

Irritable Bowel Syndrome

Diagnosis/Condition: Irritable Bowel Syndrome

(IBS)

spastic colon

Other symptoms involving

digestive system

Discipline: ND, LAc

 ICD-10 Codes:
 K58.9; R19.4; R19.8

 Origination Date:
 2011

Review/Revised Date: 04/2023 Next Review Date: 04/2025

Irritable bowel syndrome (IBS) is the most common diagnosed gastrointestinal condition in the United States (U.S.) It is characterized by chronic altered bowel habits and abdominal discomfort or pain (in the absence of a known organic cause). Prevalence of IBS in North America is estimated to be 10 -20%.¹ Younger patients and women are more likely to be diagnosed with IBS and a systematic review suggests there is an overall 2:1 female predominance in North America.² Only about 15% of those affected seek medical attention, yet IBS still constitutes 25-50% of all gastroenterologist referrals³ and is the highest cause of work absenteeism after upper respiratory infections (colds).⁴ Patients with IBS have more frequent medical visits, have more diagnostic tests, prescribed more medications, miss more workdays, have lower work productivity, hospitalized more often, and consume more overall direct costs than patients without IBS. Resource utilization is highest in patients with severe symptoms, and poor health-related quality of life (HRQOL).⁵ Some studies suggest annual direct/indirect costs of up to \$30 billion.⁶ There are many comorbidities associated with IBS, including anxiety, depression, somatization, fibromyalgia, chronic fatigue, chronic pelvic pain, interstitial cystitis, sexual dysfunction and sleep disturbances. The treatment of pain in IBS remains a challenge.⁵

The pathophysiology and cause of IBS is incompletely understood.⁸ Current research indicates that pathology involves the interaction of gut-brain immune, inflammatory, and hormonal interaction, and the multifactorial nature is evident including environmental and host factors.^{9,10,11} Three primary factors have been observed: 1) psychosocial, 2) altered intestinal motility, and 3) altered bowel sensations.¹² Recent research suggests other possible etiologies, most notably neuro-hormonal dysfunction between the CNS and the 'gut' leading to inflammatory and immune-modulated reactions of the 'brain-gut axis".¹³ Other areas of investigation that have garnered attention include alterations within intestinal microbial flora and serotonin modulation.^{14,15,16} In addition, several precipitating factors have been identified, including gender (female), family history (genetics), infection¹⁷, mucosal barrier disruptions, and a history of gastroenteritis or bowel movement disorders.^{18,19,20}

Subjective Findings and History

- Abdominal discomfort or pain with altered bowel habits (constipation, diarrhea, or alternating constipation and diarrhea) that is accompanied by at least two of the following: relief by defecation, change in frequency of stool, or change in consistency of stool.
- Abdominal pain severity, location, and character can vary. Symptoms may be triggered by food, particularly fats, or by stress.
- Other upper gastrointestinal (GI) symptoms may be associated: mucous discharge with stools, bloating, feeling of incomplete evacuation, straining, post-prandial urgency, gastroesophageal reflux (GERD), dysphagia, early satiety, intermittent dyspepsia, nausea, non-cardiac chest pain, abdominal bloating, increased gas production with flatulence or belching, abnormal stool frequency (≤3 bowel movements per week or >3 bowel movements per day), and abnormal stool form (lumpy/hard or loose/watery).
- Associated non-GI symptoms: sexual dysfunction, dysmenorrhea, dyspareunia, increased urinary frequency and urgency, and fibromyalgia symptoms.
- A subgroup of patients have a history of acute viral or bacterial gastroenteritis, which then leads to a subsequent disorder characteristic of diarrhea-predominant IBS (postinfectious IBS).
- Symptom onset at least 6 months prior to diagnosis.

Diagnosis and Differential Diagnosis

Symptom based criteria are used as a standard diagnostic tool.

The Manning Criteria was developed in 1978 and is a formulation of a symptom complex associated with IBS. The predictive ability of this criteria is conflicting.²¹

Manning Criteria for the diagnosis of IBS

- Sensation of incomplete evacuation.
- Pain relieved with defecation.
- More frequent stools at the onset of pain.
- Looser stools at the onset of pain.
- Noticeable abdominal distention.
- Passage of mucus with stool.

The Rome Criteria is a consensus definition that was created in 1992, revised in 2005 and again in 2016 in order to standardize clinical research protocols.^{22,23,24}

The ROME IV criteria suggest categorization of the syndrome into four sub-types: 1) IBS with constipation (IBS-C), 2) IBS with diarrhea (IBS-D), 3) mixed IBS, and 4) unclassified IBS and includes recurrent abdominal pain or discomfort at least 1 day per week in the last 3 months associated with 2 or more of the following criteria:

- Related to defecation.
- Onset associated with a change in frequency of stool.
- Onset associated with a change in form (appearance) of stool.

Current guidelines recommend suspicion of IBS *only* if a patient presents with abdominal pain that is either:²⁵

- 1. Relieved by defecation.
- 2. Associated with altered bowel frequency or stool form.

The presenting conditions should be accompanied by at least two of the following:

- 1. Altered stool passage (e.g., urgency or incomplete sensation).
- 2. Abdominal bloating, distension, tension, or hardness.
- 3. Symptoms made worse by eating.
- 4. Passage of mucus with stool.

In comparison to the above ROME IV criteria, (common in research, but less utilized in clinical practice), other diagnostic criteria are also suggested.²⁶

Three categories are based on symptoms:

- 1. IBS with predominant bowel dysfunction.
- 2. IBS with predominant pain.
- 3. IBS with predominant bloating.

Three additional categories are based on etiology:

- 1. Post-infectious IBS.
- 2. Food induced IBS.
- 3. Stress-induced IBS.

The American Gastroenterological Association (AGA) recommends that the diagnosis of IBS should be based upon: "the identification of positive symptoms consistent with the condition as summarized by the Rome criteria and excluding in a cost-effective manner other conditions with similar clinical presentations".^{27,28}

According to Traditional Chinese Medicine (TCM) theory, IBS corresponds to several possible disease categories: 1) abdominal pain (*Fu Tong*); 2) diarrhea (*Xie Xie*); 3) constipation (*Bian Bi*); and 4) epigastric pain (*Wei Tong*).^{29,30} Individual symptom presentations, including bowel habits and the location and nature of pain, will determine the categories and eventual pattern differentiation for each patient.

TCM practitioners view the body in terms of *Qi*-dynamics and use unique and specific terminology. This is best summarized by the axiom "One Pattern many Diseases, one Disease many Patterns"; suggesting that identification of the correct 'pattern' (e.g., Liver qi stagnation) leads to improved patient care through the selection of pattern-specific acupuncture points. In the case

of IBS, patients are categorized as one of seven patterns, which often overlap, e.g., Liver Qi stagnation with Spleen Qi deficiency. In Chinese medicine, pain is considered to be an obstruction of qi and blood, which in turn may be due to an underlying imbalance of the viscera and bowels (zang-fu).

Objective Findings and Assessment

Patients generally appear to be healthy. May exhibit anxiety or fatigue.

Acupuncture Objective Findings

Individual symptom presentations, including tongue, pulse, and abdominal diagnosis (in addition to location and nature of pain), will determine the pattern differentiation for each patient. In the case of IBS, patients are categorized as one of seven patterns, which often overlap, e.g., Liver *Qi* stagnation with Spleen *Qi* deficiency.^{32,33} As a concrete example of this, a recent secondary analysis of 113 patients identified seven primary patterns and 8 secondary patterns; most common of which, were *Liver Qi* stagnation and *Damp-Heat*.³⁴

Physical Exam

Abdominal tenderness may be present, particularly in the left lower quadrant. Abdominal distension and increased bowel sounds may be present. There may be no significant physical findings. A digital rectal examination (DRE), and a test for occult blood, should be done on all patients. In women, a pelvic examination helps rule out ovarian tumors and cysts or endometriosis, which may mimic IBS.

