

Irritable Bowel Syndrome (IBS) At a Glance

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ABSTRACT

Irritable bowel syndrome (IBS) is a common disorder characterized by abdominal pain and altered bowel habit. Hence, IBS is associated with a significantly impaired health-related quality of life (HRQOL) and reduced work productivity around the world. The incidence of IBS is rising dramatically worldwide. Currently, 7 – 10 % of people have IBS worldwide and it is 1.5 times more prevalent in younger women than in men. Much research has been undertaken during the past several decades, which has led to deep understanding about IBS, particularly the pathogenesis and management. This review summarizes the epidemiology, underlying pathophysiology, diagnosis and treatment about IBS that has been published in recent years. We hope this review can help to provide some reference in clinical practice for physicians in the management of IBS.

KEYWORDS

IBS, Spastic Bowel syndrome, Nervous Bowel, Irritable colon, Splenic Flexure Syndrome, Functional Bowel Disease

Introduction :

Irritable bowel syndrome (IBS) is a common disorder characterized by abdominal pain and altered bowel habit for at least three months.⁽¹⁾

IBS is further defined depending on the predominant bowel symptom: IBS with constipation (IBS-C) or IBS with diarrhoea (IBS-D). Those not classified as either IBS-C or IBS-D are considered as mixed IBS (IBS-M). Alternating IBS (IBS-A) defines patients whose bowel habits oscillate from diarrhoea to constipation and vice versa.

Synonyms: Spastic Bowel syndrome, Nervous Bowel, Irritable colon, mucous colitis, Splenic Flexure Syndrome, Functional Bowel Disease.⁽²⁾

Epidemiology:

IBS is a prevalent and expensive condition that is associated with a significantly impaired health-related quality of life (HRQOL) and reduced work productivity. IBS care consumes over \$ 20 billion in both direct and indirect expenditures. Moreover, patients with IBS consume over 50% more health care resources than matched controls without IBS.⁽¹⁾ Based on strict criteria, 7 – 10 % of people have IBS worldwide. Community-based data indicate that diarrhoea-predominant IBS (IBS-D) and mixed IBS (IBS-M) subtypes are more prevalent than constipation-predominant IBS (IBS-C), and that switching among subtype groups may occur. IBS is 1.5 times more common in women than in men, is more common in lower socioeconomic groups, and is more commonly diagnosed

in patients younger than 50 years of age. Prevalence estimates of IBS range from 1 % to more than 20% in North America (7%).⁽¹⁾ In Asia the prevalence is about 5%.^(3,4,5) Recently, a School-Based Study in china reported the prevalence of IBS in adolescents and children was 13.25% and the ratio of boys to girls was 1:1.8.⁽⁶⁾ Most patient with IBS in India are middle-aged men (mean age 39.4 years).⁽⁷⁾

Underlying pathophysiology:

Given the lack of definitive organic markers for IBS, the absence of a consolidated hypothesis regarding its underlying pathophysiology is not surprising. Nevertheless, important advances in research made during the past 50 years have brought us closer than ever to understanding the numerous existing aetiological factors involved in this multifaceted disorder, including environmental factors, genetic factors, previous infection, food intolerance, and abnormal serotonergic signaling in the GI tract.

Environmental factors :

The biopsychosocial model proposed by Engel⁽⁸⁾ takes into account the interplay between biologic, psychological, and social factors. This model proposes that there is an underlying biologic predisposition for IBS that may be acted on by environmental factors and psychological stressors, which contribute to disease development, the patient's perception of illness, and impact on treatment outcomes. Different studies have shown that stress can result in release of stress-related hormones that affect colonic sensorimotor function (eg,

corticotropin-releasing factor [CRF] and inflammatory mediators [eg, interleukin (IL)-1]), leading to inflammation and altering GI motility and sensation.

Genetics factors :

Twin studies have shown that IBS is twice as prevalent in monozygotic twins than in dizygotic twins.^(9,10,11) IBS may be associated with selected gene polymorphisms, including those in IL-10, G-protein GNB3, alpha adrenoceptor, and serotonin reuptake transporter (SERT).

