS patients, the use of complementary and alternative treatments remains very high

in this population of patients<sup>[16]</sup>. The main research for IBS patients should focus on better diagnostic criteria in association with a better understanding of the underlying pathophysiology of IBS that can aid in the development of new treatment approaches.

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