Diagnostic Tests

The main goal of evaluation is to rule out more serious organic disease. Clinical testing can appraise the mechanisms responsible for symptom generation, including rectal evacuation disorders, abnormal intestinal motility, visceral hypersensitivity or hypervigilance, bile acid diarrhea, sugar intolerances, barrier dysfunction, the microbiome, and chemicals released through immune activation.³⁵

Routine laboratory studies (complete blood count (CBC), blood chemistries, thyroid, ESR, Ca²⁺⁾ are normal in IBS. They are not recommended unless warranted by other symptoms. A more extensive evaluation should be considered in patients who have had a change or progression of symptoms, do not respond to general treatment measures, or have "alarm" symptoms.

"Alarm" or atypical symptoms, which are not compatible with IBS, include: Rectal bleeding, nocturnal or progressive abdominal pain, fever(s), weight loss, laboratory abnormalities such as anemia, elevated inflammatory markers, or electrolyte disturbances. Patients with these symptoms should be considered for additional testing.

- In those with <u>diarrhea</u> as the predominant symptom:
 - Stool cultures for enteropathogens, and tests to rule out *Giardia and other* parasites if there is suspected exposure.
 - Celiac disease screening with serum IgA antibody to tissue transglutaminase should be performed.
 - Twenty-four-hour stool evaluation should be considered if osmotic or secretory diarrhea or malabsorption is suspected.
 - Colonoscopy or flexible sigmoidoscopy and biopsy. Many causes of chronic diarrhea such as microscopic colitis require endoscopic evaluation.
 - Occult blood testing.
- In those with <u>constipation</u> as predominant symptom:
 - Radiography of the abdomen can detect retained stool and suggest the diagnosis of constipation.
 - Flexible sigmoidoscopy and colonoscopy. Sigmoidoscopy or colonoscopy should be performed if a structural lesion is suspected. Colonoscopy is preferred in patients who are older than 50 because of the increased risk of colon cancer in this age group.
 - Occult blood testing.
- <u>Mixed IBS</u> In patients with <u>both diarrhea and constipation</u>, screening should be performed based on medical history and other symptoms reported.
- Lactose breath testing can be considered when lactose maldigestion remains a concern despite dietary modification.
- Psychosocial Factors: Assess mental health history and symptoms. Because of the
 positive correlation between abuse and certain GI illness patterns, patients with
 refractory or severe IBS should be questioned about physical and sexual abuse. Some
 patients may have sleep disturbance, anxiety disorders, depression, or a somatization
 disorder. However, stress and emotional conflict do not always coincide with symptom
 onset and recurrence.

Plan

It is clear that there are multifactorial causes and presentations of IBS, and treatment needs to be directed at the individual presentation.

Naturopathic:³⁶

Lifestyle and Dietary Modifications^{37,38,39}

- Treatment is individualized and directed at specific symptoms.⁴⁰
- Education about IBS to establish appropriate therapeutic goals (e.g., expectations regarding the normal course or variability in symptoms, adverse effects of drugs, the appropriate working relationship between the doctor and the patient) should be established.
- There can be a risk of nutritional deficiencies with restrictive diets which must be taken into consideration and monitored. 41,42

- Avoid gas-producing and diarrhea-producing foods such as beans, onions, celery, carrots, raisins, bananas, apricots, prunes, brussels sprouts, wheat germ, and simple carbohydrates. A few contemporary studies have suggested carbohydrate malabsorption as a major contributor to IBS in some cases.⁴³
- Reduce portion size and implement pace eating. Those with abdominal distention and increased flatulence may benefit from reducing or eliminating foods containing fermentable carbohydrates (beans, cabbage). Underlying visceral hyperalgesia in IBS may explain the exaggerated discomfort experienced with consumption of gasproducing foods.
- Food allergies/sensitivities The role of food allergy in IBS is unclear. Various testing
 methods for food allergies are available, although there is conflict about their reliability
 and an elimination/challenge diet is helpful to identify change in symptoms.⁴⁴
- Gluten sensitivity Gluten sensitivity (without overt celiac disease) has been proposed
 as a cause of functional bowel disorders and an elimination/challenge diet may help to
 decipher this condition.^{45,46}
- Reduced intake of sweeteners (e.g., sorbitol, mannitol, fructose) and ethyl alcohols, which are constituents of natural and processed foods (e.g., apple and grape juice, bananas, nuts, and raisins). This may decrease flatulence, bloating, and diarrhea.⁴⁷
 Patients with evidence of lactose intolerance should reduce their intake of milk and dairy products.⁴⁸ A lower-fat diet may reduce postprandial abdominal symptoms.⁴⁹
- Restricting rapidly fermentable, short-chain carbohydrates (Fermentable Oligo-, Di- and Monosaccharides and Polyols or FODMAPs).^{50,51,52,53,54,55}
- Increased fiber intake (primarily for constipation). Dietary fiber supplements may soften stool and improve the ease of evacuation. A bulk-producing agent may be used supplemented with increased fluid intake. Alternatively, psyllium (natural) with excess water may be used. However, excessive use of fiber can lead to bloating and diarrhea, so fiber doses must be individualized. Occasionally, flatulence may be reduced by switching to a synthetic fiber preparation (e.g., methylcellulose). 56,57
- Psychologic stress, anxiety, or mood disorders should be identified, evaluated, and treated.
- Behavioral or mental health therapy. Cognitive-behavioral therapy, standard psychotherapy, biofeedback, and hypnotherapy^{58,59,60,61} may help selected IBS patients to help reduce anxiety levels, encourage health promoting behavior, increase patient responsibility and involvement, and improve pain tolerance.⁶²
- Relaxation techniques (yoga, meditation, deep breathing, progressive muscle relaxation, visualization).^{63,64}
- Regular physical activity helps relieve stress and assists in bowel function, particularly in patients with constipation.^{65,}
- Multi-component therapy incorporates elements of education, relaxation therapy, biofeedback, mediation,⁶⁶ and cognitive therapy or psychotherapy. Several studies have been done with these criteria in mind.^{67,68,69}
- Manipulative medicine.⁷⁰

- Homeopathy.^{71,72}
- Fecal Microbiome transplant (FMT).73,74,75,76,77
- Evaluation of gut microbial dysbiosis.^{78,79}

Supplementation or Nutraceuticals:80,81

- Preliminary data suggest that certain pre/probiotics (e.g., *Bifidobacterium infantis, Lactobacillus rhamnosus GG*) improve IBS symptoms, particularly bloating. Studies on specific strains are not conclusive. 82,83,84,85,86,87,88
- Some aromatic oils (carminatives) can relax smooth muscle and relieve pain caused by cramps in some patients. Peppermint oil, ginger, and fennel are the most common used agents in this class, but peppermint can also exacerbate GERD.
- Curcuma sp. (Turmeric), Cynara scolymus (artichoke leaf), Fumaria officinalis, Hypericum perforatum (St John's wort), Maranta arundinacea (Arrowroot), Mentha × piperita (peppermint oil), 89,90,91,92 Plantago psyllium.93
- Chinese herbs (Tong xie yao fang (TXYF), STW 5 and STW 5–II). 94,95
- Carmint (an Iranian herbal medicine containing total extracts of *Melissa officinalis*, *Mentha spicata*, and *Coriandrum sativum*).⁹⁶
- A Tibetan herbal digestive formula known as Padma Lax.⁹⁷
- STW 5 (Iberogast). 98,99
- C-IBS and DA-IBS formulations. 100
 - o Gwakhyangjeonggisan (GJS).¹⁰¹
 - o Tongxiening.¹⁰²
 - o Glutamine 1000-3000 mg per meal.
 - HCl with meals if indicated, enzymatic support from plant-based enzymes or true pancreatic enzymes with or after meals, probiotics and maybe specifically, saccromyces boulardii twice daily for a month or two or three.
 - o With lots of mucus, Sea-cure and colostrum have been used.
- Slippery elm tea or products with that and marshmallow and licorice may be indicated.
- Glutamine supplementation for IBS-D.¹⁰³
- Western botanical medicines have been extensively and reviewed in several research metanalyses.^{104,105,106}
- Boswellic acids. 107
- Soy isoflavones.¹⁰⁸
- Vitamin D supplementation. 109,110
- Resveratrol and other bisphenol rich products.¹¹¹
- Fiber supplements and probiotics. 112,113

Acupuncture and Traditional East Asian Medicine:

 Guidelines from the World Gastroenterology Organization include the suggestion that acupuncture may be a valuable component of the multi-modal approach to care.^{114,115}

- As a generalization, IBS involves an aspect of internal disharmony, especially within the
 Liver system and inclusion of acupuncture points to address this imbalance is of
 importance.
- Both local (abdominal) and distal acupuncture points are most often selected as the
 primary treatment of choice, with a focus on the acupoints of the Stomach, Large
 Intestine and Liver channels. Frequency of treatment: Severity of symptoms will guide
 frequency of treatment.
 - The largest RCT to date (n=531) provided 18 Tx's (3x/wk.); positive effects observed starting at week 6.¹¹⁶
 - o A large scale (n=233) pragmatic trial from UK provided 10 Tx's (1x/wk.).¹¹⁷
- Whole food nutrition is important and dietary assessment is an important part of ongoing treatment.

