

Constipation Predominant Irritable Bowel Syndrome

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Abstract: Irritable bowel syndrome (IBS) is a functional disorder characterized by abdominal discomfort and altered bowel function. New Rome III definition can be used for diagnosis. Alarm features (e.g., rectal bleeding; weight loss; iron deficiency anemia; nocturnal symptoms; family history of colorectal cancer, inflammatory bowel disease, or celiac disease) should be excluded. There is no single treatment algorithm for IBS-C patients. Symptoms in IBS C can be treated with laxatives, fiber, antispasmodic & other newer drugs.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional disorder characterized by abdominal discomfort and altered bowel function. It affects approximately 7 to 10 percent of persons in the world, and is more common in women, persons with lower socioeconomic status, and persons younger than 50 years. IBS is associated with impaired quality of life and reduced work productivity^{1, 2, 3}

Subtypes

1. Constipation predominant symptoms (IBS-C),
 2. Diarrhea predominant symptoms (IBS-D)
 3. Mixed or alternating symptoms of constipation & diarrhea
- Recent studies have demonstrated that up to 75% of IBS patients shift from 1 subtype (eg, IBS-C) to another (eg, IBS-M) during the course of their illness. This means that a change in IBS subtype should no longer be considered a warning sign that warrants investigation.

DEFINING CONSTIPATION PREDOMINANT IRRITABLE BOWEL SYNDROME

This new Rome III definition can be used in both the clinical and research setting (Table 1)^{4,5,6}. Of note, the sine qua non in the diagnosis of IBS is the presence of abdominal pain or discomfort. Other symptoms, including straining, infrequent stools, passage of rocky hard stool, incomplete evacuation, and bloating are also found in patients with chronic constipation. Evaluating the Patient With Suspected Constipation predominant Irritable Bowel Syndrome.

To simplify the diagnosis of IBS-C without overlooking a serious medical or surgical problem, a complete history & physical examination is essential.

HISTORY

Taking a thorough history including both gastrointestinal and extra-intestinal symptoms is important. The presence of multiple co-existing disorders increases the likelihood of IBS. The onset and duration of symptoms should be ascertained to make sure that the patient fulfills Rome III criteria for IBS-C. Patients should be asked about their most significant symptom, as this will influence treatment decisions. Alarm features (e.g. rectal bleeding; weight loss; iron deficiency anemia; nocturnal symptoms; family history of colorectal cancer, inflammatory bowel disease, or celiac disease) should be excluded.

PHYSICAL EXAMINATION

The physical examination in patients with IBS-C is generally normal / vague fullness or mild tenderness over the sigmoid colon. Presence of an abdominal mass, bruits, succussion splash, and rebound tenderness and guarding suggest an alternative diagnosis. A digital rectal exam should be performed in all patients to rule out rectal cancer, rectocele or co-

Table 1: IBS Defined^{4,5,6}

Rome III Criteria
- Symptom onset at least 6 months prior to diagnosis
- Symptoms present during the last 3 months, with a minimum of 3 days of symptoms per month
- Recurrent abdominal pain or discomfort associated with 2 or more of the following:
- Improvement with defecation
- Onset associated with a change in stool frequency
- Onset associated with a change in stool form (appearance)
- One or more of the following symptoms on at least 25% of occasions for subgroup identification:
- Abnormal stool frequency (< 3/week)
- Abnormal stool form (lumpy/hard)
- Abnormal stool passage (straining, incomplete evacuation)
- Bloating or feeling of abdominal distension
- Passage of mucus
- Frequent, loose stools
The ACG (2002) defines IBS-C
- Abdominal discomfort associated with altered bowel habits
- Symptoms of constipation include infrequent stools, straining, feelings of incomplete evacuation, difficult evacuation, passage of rocky, hard stools

existing mechanical process (ie, prolapse), and to quickly assess the patient for co-existing pelvic floor dyssynergia (PFD). The latter can be easily done by asking the patient to push the examining finger out during simulated defecation. Inappropriate contraction of the external anal sphincter muscle during this maneuver is one sign of PFD & further can be confirmed by anorectal manometry. The presence of an anal fissure may explain rectal bleeding, especially in patients with significant anorectal pain. This reassures the patient that their complaints are being taken seriously, even if their symptoms are classic for IBS, and warning signs are absent on review. In addition, patients may have more than one disease process occurring at the same time (ie, celiac disease, hypothyroidism) and a thorough examination may uncover the secondary diagnosis.