Post-infectious IBS (PI-IBS):

Culture positive gastroenteritis is a very strong risk factor for IBS. Different prospective studies show IBS symptoms developed in 7% to 32% of patients after they recovered from bacterial gastroenteritis.^(12,13,14) Specific risk factors for the development of PI-IBS have been identified, including younger age, female sex, presence of severe infectious gastroenteritis for a prolonged period, use of antibiotics to treat this infection, and presence of concomitant psychological disorders (eg, anxiety).^(12,13,15,16)

Small Intestinal bacterial overgrowth

Pimentel and colleagues^(17,18) have shown that, when measured by the lactose hydrogen breath test (LHBT), small intestinal bacterial overgrowth (SIBO) has been detected in 78% to 84% of patients with IBS. Hence, a higher than usual population of bacteria in the small intestine has been proposed as a potential aetiological factor in IBS. While another study involving a review for the presence of gastrointestinal-related symptoms (including IBS) has shown that a sensitivity of the LHBT for SIBO has been shown to be as low as 16.7%, and specificity approximately 70% and the test alone for small intestinal bacterial overgrowth were poor. Hence, combination with scintigraphy resulted in 100% specificity to assess the treatment response, because double peaks in serial breath hydrogen concentrations may occur as a result of lactulose fermentation by cecal bacteria.^(19,20)

Food intolerance :

Approximately 60% of IBS patients believe and different studies show that allergy to certain foods could trigger IBS symptoms. Recent research involving exclusion of foods patients had immunoglobulin (Ig) G antibodies, which are associated with a more delayed response after antigen exposure than IgE antibodies, resulted in significantly better symptom improvement than in patients in the non-exclusion group.⁽²¹⁾

Serotonin signaling in Gastrointestinal (GI) tract:

Normal gut physiology is predicated to be an interaction between the GI musculature and the autonomic nervous system (ANS), and central nervous system (CNS) by the

neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) . Impairment in this interaction affects GI motility, secretion, and visceral sensitivity leading to the symptoms associated with IBS.⁽²²⁾

Preliminary steps toward making a positive diagnosis of IBS:

A careful history and physical examination are frequently helpful in establishing the diagnosis. A variety of criteria have been developed to identify a combination of symptoms to diagnose IBS. Different guidelines from different studies help in making a positive diagnosis of IBS based primarily on the pattern and nature of symptoms, without the need for excessive laboratory testing. In 1978, Manning and colleagues^(23,24) proposed diagnostic criteria for IBS that were found to have a reasonable sensitivity of 78% and a specificity of 72%.⁽¹⁾ In 1984, Kruis and colleagues developed another diagnostic criteria with a high sensitivity of 77% and a specificity 89%. Likewise, in 1990 Rome I⁽²⁵⁾ criteria came with a sensitivity of 71% and specificity of 85%. RomeII(1999)⁽²⁶⁾ and Rome III(2006)⁽²⁷⁾ have not been evaluated yet. None of the symptom based diagnostic criteria have been evaluated and ideal reliability found.⁽¹⁾

Summary of diagnostic criteria used to define IBS:⁽¹⁾

In 1978, Manning defined IBS as a collection of symptoms, given below, but did not describe their duration. The number of symptoms that need to be present to diagnose IBS was also not reported in the paper, but a threshold of three positive is the most commonly used:

- a) Abdominal pain relieved by defecation
- b) More frequent stools with onset of pain
- c) Looser stools with onset of pain
- d) Mucus per rectum
- e) Feeling of incomplete emptying
- f) Patient-reported visible abdominal distension

Kruis in 1984, defined IBS by a logistic regression model that describes the probability of IBS. Symptoms need to be present for more than two years. Symptoms are as follows:

- a) Abdominal pain, flatulence, or bowel irregularity
- b) Description of character and severity of abdominal pain
- c) Alternating constipation and diarrhea

Signs that exclude IBS (each determined by the physician) :

- a) Abnormal physical findings and/or history pathognomonic for any diagnosis other than IBS
- b) Erythrocyte sedimentation rate >20 mm/2 h
- c) Leukocytosis >10,000/cc
- d) Anaemia (Hemoglobin < 12 for women or < 14 for men)
- e) Impression, the physician could perform a PR and see blood or the patient may report it.

Again in 1990, Rome I defined IBS as abdominal pain or discomfort relieved with defecation, or associated with a change in stool frequency or consistency, PLUS two or more of the

following symptoms on at least 25% of occasions or days for three months:

- a) Altered stool frequency
- b) Altered stool form
- c) Altered stool passage
- d) Passage of mucus
- e) Bloating or distension

Rome II, in 1999, redefined the criteria as abdominal discomfort or pain that has two of three features for 12 weeks (need not be consecutive) in the last one year.

- a) Relieved with defecation
- b) Onset associated with a change in frequency of stool
- c) Onset associated with a change in form of stool

Recently, Rome III (2006) defined IBS as recurrent abdominal pain or discomfort three days per month in the last three months associated with two or more of:

- a) Improvement with defecation
- b) Onset associated with a change in frequency of stool
- c) Onset associated with a change in form of stool

The role of routine diagnostic investigation in patients with IBS:

Routine diagnostic investigation is based on the age of the patient, family history of selected organic diseases including colorectal cancer, inflammatory bowel disease (IBD), coeliac sprue and the presence of 'alarm' features (table 1), such as rectal bleeding, weight loss, iron deficiency anaemia and nocturnal symptoms.⁽¹⁾ In patient with typical IBS symptoms and no alarm features, routine diagnostic investigation (complete blood count, serum chemistry, thyroid function tests, stool for ova and parasites and abdominal imaging) is not recommended⁽¹⁾ because of a low likelihood of uncovering organic disease.