Acupuncture Research:

Although >30 RCTs have been published, most are in Chinese; 14 are English language. 118,119,120,121,122,123,124,125,126,127,128,129,130,131 With the exception of one recent pilot study 115, the most recent systematic reviews include and summarize these trials, 132,133,134 as well as others published in Chinese and not indexed in PubMed. Based on the literature, the following conclusions can be drawn:

The evidence is promising to suggest benefit from acupuncture for the treatment of IBS; more research is required to draw definitive conclusions.

- A 2022 network meta-analysis of acupuncture (25 RCTs; n=3,041) suggests,
 "Acupuncture provided additional benefits to usual care, and it might be considered as adjunctive therapy..."
- A 2022 meta-analysis (31 RCTs; n=3,468) concluded that although the quality of evidence was variable, "...acupuncture and/or moxibustion are beneficial for symptom severity, abdominal pain and quality of life." 123
- A 2022 network meta-analysis for IBS-D (21 RCTs; n=1,626) concluded that Acupuncture [and various moxa therapies] were superior to pinaverium bromide (a medication used in China but not FDA approved) but call for more research.
- Two earlier reviews (2012 & 2019) suggest that acupuncture is more effective than medications commonly utilized in China (demonstrated to provide modest benefit for IBS: PEG 4000 & pinaverium bromide).^{135,136}

Chinese Herb Research:

- Two recent meta-analyses suggest the benefits of various herbal formulation; more research is required to draw definitive conclusions.
 - A 2021 network meta-analysis (28 RCTs; n=3,323) suggests that, "Chinese Herbal medicines could be beneficial for patients with IBS in relieving their clinical symptoms and should be recommended as alternative therapies." ¹³⁷

A 2021 network meta-analysis (28 RCTs; n=3,323) suggests that herbal formula were as effective as common anti-spasmodic medications (e.g., drotaverine), "Chinese Herbal medicines and antispasmodics were efficacious for improvement of global IBS symptoms and abdominal pain." ¹³⁸

Moxibustion:

- Two network meta-analyses (both from 2022) suggest that combining moxibustion with acupuncture leads to better effects, however the caution is warranted due to low quality trials (n=6).^{122,123}
- A 2022 meta-analysis (11 RCTs; n=725) of moxa for IBS-D suggests the results are preliminary, but promising, and but calls for more research.¹³⁹

Behavioral and cognitive approaches:

- Diet changes:¹⁴⁰
 - Some foods make IBS worse including fatty foods like French fries, milk products like cheese or ice cream, chocolate, alcohol, caffeine (found in coffee and some sodas), carbonated drinks like soda.
 - o Dietary fiber improves IBS symptoms.
 - o Eating smaller meals may improve IBS.
- Stress reduction through regular exercise, meditation, massage, yoga, or counseling.¹⁴¹
- There is some limited support for comprehensive Cognitive Behavioral Therapy (CBT) approaches^{142,143} which may include information and education, progressive muscle relaxation, training in illness-related cognitive coping strategies, problem-solving, and assertiveness training.^{144,145}

Prescription Medications:¹⁴⁶

Drug therapy is directed toward the dominant symptoms¹⁴⁷. The chronic use of prescription medications for IBS should be avoided.

- Anticholinergic/antispasmodic drugs (e.g., *hyoscyamine*, *cimetropium*, *pinaverium*) may be used for their antispasmodic effects.
- Prokinetic and prosecretory agents.¹⁴⁸
- Bile acid modulators.
- Chloride channel activator lubiprostone may help patients with constipation.
- In patients with diarrhea, anti-diarrheal medications, such as oral diphenoxylate or loperamide may be given before meals. The dose of loperamide should be titrated upward to reduce diarrhea while avoiding constipation.^{149,150,151}
- For many patients, tricyclic antidepressants (TCAs) help relieve symptoms of diarrhea, abdominal pain, and bloating. These drugs are thought to reduce pain by downregulating the activity of spinal cord and cortical afferent pathways arriving from the intestine.
- Secondary amine TCAs (e.g., nortriptyline, desipramine) are often better tolerated than parent tertiary amines (e.g., amitriptyline, imipramine, doxepin) because of fewer

anticholinergic, sedating antihistaminic, and α -adrenergic adverse effects. Treatment should begin with a very low dose of a TCA increasing as necessary and tolerated. ¹⁵²

Serotonin receptor modulation may be of benefit.
 SSRIs/SNRIs are also useful, particularly for patients with anxiety or an affective disorder, but may exacerbate diarrhea.
 Antibiotics (rifaximin).^{153,154}

Referral Criteria

- Pain associated with anorexia, malnutrition, or weight loss. This constellation is extremely rare in IBS unless there are concurrent alternate factors, such as major psychological illness.
- Pain that is progressive, awakens the patient from sleep, or prevents sleep.
- Large volume diarrhea, persistent fever, bloody stools, nocturnal diarrhea, and greasy stools are NOT associated with IBS and suggest an organic disease.
- Rectal bleeding or persistent presence of occult blood not explained by hemorrhoids.

Resources for Clinicians

Rome IV includes a section called "Twelve Steps to Enhance the Therapeutic Relationship" which is a recommended guide to partner with patients to improve treatment outcomes. Rome Foundation. What's new for Rome IV. http://theromefoundation.org/rome-iv/whats-new-for-rome-iv/.

Hookway C, Buckner S, Crosland P, Longson D. Irritable bowel syndrome in adults in primary care: summary of updated NICE guidance. *BMJ*. 2015;350(701).

Society for Acupuncture Research. Acupuncture for the Treatment of Irritable Bowel Syndrome. April 2019. www.AcupunctureResearch.org

Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. N Engl J Med. 2017;376(26):2566-2578.

<u>Defrees DN, Bailey J. Irritable Bowel Syndrome: Epidemiology, Pathophysiology, Diagnosis, and Treatment. *Prim Care.* 2017;44(4):655-671.</u>

Resources for Patients

International Foundation for Functional Gastrointestinal Disorders. About Irritable Bowel Syndrome. http://www.aboutibs.org/

Medline Plus. National Library of Medicine. Irritable Bowel Syndrome. http://www.nlm.nih.gov/medlineplus/irritablebowelsyndrome.html

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Paine P.Aliment Pharmacol Ther. 2021 Dec;54 Suppl 1:S75-S88. doi: 10.1111/apt.16550.PMID: 34927753 Review.

¹ Brandt LJ, Bjorkman D, Fennerty MB, Locke GR, Olden K, Peterson W, Quigley E, Schoenfeld P, Schuster M, Talley N. Systematic review on the management of irritable bowel syndrome in North America. *Am J Gastroenterol* 2002, 97(11 Suppl):S7-26.

² American College of Gastroenterology Task Force on Irritable Bowel Syndrome. Brandt LJ, Chey WD, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009; 104 Suppl 1:S1.

³ Everhart, JE, Renault, PF. Irritable bowel syndrome in office-based practice in the United States. *Gastroenterology* 1991; 100:998.

⁴ Schuster, MM. Diagnostic evaluation of the irritable bowel syndrome. Gastroenterol Clin North Am 1991; 20:269.