DIAGNOSTIC TESTING

Previously IBS-C was a diagnosis of exclusion, and that all patients required extensive testing. However, several studies have demonstrated that routine tests are not required in younger patients who fit symptom-based criteria for IBS and who have a normal physical examination without any identifiable warning signs or “red flags” (hematochezia; occult blood in the stool; anemia, ascites, hepatosplenomegaly, or an abdominal mass; unintentional weight loss [$> 10\%$ of body weight]; a family history of

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colorectal cancer or inflammatory bowel disease; and anorexia.) Thyroid-stimulating hormone level should be checked, especially if patients have symptoms of fatigue. If bloating is a predominant complaint, and the patient fails to respond to empiric therapy (e.g., avoidance of all dairy products and all food products with fructose for 10 days; no added fiber diet), then serologic tests for celiac disease can be ordered because the prevalence of celiac disease is higher among patients with IBS than the general population⁸. For patients younger than 40 years of age without warning signs and with the predominant complaint of constipation, if empiric therapy fails, then flexible sigmoidoscopy is a reasonable first test. Colonoscopy should be performed in: patients 50 years of age or older, with a family history of inflammatory bowel disease or colorectal cancer, and patients with anemia or occult bleeding^{9, 10}.

Patients with IBS-C with very infrequent stools (i.e. < 1 per week) may have co-existing pelvic floor dysfunction, but should also be evaluated for colonic inertia. The evaluation for colonic inertia involves the patient ingesting a capsule with 24 radio-opaque markers on the morning of Day 0 and then having an abdominal radiograph obtained 24, 72 and 120 hours later (Days 1, 3 and 5). The number and location of the markers are recorded, allowing the diagnoses of colonic inertia, outlet obstruction, or normal transit to be made^{11, 12}.

Persistent symptoms, warning signs, failure to respond to empiric therapy, or concern about co-existing disorders may all lead to referrals for a specific diagnostic test.

MEDICAL MANAGEMENT

There is no single treatment algorithm for IBS-C patients. Medications can improve the symptoms in IBS are laxatives, antispasmodic drugs, or possibly with a dual mechanism at the periphery and at a central level (i.e. selective serotonin reuptake inhibitors (SSRIs), serotonin receptor modulators, tricyclic antidepressants, neurokinin antagonists, opioid drugs).

Smooth Muscle Relaxants are not shown significant benefits above placebo. Nevertheless, patients who improve with antispasmodic drugs, particularly those whose symptoms are induced by meals and those who complain of tenesmus. When used for meal induced symptoms, anticholinergics should be prescribed 30-60 minutes before meals so that peak serum levels of the drug coincide with peak symptoms.

A recent meta-analysis of 22 studies involving 1778 patients and 12 different antispasmodic agents demonstrated modest improvements in global IBS symptoms and abdominal pain.

Selective Serotonin Reuptake Inhibitors (SSRIs) - Only six studies have been conducted to date, two each involving fluoxetine, paroxetine and citalopram. Most patients noted an improvement in overall well-being, although none of the studies showed any benefit with regards to bowel habits and abdominal pain was generally not improved. The paroxetine study provided some of the first evidence supporting the use of SSRIs in treating functional bowel disorders. One citalopram trial employed a controlled, crossover design and demonstrated a significant improvement in abdominal pain, bloating and general well being independent of psychological improvement. It is felt that SSRIs primarily mediate pain centrally, but they may also have effects on the enteric nervous system. Selective serotonin and norepinephrine inhibitors (SSNRI/SNRI) such as venlafaxine and duloxetine may also have a role in the treatment of IBS pain. Given its clinical effectiveness in treating these conditions, the medication has been applied off-label for visceral hypersensitivity syndromes, including IBS.