Table-1 Lists of alarm features:

Rectal bleeding
Weight loss
Iron deficiency anaemia
Nocturnal symptoms: abdominal pain
family history of selected organic diseases: colorectal cancer, Inflammatory Bowel Disease (IBD), coeliac sprue

Summary of diagnostic investigation in patient with IBS : ^(1,2)

Diagnostic Investigations :

Routine serologic screening for coeliac sprue for patients with IBS-D and IBS-M.

Lactose Breath test done in lactose maldigestion despite dietary modification.

Colonoscopic Imaging done in IBS patient (>50 yrs age) with alarm feature to rule out organic diseases and screening of colorectal cancer.

Colonoscopy with random biopsies taken in IBS-D to rule out microscopic colitis.

Management of IBS:

The goal of IBS management is to provide relief of symptoms and improve overall well-being.⁽²⁸⁾ Most studies use a combination therapy including patient education and psychological therapies, diet and fibre therapy along with different types of new emerging pharmacological therapies.

Patient education and psychological therapies:

The majority of patients with IBS have anxiety, depression and features of somatization. Psychological therapies, including cognitive behavioral therapy, dynamic psychotherapy, hypnotherapy⁽¹⁾ shed new light on the management of patients with IBS. The outcome of psychological therapies is improved when delivered by a trained professional (physician, occupational therapist, nurse).⁽²⁹⁾ A study by Guthrie⁽³⁰⁾ showed that psychological therapy is feasible and effective in two thirds of patients with IBS who do not respond to standard medical treatment.

Role of diet in IBS:

The concept of food intolerance and the consequent elimination of certain foods from the diet benefit symptoms of IBS. However, there is no sufficient evidence to support this.⁽¹⁾

Therapeutic effect of dietary fibre, bulking agents and laxatives: The quality of evidence supporting the recommended use of dietary fibre or bulking agents to regularize bowel function is poor.⁽³¹⁾ Ispaghula husk (Psyllium hydrophilic mucilloid) and calcium polycarbophil are moderately effective and can be given a conditional recommendation because of the weakest type of evidence.⁽¹⁾ Polyethylene glycol (PEG) laxative has a role in improving stool frequency but no effect on abdominal pain. Different clinical studies and expert opinion suggest that increased fibre intake may cause bloating, abdominal distension and flatulence.⁽³²⁾ So gradual adjustment of dose is advised for the use of these agents.

Therapeutic effect of antispasmodic agents including peppermint oil:

Certain antispasmodics (hyoscine, cimetropium, and pinaverium and peppermint oil) may provide short-term relief of abdominal pain/discomfort in IBS.^(33,34) Evidence for safety and tolerability.

Agent	Mechanism of action	Targeted disorder	Clinical status
Crofelemer	CFTR	IBS-D	Phase 2b complete
Linaclotide	Guanylate cyclase-c agonist	IBS-C	Phase 3
Arverapamil	Calcium channel blocker	IBS-D	Phase 3
Asimadoline	Kappa opioid agonist	IBS	Phase 2b complete
Mitemincinal	Motilin receptor agonist	IBS-C	Phase 2
Ramosetron	5-HT ₃ antagonist	IBS-D	Phase 3
TD-5108	5-HT ₄ agonist	IBS-C	Phase 2
DDP-773	5-HT ₃ agonist	IBS-C	Phase 2
DDP-225	5-HT ₃ antagonist and NE reuptake inhibition	IBS-D	Phase 2
BMS-562086	Corticotropin-releasing hormone antagonist	IBS-D	Phase 2
GW876008	Corticotropin-releasing hormone antagonist	IBS	Phase 2
GTP-010	Glucagon-like peptide	IBS pain	Phase 2
AGN-203818	Alpha receptor agonist	IBS pain	Phase 2
Solabegron	Beta-3 receptor agonist	IBS	Phase 2
Espindolol (AGI-011)	Beta receptor antagonist	IBS (all subtypes)	Phase 2
Dextofisopam	2,3 benzodiazepinereceptors	IBS-D and IBS-M	Phase 3

Table 1: Source: ACG Task Force on IBS(2009)

of these agents are very limited. The commonest adverse effects are dry mouth, dizziness and blurred vision.⁽³⁴⁻³⁶⁾

Therapeutic effect of anti-diarrhoeal medications:

The anti-diarrhoeal agent 'Loperamide' is effective at slowing down colonic transit and improving stool consistency for the treatment of IBS-D with no severe adverse effects.⁽³⁷⁾ But safety and tolerability data are still lacking in many studies.