⁵ American College of Gastroenterology IBS Task Force. An Evidence-Based Position Statement on the Management of Irritable Bowel Syndrome. *Am J Gastroenterol* 2009; 104:S1.

⁶ Sandler, RS, et al. The burden of selected digestive diseases in the United States. Gastroenterology 2002; 122:1500.

⁷ Review article: current and future treatment approaches for pain in IBS.

⁸ Horwitz BJ, Fisher RS. The irritable bowel syndrome. N Engl J Med. 2001;344(24):1846-50.

⁹ Recent advances in the treatment of irritable bowel syndrome.Bonetto S, Fagoonee S, Battaglia E, Grassini M, Saracco GM, Pellicano R.Pol Arch Intern Med. 2021 Aug 30;131(7-8):709-715. doi: 10.20452/pamw.16067. Epub 2021 Aug 30.PMID: 34463082 Review.

¹⁰ Gut bless you: The microbiota-gut-brain axis in irritable bowel syndrome. Hillestad EMR, van der Meeren A, Nagaraja BH, Bjørsvik BR, Haleem N, Benitez-Paez A, Sanz Y, Hausken T, Lied GA, Lundervold A, Berentsen B.World J Gastroenterol. 2022 Jan 28;28(4):412-431. doi: 10.3748/wjg.v28.i4.412.PMID: 35125827 Review.

- ¹¹ Immune activation in irritable bowel syndrome: what is the evidence?
- Aguilera-Lizarraga J, Hussein H, Boeckxstaens GE.Nat Rev Immunol. 2022 Nov;22(11):674-686. doi: 10.1038/s41577-022-00700-9. Epub 2022 Mar 16.PMID: 35296814 Review.
- ¹² Camilleri M. Mechanisms in IBS: something old, something new, something borrowed. *Neurogastroenterol Motil*. 2005;17(3):311-6.
- ¹³ Camilleri M, Di Lorenzo C. Brain-gut axis: from basic understanding to treatment of IBS and related disorders. *Journal of pediatric gastroenterology and nutrition*. 2012;54(4):446-53
- ¹⁴ Katiraei P, Bultron G. Need for a comprehensive medical approach to the neuro-immuno-gastroenterology of irritable bowel syndrome. *World J Gastroenterol*. 2011;17(23):2791-800.
- ¹⁵ Ohman L, Simren M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nature reviews Gastroenterology & hepatology*. 2010;7(3):163-73.
- ¹⁶ Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. *Am J Gastroenterol*. 2000;95(12):3503-6.
- ¹⁷ Barbara G, Grover M, Bercik P, et al. Rome Foundation Working Team Report on Post-Infection Irritable Bowel Syndrome. *Gastroenterology*. 2019;156(1):46-58.e7.
- ¹⁸ Camilleri M, Di Lorenzo C. Brain-gut axis: from basic understanding to treatment of IBS and related disorders. *Journal of pediatric gastroenterology and nutrition*. 2012;54(4):446-53
- ¹⁹ Saito YA, Petersen GM, Larson JJ, et al. Familial aggregation of irritable bowel syndrome: a family case-control study. *Am J Gastroenterol*. 2010;105(4):833-41.
- ²⁰ Camilleri M. Evolving concepts of the pathogenesis of irritable bowel syndrome: to treat the brain or the gut? *Journal of pediatric gastroenterology and nutrition*. 2009;48 Suppl 2(S46-8.
- ²¹ Manning, AP, Thompson, WG, Heaton, KW, Morris, AF. Towards positive diagnosis of the irritable bowel. *Br Med J* 1978; 2:653.
- ²² Drossman DA, Douglas A, eds. *Rome III: The Functional Gastrointestinal Disorder*. 3rd edition ed: Degnon Associates; 2006
- ²³ Rome Foundation. Diagnostic Criteria for Functional Gastrointestinal Disorders. http://www.romecriteria.org/documents/Rome II App A.pdf (Accessed 3/14/19)
- ²⁴ Rome Foundation. What's new for Rome IV. http://theromefoundation.org/rome-iv/whats-new-for-rome-iv/. Accessed on April 16th, 2017.
- ²⁵ Hookway C, Buckner S, Crosland P, Longson D. Irritable bowel syndrome in adults in primary care: summary of updated NICE guidance. *BMJ*. 2015;350(h701.
- ²⁶ Quigley EM, Abdel-Hamid H, Barbara G, et al. A global perspective on irritable bowel syndrome: a consensus statement of the World Gastroenterology Organisation Summit Task Force on irritable bowel syndrome. *Journal of clinical gastroenterology*. 2012;46(5):356-66.
- ²⁷ American Gastroenterology Association. American Gastroenterological Association medical position statement: irritable bowel syndrome. *Gastroenterology* 2002; 123:2105.
- ²⁸ American Gastroenterological Association. Medical Position Statement on IBS, March, 2006. http://www.gastro.org/practice/medical-position-statements(accessed 3/14/19).
- ²⁹ Wu, Y. and W. Fisher, Practical Therapeutics of Traditional Chinese Medicine. 1997: p. 265-271 CY Brookline.
- ³⁰ Maciocia, G., The Practice of Chinese Medicine: The Treatment of Disease with Acupuncture and Chinese Herbs. 2nd ed. 2008, Philadelphia: Churchill Livingstone Elsevier.
- ³¹ Maciocia G. "Foundations of Chinese Medicine: A Comprehensive Text for Acupuncturists and Herbalists", 2 edn. Oxford: Churchill Livingstone; 2005.
- ³² Wu Y, Fisher W. Practical Therapeutics of Traditional Chinese Medicine. 1997:265-71 CY Brookline.
- ³³ Maciocia G. The Practice of Chinese Medicine: The Treatment of Disease with Acupuncture and Chinese Herbs. 2nd ed. Philadelphia: Churchill Livingstone Elsevier; 2008.
- ³⁴ Stuardi T, MacPherson H. Acupuncture for irritable bowel syndrome: diagnosis and treatment of patients in a pragmatic trial. J Altern Complement Med. 2012;18(11):1021-7
- ³⁵ Irritable bowel syndrome: treatment based on pathophysiology and biomarkers.
- Camilleri M, Boeckxstaens G.Gut. 2023 Mar;72(3):590-599. doi: 10.1136/gutjnl-2022-328515. Epub 2022 Oct 28.PMID: 36307180 Review