Alternative and Complementary Medicine Peppermint, germanium, lavender oils and their derivatives have been used in the treatment of irritable bowel syndrome and other GI disorders. All of these agents may act to relax smooth muscle via a c AMP-dependent mechanism. A recent

Table 2: Common Disorders Associated With Irritable Bowel Syndrome⁷

A. Overlapping gastrointestinal disorders: ~40%
Gastroesophageal reflux disease
Functional dyspepsia
Lactose intolerance (25% of US adults)
Fructose intolerance
B. Associated nongastrointestinal disorders:
Fibromyalgia
Chronic fatigue syndrome
Migraine headaches
Temporomandibular joint syndrome
Interstitial cystitis
Dyspareunia

meta-analysis of four clinical trials involving 329 patients treated with peppermint oil suggested a significant benefit in overall IBS symptoms. Carmint is another herbal supplement that includes coriander, lemon and mint extracts. It has been used for its potential antispasmodic and sedative properties. A recent trial randomized 32 IBS patients to receive carmint or placebo. After 8 weeks, the carmint-treated group demonstrated significant improvements in the severity and frequency of abdominal pain and discomfort.

A recent meta-analysis suggests that the benefit of acupuncture on IBS symptoms is no better than placebo. Limited data on hypnotherapy suggests that it may be considered as an adjunct for treatment refractory patients. Cognitive behavioral therapy may be effective in improving patient coping strategies.

DIETARY FACTORS

Research studies have demonstrated that the average volume of intestinal gas is not significantly different in IBS patients compared with healthy controls. However, IBS patients have impaired gas transit & visceral hypersensitivity contribute to symptoms of bloating and abdominal pain. Symptoms of abdominal distention and bloating have been described in the malabsorption of lactose, fructose and sorbitol. Lactose intolerance is common, affecting approximately 5% of Northern Europeans and up to 90% of persons of Asian and African descent. In fact, some patients with IBS suffer from symptoms attributable to undiagnosed lactose intolerance. In the study by Bohmer and colleagues, 24% of IBS patients had lactose malabsorption *versus* 5.7% of healthy controls ($p < 0.009$). However, 40% of patients with IBS reported symptoms after lactose intake as opposed to 20% in healthy controls ($p = 0.01$). Fructose consumption has rapidly risen more than 1000-fold in the last 30 years and accounts for more than 40% of total caloric sweeteners added to food and beverages, particularly soft drinks. Fructose intolerance presents similarly to lactose intolerance. While the overall prevalence of fructose intolerance is unknown, a recent study did evaluate symptom response in IBS patients after eliminating dietary fructose. This prospective trial involved 26 patients with IBS and an abnormal fructose breath test, all of whom received instruction on a nonfructose diet. Of the 14 IBS patients that were compliant with the diet, there was a statistically significant reduction in symptoms of belching, bloating, fullness and diarrhea. In the 12 noncompliant patients, there was no improvement in symptoms.

Probiotics 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. A prospective trial of 77 IBS patients randomized them to receive *Bifidobacterium infantis* 35624, *Lactobacillus* or placebo in a malted drink. The authors found that patients randomized to *B. infantis* had improvement in symptoms of abdominal pain/discomfort and bloating in the setting of a normalized IL-10/IL-12 ratio.

Lifestyle Modifications Many clinicians initiate treatment for symptoms of IBS and constipation with lifestyle modifications, which may include changes in fluid intake, exercise and diet. Unfortunately, data to support these interventions is limited.

Bowel Training and Education Constipation develops in some IBS patients because they ignore the urge to have a bowel movement. In many patients this urge occurs upon awakening or shortly after eating. Many IBS-C patients (especially those with overlapping pelvic floor dysfunction) note an improvement in symptoms of constipation if they can re-establish a set time to use the bathroom each day. A simple bowel regimen means getting up at approximately the same time each day, eating breakfast (to help initiate the gastrocolic reflex) and then using the bathroom at a routine, scheduled time each day, typically 30-45 minutes after the morning meal.

Over-the-counter Medications Stool softeners are emollients which soften and lubricate the stool. In usual doses, docusate may increase the fluid content of stool by 3-5%. Although safe and inexpensive, stool softeners are rarely helpful in the treatment of IBS-C. No randomized, controlled trials have been performed in patients with IBS. Typical agents include magnesium hydroxide (Phillips Milk of Magnesia), magnesium sulfate, or magnesium citrate. No studies have been performed in patients with IBS-C & should be avoided in patients with renal dysfunction.