Therapeutic effect of antibiotics:

Many studies show well tolerance of a short term course of non-absorbable antibiotics (Rifaximin) is most effective for improvement of global symptoms in IBS-D and IBS patient with the predominant symptom of bloating and other associated symptoms, such as diarrhoea and abdominal pain.⁽³⁸⁻⁴⁰⁾ While, the United States Food and Drug Administration (FDA or USFDA) approved Rifaximin for treatment of traveler's diarrhoea. Other antibiotics, Neomycin⁽⁴¹⁾, Clarithromycin and Metronidazole⁽⁴²⁾ have been well evaluated for the management of IBS.

Therapeutic effect of Probiotics:

Probiotics have a large number of properties that can benefit IBS. Bifidobacteria is the active agent in probiotic combination therapy. Whereas many studies show Lactobacilli to have no impact on symptoms.⁽⁴³⁾ But one Korean study concluded that the composite probiotics containing Bifidobacterium bifidum BGN4, Lactobacillus acidophilus AD031, and other species are safe and effective, especially in patients who excrete

normal or loose stools.⁽⁴⁴⁾ Recently, P Moayyedi and colleague in their systematic review recommend that probiotics appear to be efficacious in IBS patients, but the magnitude of benefit and the most effective species and strain are uncertain.⁽⁴⁵⁾

Therapeutic effect of the 5HT₃ receptor antagonists:

Alosetron (5-HT₃ receptor antagonists), with dosage of 0.5 to 1 mg daily, is more effective and the commonest drug used for treatment of patients with IBS-D in spite of serious side effects including constipation and colon ischemia. The balance model of benefits and harms for 'Alosetron' is most encouraging in women who have not responded to conventional therapies.^(46,47)

Therapeutic effect of 5-HT₄ receptor agonists:

Tegaserod (5-HT₄ receptor agonist) is more effective for the treatment of IBS-C mostly in female and IBS-M. The side effects reported among the patient receiving Tegaserod are diarrhoea (commonest), cardiovascular events i.e. myocardial infarction, unstable angina, or stroke.^(48,49) Currently Tegaserod is available from FDA through an emergency investigational new drug protocol. Other 5-HT₄ agonists (Cisapride, Renzapride) have not demonstrated improvement compared with placebo.^(50,51)

Therapeutic effect of the selective C-2 chloride channel activators:

Lubiprostone (selective C-2 chloride channel activator) is effective for relieving symptoms of IBS-C, mostly in women,

and has less frequent side-effects including nausea(8%), diarrhea(6%) and abdominal pain(5%).⁽⁵²⁾

Therapeutic effect of antidepressants :

Patients with prominent symptom of abdominal pain in IBS that fails to respond to peripherally acting agents often are considered for treatment with antidepressants (TCAs and SSRIs), however, limited data on safety and tolerability of these agents is shown.⁽⁵³⁾ Antidepressants have the combined effect of both central and peripheral mechanism in IBS.⁽⁵⁴⁾ SSRIs are better tolerated than TCAs and have a prokinetic effect hence work better in IBS-C.^(53,55) whereas TCAs are of greater benefit for IBS-D.

Therapeutic effect of herbal therapies and acupuncture:

Unique Chinese herbal mixtures show a benefit in IBS management.⁽⁵⁶⁾ Traditional Chinese herbal remedies are routinely used in China to treat the condition, but so far have not been generally accepted by conventional Western medicine.^(56,57) Bensoussan and colleague in one randomized, double-blind, placebo-controlled trial concluded that the Chinese herbal formulations appear to offer improvement in symptoms for some patients with IBS.⁽⁵⁷⁾ A systematic review of different trials of acupuncture was inconclusive because of heterogenous outcomes.^(58,59) Hence further work is needed before any recommendations on acupuncture or herbal mixtures therapy.

Emerging therapies :

The improved understanding of underlying mechanisms in IBS is beneficial for the development of new pharmacological treatment options.

A brief overview of emerging agents in IBS therapy summarized in Table 1 ⁽¹⁾

Conclusion:

IBS is a true medical disorder that has significant impact on those in agony with regard to symptom severity, disability, and impaired quality of life, which exceeds that of most GI disorders. Advances in research over the past several decades have paved the way for an ameliorable understanding of the underlying pathophysiology and standardized symptom-based approaches that can be implemented in making a positive diagnosis and development of innovative treatment options for multiple IBS symptoms. Although many unanswered questions remain, the progress is promising and it has equipped physicians better to efficiently diagnose IBS and choose from a growing armamentarium of treatment options.

Competing Interests

None declared

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