Irritable Bowel Syndrome Clinical Pathway

- ³⁶ Grundmann O, Yoon SL. Complementary and alternative medicines in irritable bowel syndrome: an integrative view. *World J Gastroenterol*. 2014;20(2):346-62.
- ³⁷ Grace S, Barnes L, Reilly W, Vlass A, De permentier P. An integrative review of dietetic and naturopathic approaches to functional bowel disorders. *Complement Ther Med*. 2018;41:67-80.
- ³⁸ Goldenberg JZ, Ward L, Day A, Cooley K. Naturopathic Approaches to Irritable Bowel Syndrome-A Delphi Study. *J Altern Complement Med*. 2019;25(2):227-233.
- ³⁹ Nutrient Intake, Diet Quality, and Diet Diversity in Irritable Bowel Syndrome and the Impact of the Low FODMAP Diet. Staudacher HM, Ralph FSE, Irving PM, Whelan K, Lomer MCE.J Acad Nutr Diet. 2020 Apr;120(4):535-547. doi: 10.1016/j.jand.2019.01.017. Epub 2019 Apr 24.PMID: 31029650 Clinical Trial.
- ⁴⁰ Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA*. 2015;313(9):949-58.
- ⁴¹ Narrative review: Risk of eating disorders and nutritional deficiencies with dietary therapies for irritable bowel syndrome.
- Simons M, Taft TH, Doerfler B, Ruddy JS, Bollipo S, Nightingale S, Siau K, van Tilburg MAL.Neurogastroenterol Motil. 2022 Jan;34(1):e14188. doi: 10.1111/nmo.14188. Epub 2021 Jul 13.PMID: 34254719 Review.
- ⁴² Association between irritable bowel syndrome and micronutrients: A systematic review.
- Bek S, Teo YN, Tan XH, Fan KHR, Siah KTH.J Gastroenterol Hepatol. 2022 Aug;37(8):1485-1497. doi: 10.1111/jgh.15891. Epub 2022 May 28.PMID: 35581170 Review.
- ⁴³ Austin, GL, et al. A very low-carbohydrate diet improves symptoms and quality of life in diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2009; 7:706.
- ⁴⁴ Yoon SL, Grundmann O, Koepp L, and Farrell L. Management of Irritable Bowel Syndrome (IBS) in Adults: Conventional and Complementary/Alternative Approaches. *Alternative Medicine Review* 2011; 16 (2).
- ⁴⁵ Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. *Am J Gastroenterol* 2009; 104:1587.
- ⁴⁶ Calasso M, Francavilla R, Cristofori F, De angelis M, Gobbetti M. New Protocol for Production of Reduced-Gluten Wheat Bread and Pasta and Clinical Effect in Patients with Irritable Bowel Syndrome: A randomised, Double-Blind, Cross-Over Study. *Nutrients*. 2018;10(12.)
- ⁴⁷ Shepherd, SJ, Parker, FC, Muir, JG, Gibson, PR. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *Clin Gastroenterol Hepatol* 2008; 6:765.
- ⁴⁸ Yang J, Deng Y, Chu H, Cong Y, Zhao J, Pohl D, Misselwitz B, Fried M, Dai N, Fox M. Prevalence and presentation of lactose intolerance and effects on dairy product intake in healthy subjects and patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2013;11:262-268.
- ⁴⁹ Gupta D, Ghoshal UC, Misra A, et al. Lactose intolerance in patients with irritable bowel syndrome from northern India: a case-control study. *J Gastroenterol Hepatol* 2007;22:2261-2265.
- ⁵⁰ Rao SS, Yu S, Fedewa A. Systematic review: dietary fibre and FODMAP-restricted diet in the management of constipation and irritable bowel syndrome. *Aliment Pharmacol Ther*. 2015;41(12):1256-70.
- ⁵¹ Probiotics, prebiotics, and low FODMAP diet for irritable bowel syndrome What is the current evidence? Ooi SL, Correa D, Pak SC.Complement Ther Med. 2019 Apr;43:73-80. doi: 10.1016/j.ctim.2019.01.010. Epub 2019 Jan 16.PMID: 30935559
- Diet or medication in primary care patients with IBS: the DOMINO study a randomised trial supported by the Belgian Health Care Knowledge Centre (KCE Trials Programme) and the Rome Foundation Research Institute. Carbone F, Van den Houte K, Besard L, Tack C, Arts J, Caenepeel P, Piessevaux H, Vandenberghe A, Matthys C, Biesiekierski J, Capiau L, Ceulemans S, Gernay O, Jones L, Maes S, Peetermans C, Raat W, Stubbe J, Van Boxstael R, Vandeput O, Van Steenbergen S, Van Oudenhove L, Vanuytsel T, Jones M, Tack J; DOMINO Study Collaborators; Si Efficacy of a low-FODMAP diet in adult irritable bowel syndrome: a systematic review and meta-analysis. van Lanen AS, de Bree A, Greyling A.Eur J Nutr. 2021 Sep;60(6):3505-3522. doi: 10.1007/s00394-020-02473-0. Epub 2021 Feb 14.PMID: 33585949
- ⁵⁴ Long-Term Effects of a Web-Based Low-FODMAP Diet Versus Probiotic Treatment for Irritable Bowel Syndrome, Including Shotgun Analyses of Microbiota: Randomized, Double-Crossover Clinical Trial.
- Ankersen DV, Weimers P, Bennedsen M, Haaber AB, Fjordside EL, Beber ME, Lieven C, Saboori S, Vad N, Rannem T, Marker D, Paridaens K, Frahm S, Jensen L, Rosager Hansen M, Burisch J, Munkholm P.J Med Internet Res. 2021 Dec 14;23(12):e30291. doi: 10.2196/30291.PMID: 34904950 Clinical Trial.

Irritable Bowel Syndrome Clinical Pathway

- ⁵⁵ Irritable bowel syndrome and diet. Weber HC. Curr Opin Endocrinol Diabetes Obes. 2022 Apr 1;29(2):200-206. doi: 10.1097/MED.0000000000000720. PMID: 35131984 Review.
- ⁵⁶ Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med.* 2000;133:136-147.
- ⁵⁷ Akehurst R, Kaltenthaler E. Treatment of irritable bowel syndrome: a review of randomised controlled trials. *Gut.* 2001;48:272-282.
- ⁵⁸ Lindfors, P, et al. "Long-term effects of hypnotherapy in patients with refractory irritable bowel syndrome". *Scandinavian Journal of Gastroenterology* 2012; 47 (4).
- ⁵⁹ Moser G, Trägner S, Gajowniczek EE, et al. Long-term success of GUT-directed group hypnosis for patients with refractory irritable bowel syndrome: a randomized controlled trial. *Am J Gastroenterol.* 2013;108:602-609.
- ⁶⁰ Rutten JM, Reitsma JB, Vlieger AM, et al. Gut-directed hypnotherapy for functional abdominal pain or irritable bowel syndrome in children: a systematic review. *Archives of Disease in Childhood*. 2013;98(4):252-257.
- ⁶¹ Peter J, Fournier C, Keip B, et al. Intestinal Microbiome in Irritable Bowel Syndrome before and after Gut-Directed Hypnotherapy. *Int J Mol Sci.* 2018;19(11)
- ⁶² Lackner JM, Jaccard J, Krasner SS, et al. How does cognitive behavior therapy for irritable bowel syndrome work? A meditational analysis of a randomized clinical trial. *Gastroenterology* 2007; 133:433.
- ⁶³ Kerse N, Elley CR, Robinson E, et al. Is physical activity counseling effective for older people? A cluster randomized, controlled trial in primary care. *J Am Geriatr Soc* 2005;53:1951-6.
- ⁶⁴ Evans S, Lung KC, Seidman LC, Sternlieb B, Zeltzer LK, Tsao JC. Iyengar yoga for adolescents and young adults with irritable bowel syndrome. *J Pediatr Gastroenterol Nutr*. 2014;59(2):244-53.
- 65 Viera AJ, Hoag S, Shaughnessy J. Management of irritable bowel syndrome. Am Fam Physician 2002;66:1867-74.
- ⁶⁶ Meditation and Irritable Bowel Syndrome, a Systematic Review and Meta-Analysis.
- Baboş CI, Leucuța DC, Dumitrașcu DL.J Clin Med. 2022 Nov 2;11(21):6516. doi: 10.3390/jcm11216516.PMID: 36362745 Review.
- ⁶⁷ Zia JK, Barney P, Cain KC, Jarrett ME, Heitkemper MM. A Comprehensive Self-Management Irritable Bowel Syndrome Program Produces Sustainable Changes in Behavior After 1 Year. *Clin Gastroenterol Hepatol.* 2016;14(2):212-9.e1-2.
- ⁶⁸ Liegl G, Plessen CY, Leitner A, Boeckle M, Pieh C. Guided self-help interventions for irritable bowel syndrome: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol*. 2015;27(10):1209-21.
- ⁶⁹ Biofeedback for treatment of irritable bowel syndrome. Goldenberg JZ, Brignall M, Hamilton M, Beardsley J, Batson RD, Hawrelak J, Lichtenstein B, Johnston BC.Cochrane Database Syst Rev. 2019 Nov 12;2019(11):CD012530. doi: 10.1002/14651858.CD012530.pub2.PMID: 31713856
- ⁷⁰ Florance BM, et al. "Osteopathy improves the severity of irritable bowel syndrome: a pilot randomized sham-controlled study". *European Journal of Gastroenterology & Hepatology* 2012; 24 (8): 944-9.
- ⁷¹ Peckham EJ, Nelson EA, Greenhalgh J, Cooper K, Roberts ER, Agrawal A. Homeopathy for treatment of irritable bowel syndrome. *Cochrane Database Syst Rev.* 2013;11.
- ⁷² An open-label randomized pragmatic non-inferiority pilot trial to compare the effectiveness of Dysentery compound with individualized homeopathic medicines in irritable bowel syndrome. Nahar L, Paul S, Chattopadhyay A, Koley M, Saha S.J Complement Integr Med. 2019 Jun 14;16(4):/j/jcim.2019.16.issue-4/jcim-2018-0217/jcim-2018-0217.xml. doi: 10.1515/jcim-2018-0217.PMID: 31199766 Clinical Trial.
- ⁷³ Halkjær SI, Boolsen AW, Günther S, Christensen AH, Petersen AM. Can fecal microbiota transplantation cure irritable bowel syndrome?. *World J Gastroenterol*. 2017;23(22):4112-4120.
- ⁷⁴ El-salhy M, Mazzawi T. Fecal microbiota transplantation for managing irritable bowel syndrome. *Expert Rev Gastroenterol Hepatol*. 2018;12(5):439-445.
- ⁷⁵ Gut Microbiota Manipulation in Irritable Bowel Syndrome.
- $Mazzawi\ T. Microorganisms.\ 2022\ Jun\ 30; 10(7): 1332.\ doi:\ 10.3390/microorganisms 10071332. PMID:\ 35889051\ Review.$
- ⁷⁶ Fecal microbiota transplantation in the treatment of irritable bowel syndrome: a single-center prospective study in Japan. Hamazaki M, Sawada T, Yamamura T, Maeda K, Mizutani Y, Ishikawa E, Furune S, Yamamoto K, Ishikawa T, Kakushima N, Furukawa K, Ohno E, Honda T, Kawashima H, Ishigami M, Nakamura M, Fujishiro M.BMC Gastroenterol. 2022 Jul 14;22(1):342. doi: 10.1186/s12876-022-02408-5.PMID: 35836115 Clinical Trial.