These agents include senna, cascara, aloe, castor oil and bisacodyl, and have two major mechanisms of action. One, they directly stimulate the colon and increase colonic contractions. Two, they increase fluid secretion in the intestinal tract, which increases intestinal transit. One study evaluated the efficacy of aloe vera in the treatment of 58 patients (18-65 years) with IBS-C. Symptom improvement at the end of the 4-week trial and at 3-months was similar in both the placebo group and the aloe vera treatment group. Based on this small study, aloe vera cannot be recommended as a treatment for IBS-C. The other agents listed above have not been prospectively studied in IBS patients and should be used on an as needed basis only. Patients should be cautioned that excessive use may lead to chronic watery diarrhea and the development of electrolyte disturbances. Fiber has become a cornerstone of IBS treatment for many practitioners. While the efficacy of fiber supplementation remains unclear, given its safety profile, the potential for a positive placebo effect and its low cost, fiber remains an excellent first choice in the treatment of IBS-C. Four of twelve randomized studies in IBS noted an improvement in stool frequency (polycarbophil and ispaghula husk), while one noted an improvement in stool evacuation. No study has demonstrated an improvement in abdominal pain with the use of any type of fiber product. In addition, 30-50% of patients treated with a fiber product will have a significant increase in gas, bloating, and abdominal distention. In summary, fiber supplementation using a soluble fiber product such as ispaghula is a reasonable treatment option for symptoms of constipation in patients with IBS, if the patient is fiber deficient.

Prescription Medications Polyethylene glycol (PEG) is a high-molecular-weight osmotic agent that is neither absorbed nor metabolized as it passes through the GI tract. It is FDA-approved for the treatment of chronic constipation, but is not currently approved for the treatment of IBS-C. One study evaluated the efficacy of PEG in 48 adolescents (ages 13-18; 60% women) diagnosed with IBS-C using the Rome II criteria. Patients were randomized to receive either 17 g of PEG each day or 17 g of PEG in addition to 6 mg of tegaserod twice daily during the 4-week study period. Stool frequency increased in both groups ($p < 0.05$) during the study period, although abdominal pain improved only in the PEG-tegaserod

group ($p < 0.05$). No adverse events were reported in either group.

Lactulose is not be metabolized by the small intestine, so it passes unchanged into the colon where it is broken down and fermented by colonic bacteria. Lactulose improves symptoms in patients with chronic constipation. It was approved by the FDA for the treatment of women with IBS-C in July 2002 based on the results of two pivotal studies and the results of four large, randomized, double-blind placebo controlled studies showing improvement in both global and individual IBS symptoms compared with placebo.

FUTURE THERAPIES

Prucalopride is a highly selective 5-HT₄ receptor agonist that improves colonic motility, colonic transit and symptoms of constipation in patients with chronic constipation [Camilleri *et al.* 2008; Emmanuel *et al.* 2002].

Pumosetrag - a 5-HT₄ partial agonist with prokinetic properties, used in dosages of 1.4mg tid for 28 days in treatment for IBS-C. It demonstrated favorable effects in 53.8% of subjects compared with 15.4% of subjects in the placebo group [Paterson, 2008a]. Adverse events occurred with similar frequency in all treatment groups and the majority were mild side effects.

Compared with placebo, lubiprostone in a dosage of 8 mcg twice daily is more effective for the relief of global IBS symptoms in women with IBS-C (grade 1B). [Johanson *et al.* 2006] Lubiprostone acts locally within the intestinal tract, is rapidly metabolized, and has very low systemic Lubiprostone selectively stimulates type 2 chloride channels in epithelial cells of the gastrointestinal tract thereby causing an efflux of chloride into the intestinal lumen [Cuppoletti *et al.* 2004]. Fluid secretion into the gastrointestinal lumen provides a bolus effect that softens stool, increases intestinal transit, and improves symptoms of constipation/bioavailability. Lubiprostone is approved by the FDA for use in women with IBS-C. Adverse effects of lubiprostone include nausea, diarrhea, and abdominal pain. It should not be used in persons with mechanical bowel obstruction or preexisting diarrhea, pregnancy.

Linacotide appears to significantly improve abdominal pain and relieve constipation

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