77 Emerging Role of the Gut Microbiome in Irritable Bowel Syndrome.

The CHP Group

Irritable Bowel Syndrome Clinical Pathway

- Singh P, Lembo A.Gastroenterol Clin North Am. 2021 Sep;50(3):523-545. doi: 10.1016/j.gtc.2021.03.003. Epub 2021 Jun 25.PMID: 34304786 Review.
- ⁷⁸ Bacillus spp. Spores-A Promising Treatment Option for Patients with Irritable Bowel Syndrome. Catinean A, Neag AM, Nita A, Buzea M, Buzoianu AD.Nutrients. 2019 Aug 21;11(9):1968. doi: 10.3390/nu11091968.PMID: 31438618
- ⁷⁹ Gut Microbial Dysbiosis in the Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of Case-Control Studies. Wang L, Alammar N, Singh R, Nanavati J, Song Y, Chaudhary R, Mullin GE.J Acad Nutr Diet. 2020 Apr;120(4):565-586. doi: 10.1016/j.jand.2019.05.015. Epub 2019 Aug 28.PMID: 31473156
- ⁸⁰ Rahimi R, Abdollahi M. Herbal medicines for the management of irritable bowel syndrome: a comprehensive review. *World Journal of Gastroenterology*. 2012;18(7):589-600.
- ⁸¹ Fifi AC, Axelrod CH, Chakraborty P, Saps M. Herbs and Spices in the Treatment of Functional Gastrointestinal Disorders: A Review of Clinical Trials. *Nutrients*. 2018;10(11)
- ⁸² L. O'Mahony, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles, *Gastroenterology* 2005; 128:541–551.
- ⁸³ Didari T, Mozaffari S, Nikfar S, Abdollahi M. Effectiveness of probiotics in irritable bowel syndrome: Updated systematic review with meta-analysis. *World J Gastroenterol*. 2015;21(10):3072-84.
- ⁸⁴ The efficacy and safety of probiotics in patients with irritable bowel syndrome: Evidence based on 35 randomized controlled trials. Niu HL, Xiao JY.Int J Surg. 2020 Mar;75:116-127. doi: 10.1016/j.ijsu.2020.01.142. Epub 2020 Jan 31.PMID: 32014597
- 85 Efficacy of Probiotics for Irritable Bowel Syndrome: A Systematic Review and Network Meta-Analysis. Zhang T, Zhang C, Zhang J, Sun F, Duan L.Front Cell Infect Microbiol. 2022 Apr 1;12:859967. doi: 10.3389/fcimb.2022.859967. eCollection 2022.PMID: 35433498 PMC Review.
- ⁸⁶ Adjunctive treatment with probiotics partially alleviates symptoms and reduces inflammation in patients with irritable bowel syndrome.
- Xu H, Ma C, Zhao F, Chen P, Liu Y, Sun Z, Cui L, Kwok LY, Zhang H.Eur J Nutr. 2021 Aug;60(5):2553-2565. doi: 10.1007/s00394-020-02437-4. Epub 2020 Nov 22.PMID: 33225399 Clinical Trial.
- ⁸⁷ Probiotics, Prebiotics, and Synbiotics: Implications and Beneficial Effects against Irritable Bowel Syndrome.Simon E, Călinoiu LF, Mitrea L, Vodnar DC.Nutrients. 2021 Jun 20;13(6):2112. doi: 10.3390/nu13062112.PMID: 34203002
- ⁸⁸ Irritable Bowel Syndrome, Depression, and Neurodegeneration: A Bidirectional Communication from Gut to Brain. Aziz MNM, Kumar J, Muhammad Nawawi KN, Raja Ali RA, Mokhtar NM.Nutrients. 2021 Aug 31;13(9):3061. doi: 10.3390/nu13093061.PMID: 34578939 Review.
- ⁸⁹ Cappello G, Spezzaferro M, Grossi L, Manzoli L, Marzio L. Peppermint oil (Mintoil®) in the treatment of irritable bowel syndrome: a prospective double blind placebo-controlled randomized trial. *Dig. Liver Dis.* 39(6), 530-536 (2007).
 ⁹⁰ Alam MS, Roy PK, Miah AR, et al. Efficacy of Peppermint oil in diarrhea predominant IBS a double blind randomized placebo controlled study. *Mymensingh Med J.* 2013;22:27-30.
- ⁹¹ Alammar N, Wang L, Saberi B, et al. The impact of peppermint oil on the irritable bowel syndrome: a meta-analysis of the pooled clinical data. *BMC Complement Altern Med*. 2019;19(1):21.
- ⁹² Efficacy and Safety of Peppermint Oil in a Randomized, Double-Blind Trial of Patients With Irritable Bowel Syndrome. Weerts ZZRM, Masclee AAM, Witteman BJM, Clemens CHM, Winkens B, Brouwers JRBJ, Frijlink HW, Muris JWM, De Wit NJ, Essers BAB, Tack J, Snijkers JTW, Bours AMH, de Ruiter-van der Ploeg AS, Jonkers DMAE, Keszthelyi D.Gastroenterology. 2020 Jan;158(1):123-136. doi: 10.1053/j.gastro.2019.08.026. Epub 2019 Aug 27.PMID: 31470006 Clinical Trial.
- ⁹³ Rahimi R, Abdollahi M. "Herbal medicines for the management of irritable bowel syndrome: a comprehensive review". *World Journal of Gastroenterology* 2012; 18 (7): 589 600.
- ⁹⁴ Liu, JP, Yang, M, Liu, YX, et al. Herbal medicines for treatment of irritable bowel syndrome. *Cochrane Database Syst Rev* 2006.
- ⁹⁵ Bensoussan A, et al. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. *IAMA* 1998;280:1585-1589.
- ⁹⁶ Vejdani R. The efficacy of an herbal medicine, Carmint, on the relief of abdominal pain and bloating in patients with irritable bowel syndrome: a pilot study. *Dig Dis Sci* 2006 Aug; 51(8):1501-7.

- ⁹⁷ Sallon S, et al. A novel treatment for constipation-predominant irritable bowel syndrome using padma lax, a Tibetan herbal formula. *Digestion* 2002;65(3):161–71.
- ⁹⁸ Ottillinger B, Storr M, Malfertheiner P, Allescher HD. STW 5 (Iberogast®)--a safe and effective standard in the treatment of functional gastrointestinal disorders. *Wien Med Wochenschr*. 2013;163:65-72
- ⁹⁹ Madisch A, Vinson BR, Abdel-aziz H, et al. Modulation of gastrointestinal motility beyond metoclopramide and domperidone: Pharmacological and clinical evidence for phytotherapy in functional gastrointestinal disorders. *Wien Med Wochenschr*. 2017;167(7-8):160-168.
- ¹⁰⁰ Hawrelak JA, Myers SP. Effects of two natural medicine formulations on irritable bowel syndrome symptoms: a pilot study. *J Altern Complement Med* 2010;16:1065–1071.
- ¹⁰¹ Ko SJ, et al. "Effect of herbal extract granules combined with probiotic mixture on irritable bowel syndrome with diarrhea: study protocol for a randomized controlled trial". *Trials* 2012, 12.
- ¹⁰² Post-marketing Re-evaluation of Tongxiening Granules () in Treatment of Diarrhea-Predominant Irritable Bowel Syndrome: A Multi-center, Randomized, Double-Blind, Double-Dummy and Positive Control Trial. Tang XD, Zhang SS, Hou XH, Li ZH, Chen SN, Feng PM, Yang XN, Li HZ, Wu JQ, Xia PJ, Yang XJ, Zhou HJ, Wang HY, Ai YW, Li K.Chin J Integr Med. 2019 Dec;25(12):887-894. doi: 10.1007/s11655-019-3030-x. Epub 2019 Jul 10.PMID: 31292845 Clinical Trial.
- ¹⁰³ Efficacy of Fecal microbiota transplantation for patients with irritable bowel syndrome in a randomized, double-blind, placebo controlled study.
- Magdy El-Salhy, Jan Gunnar Hatlebakk, Odd Helge Gilja, Anja Brathen Kristoffersen, Trygve Hausken. Gut 2020 May;69(5):859-867. Doi: 10.1136/jutjnl-2019-319630. Epub 2019 Dec 18.
- ¹⁰⁴ Western herbal medicines in the treatment of irritable bowel syndrome: A systematic review and meta-analysis. Hawrelak JA, Wohlmuth H, Pattinson M, Myers SP, Goldenberg JZ, Harnett J, Cooley K, Van De Venter C, Reid R, Whitten DL.Complement Ther Med. 2020 Jan;48:102233. doi: 10.1016/j.ctim.2019.102233. Epub 2019 Nov 3.PMID: 31987249
- ¹⁰⁵ Herbal medicine in the treatment of functional gastrointestinal disorders: A systematic review with meta-analysis. Tan N, Gwee KA, Tack J, Zhang M, Li Y, Chen M, Xiao Y.J Gastroenterol Hepatol. 2020 Apr;35(4):544-556. doi: 10.1111/jgh.14905. Epub 2019 Nov 7.PMID: 31674057 Review.
- 106 [Therapeutic effect of herb-separated moxibustion at Jinsuo (GV 8)-eight-diagram points on diarrhea-type irritable bowel syndrome of liver stagnation and spleen deficiency]. Hao LJ, Shi ZM.Zhongguo Zhen Jiu. 2020 Jul 12;40(7):702-6. doi: 10.13703/j.0255-2930.20190621-k0007.PMID: 32648391 Clinical Trial. Chinese.
- 107 Oral administration of a lecithin-based delivery form of boswellic acids (Casperome) for the prevention of symptoms of irritable bowel syndrome: a randomized clinical study. Riva A, Giacomelli L, Togni S, Franceschi F, Eggenhoffner R, Zuccarini MC, Belcaro G.Minerva Gastroenterol Dietol. 2019 Mar;65(1):30-35. doi: 10.23736/S1121-421X.18.02530-8.PMID: 30676012 Clinical Trial.
- ¹⁰⁸ Soy isoflavones and cholecalciferol reduce inflammation, and gut permeability, without any effect on antioxidant capacity in irritable bowel syndrome: A randomized clinical trial. Jalili M, Vahedi H, Poustchi H, Hekmatdoost A.Clin Nutr ESPEN. 2019 Dec;34:50-54. doi: 10.1016/j.clnesp.2019.09.003. Epub 2019 Oct 2.PMID: 31677711 Clinical Trial.
- ¹⁰⁹ Vitamin D supplementation for irritable bowel syndrome: A systematic review and meta-analysis. Chong RIH, Yaow CYL, Loh CYL, Teoh SE, Masuda Y, Ng WK, Lim YL, Ng QX.J Gastroenterol Hepatol. 2022 Jun;37(6):993-1003. doi: 10.1111/jgh.15852. Epub 2022 Apr 20.PMID: 35396764
- ¹¹⁰ The efficacy of vitamin D supplementation for irritable bowel syndrome: a systematic review with meta-analysis. Huang H, Lu L, Chen Y, Zeng Y, Xu C.Nutr J. 2022 May 5;21(1):24. doi: 10.1186/s12937-022-00777-x.PMID: 35509010 Review
- ¹¹¹ Efficacy and safety of biophenol-rich nutraceuticals in adults with inflammatory gastrointestinal diseases or irritable bowel syndrome: A systematic literature review and meta-analysis.
- Giang J, Lan X, Crichton M, Marx W, Marshall S.Nutr Diet. 2022 Feb;79(1):76-93. doi: 10.1111/1747-0080.12672. Epub 2021 May 7.PMID: 33960587 Review.
- ¹¹² Diet, fibers, and probiotics for irritable bowel syndrome.
- Galica AN, Galica R, Dumitrașcu DL.J Med Life. 2022 Feb;15(2):174-179. doi: 10.25122/jml-2022-0028.PMID: 35419092 Review.

Irritable Bowel Syndrome Clinical Pathway

- ¹¹³ Psyllium reduces inulin-induced colonic gas production in IBS: MRI and in vitro fermentation studies. Gunn D, Abbas Z, Harris HC, Major G, Hoad C, Gowland P, Marciani L, Gill SK, Warren FJ, Rossi M, Remes-Troche JM, Whelan K, Spiller RC.Gut. 2022 May;71(5):919-927. doi: 10.1136/gutjnl-2021-324784. Epub 2021 Aug 5.PMID: 34353864 Clinical Trial.
- ¹¹⁴ Quigley EM, Abdel-Hamid H, Barbara G, et al. A global perspective on irritable bowel syndrome: a consensus statement of the World Gastroenterology Organisation Summit Task Force on irritable bowel syndrome. *Journal of clinical gastroenterology*. 2012;46(5):356-66.
- ¹¹⁵ Effect of Acupuncture in Patients With Irritable Bowel Syndrome: A Randomized Controlled Trial. Pei L, Geng H, Guo J, Yang G, Wang L, Shen R, Xia S, Ding M, Feng H, Lu J, Li J, Liu L, Shu Y, Fang X, Wu X, Wang X, Weng S, Ju L, Chen X, Shen H, Sun J.Mayo Clin Proc. 2020 Aug;95(8):1671-1683. doi: 10.1016/j.mayocp.2020.01.042. Epub 2020 Jun 1.PMID: 32499125 Clinical Trial.
- ¹¹⁶ Pei L, Geng H, Guo J, Yang G, Wang L, Shen R, et al. Effect of Acupuncture in Patients With Irritable Bowel Syndrome: A Randomized Controlled Trial. Mayo Clin Proc. 2020;95(8):1671-83.
- ¹¹⁷ MacPherson H, Tilbrook H, Bland JM, Bloor K, Brabyn S, Cox H, et al. Acupuncture for irritable bowel syndrome: primary care based pragmatic randomised controlled trial. BMC Gastroenterol. 2012;12:150.
- ¹¹⁸ Anastasi, J.K., D.J. McMahon, and G.H. Kim, Symptom management for irritable bowel syndrome: a pilot randomized controlled trial of acupuncture/moxibustion. Gastroenterol Nurs, 2009. 32(4): p. 243-55.
- ¹¹⁹ Fireman, Z., et al., Acupuncture treatment for irritable bowel syndrome. A double-blind controlled study. Digestion, 2001. 64(2): p. 100-3.
- ¹²⁰ Forbes, A., et al., Acupuncture for irritable bowel syndrome: a blinded placebo-controlled trial. World J Gastroenterol, 2005. 11(26): p. 4040-4.
- ¹²¹ Lowe, C., et al., Sham acupuncture is as efficacious as true acupuncture for the treatment of IBS: A randomized placebo controlled trial. Neurogastroenterol Motil, 2017. 29(7)
- ¹²² MacPherson, H., et al., Acupuncture for irritable bowel syndrome: 2-year follow-up of a randomised controlled trial. Acupunct Med, 2017. 35(1): p. 17-23.
- ¹²³ MacPherson, H., et al., Acupuncture for irritable bowel syndrome: primary care based pragmatic randomised controlled trial. BMC Gastroenterol, 2012. 12: p. 150.
- ¹²⁴ Park, H.J. and C. Cha, The effect of Korean hand acupuncture on young, single Korean students with irritable bowel syndrome. Gastroenterol Nurs, 2012. 35(6): p. 403-14.
- ¹²⁵ Pei, L., et al., Effect of Acupuncture in Patients With Irritable Bowel Syndrome: A Randomized Controlled Trial. Mayo Clin Proc, 2020. 95(8): p. 1671-1683.
- ¹²⁶ Qi, L.Y., et al., Acupuncture for the Treatment of Diarrhea-Predominant Irritable Bowel Syndrome: A Pilot Randomized Clinical Trial. JAMA Netw Open, 2022. 5(12): p. e2248817
- ¹²⁷Reynolds, J.A., J.M. Bland, and H. MacPherson, Acupuncture for irritable bowel syndrome an exploratory randomised controlled trial. Acupunct Med, 2008. 26(1): p. 8-16.
- ¹²⁸ Schneider, A., et al., Acupuncture treatment in irritable bowel syndrome. Gut, 2006. 55(5): p. 649-54.
- ¹²⁹ Stamuli, E., et al., Cost-effectiveness of acupuncture for irritable bowel syndrome: findings from an economic evaluation conducted alongside a pragmatic randomised controlled trial in primary care. BMC Gastroenterol, 2012. 12: p. 149.
- ¹³⁰ Stuardi, T. and H. MacPherson, Acupuncture for irritable bowel syndrome: diagnosis and treatment of patients in a pragmatic trial. J Altern Complement Med, 2012. 18(11): p. 1021-7.
- ¹³¹ Sun, J.H., et al., Clinical evaluation of Soothing Gan and invigorating Pi acupuncture treatment on diarrhea-predominant irritable bowel syndrome. Chin J Integr Med, 2011. 17(10): p. 780-5
- ¹³² Gan, Y., et al., Acupuncture in addition to usual care for patients with irritable bowel syndrome: a component network meta-analysis. Acupunct Med, 2022. 40(5): p. 403-414.
- ¹³³ Jiang, X., et al., Acupuncture and Moxibustion in the Treatment of Adult Diarrhea Irritable Bowel Syndrome: A Network Meta-analysis. Comput Math Methods Med, 2022. 2022: p. 9919839.
- ¹³⁴ Yang, Y., et al., Clinical evidence of acupuncture and moxibustion for irritable bowel syndrome: A systematic review and meta-analysis of randomized controlled trials. Front Public Health, 2022. 10: p. 1022145.
- ¹³⁵ Manheimer, E., et al., Acupuncture for treatment of irritable bowel syndrome. Cochrane Database Syst Rev, 2012. 5: p. CD005111.

Irritable Bowel Syndrome Clinical Pathway

- ¹³⁶ Zheng, H., et al., Comparison between the Effects of Acupuncture Relative to Other Controls on Irritable Bowel Syndrome: A Meta-Analysis. Pain Res Manag, 2019. 2019: p. 2871505.
- ¹³⁷ Wu, Y.B., et al., Pharmacological treatments of Chinese herbal medicine for irritable bowel syndrome in adults: A network meta-analysis of randomized controlled trials. PLoS One, 2021. 16(8): p. e0255665.
- ¹³⁸ Chen, M., et al., Chinese herbal medicine versus antispasmodics in the treatment of irritable bowel syndrome: A network meta-analysis. Neurogastroenterol Motil, 2021. 33(8): p. e14107.
- ¹³⁹ Dai, Y.Q., et al., Moxibustion for diarrhea-predominant irritable bowel syndrome: A systematic review and metaanalysis of randomized controlled trials. Complement Ther Clin Pract, 2022. 46: p. 101532.
- ¹⁴⁰ Mckenzie YA, Bowyer RK, Leach H, et al. British Dietetic Association systematic review and evidence-based practice guidelines for the dietary management of irritable bowel syndrome in adults (2016 update). *J Hum Nutr Diet*. 2016;29(5):549-75.
- ¹⁴¹ National Institute of Diabetes and Digestive and Kidney Disease. Irritable Bowel Syndrome. http://digestive.niddk.nih.gov/ddiseases/pubs/ibs_ez/_ (3/14/19).
- ¹⁴² Toner, B. Cognitive-Behavioral Treatment of Irritable Bowel Syndrome. CNS Spectr. 2005;10(11):883-890
- ¹⁴³ Ford AC. Intending to Treat Patients With Irritable Bowel Syndrome With Cognitive-Behavioral Therapy. *Gastroenterology*. 2018;155(6):2024.
- ¹⁴⁴ Heymann-mönnikes I, Arnold R, Florin I, Herda C, Melfsen S, Mönnikes H. The combination of medical treatment plus multicomponent behavioral therapy is superior to medical treatment alone in the therapy of irritable bowel syndrome. *Am J Gastroenterol*. 2000;95(4):981-94.
- ¹⁴⁵ Cong X, Perry M, Bernier KM, Young EE, Starkweather A. Effects of Self-Management Interventions in Patients With Irritable Bowel Syndrome: Systematic Review. *West J Nurs Res.* 2018;40(11):1698-1720.
- ¹⁴⁶ Chey WD, Maneerattaporn M, Saad R. Pharmacologic and complementary and alternative medicine therapies for irritable bowel syndrome. *Gut and Liver* 2011; 5 (3): 253-66.
- ¹⁴⁷ Alammar N, Stein E. Irritable Bowel Syndrome: What Treatments Really Work. *Med Clin North Am.* 2019;103(1):137-152.
- ¹⁴⁸ Rao AS, Wong BS, Camilleri M, et al. Chenodeoxycholate in females with irritable bowel syndrome-constipation: a pharmacodynamic and pharmacogenetic analysis. *Gastroenterology* 2010;139:1549–1558.
- ¹⁴⁹ Cann PA, Read NW, Holdsworth CD, Barends D. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). *Dig Dis Sci* 1984; 29:239.
- ¹⁵⁰ Hovdenak N. Loperamide treatment of the irritable bowel syndrome. *Scand J Gastroenterol Suppl* 1987; 130:81.
- ¹⁵¹ Efskind PS, Bernklev T, Vatn MH. A double-blind placebo-controlled trial with loperamide in irritable bowel syndrome. *Scand J Gastroenterol* 1996; 31:463.
- ¹⁵² Clouse RE, Lustman PJ, Geisman RA, Alpers DH. Antidepressant therapy in 138 patients with irritable bowel syndrome: a five-year clinical experience. Aliment *Pharmacol Ther* 1994; 8:409.
- ¹⁵³ Frissora CL, Cash BD. Review article: the role of antibiotics vs. conventional pharmacotherapy in treating symptoms of irritable bowel syndrome. *Aliment Pharmacol Ther* 2007;25:1271–1281.
- ¹⁵⁴ Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 2011;364:22–32.
- ⁷⁷Stamuli E, Bloor K, MacPherson H, et al. Cost-effectiveness of acupuncture for irritable bowel syndrome: findings from an economic evaluation conducted alongside a pragmatic randomised controlled trial in primary care. *BMC Gastroenterol.* 2012;12:149.
- ⁷⁸Anastasi JK, McMahon DJ, Kim GH. Symptom management for irritable bowel syndrome: a pilot randomized controlled trial of acupuncture/moxibustion. *Gastronterol Nurs*. 2009;32(4):243-55