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Current Strategies in the Management of Irritable Bowel Syndrome

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Abstract

Irritable bowel syndrome (IBS) is one of the most studied and discussed problems in the field of gastroenterology, yet it often remains perplexing to both clinicians and patients. Some of the apprehension comes from a void of objective data that defines a diagnosis in most disorders. This level of comfort is not appreciated in the evaluation of IBS, where the art of medicine and subjective impressions are the cornerstones of proper assessment. Though this paper focuses on management, a review of pathophysiology and specific guidelines establishing a diagnosis of IBS will be addressed.

Keywords: Irritable bowel syndrome; Dyspepsia; Diarrhea; Constipation

Introduction

Irritable bowel syndrome (IBS) is one of the most studied and discussed problems in the field of gastroenterology, yet it often remains perplexing to both clinicians and patients. Some of the apprehension comes from a void of objective data that defines a diagnosis in most disorders. This level of comfort is not appreciated in the evaluation of IBS, where the art of medicine and subjective impressions are the cornerstones of proper assessment. Though this paper focuses on management, a review of pathophysiology and specific guidelines establishing a diagnosis of IBS will be addressed.

Epidemiology

IBS is a very common disorder seen in physicians' offices. It is thought that 28% percent of referrals to gastroenterologists are for IBS and perhaps 12% of primary care visits involve evaluation or treatment for this condition [1]. It is more often seen in females whom have a prevalence at least 2 times greater than that of males [2,3]. Women often have more severe symptoms [4] and some studies suggest they seek health care more often [5]. Though IBS is more often seen in patients under 45, it is commonly diagnosed in elderly patients as well. Additionally it is frequently seen in adolescents and students in their high school and college years [6].

Clinical Features

IBS features many symptoms but the salient or most accentuated of these is pain or a level of discomfort. Without some degree of pain or discomfort, one cannot have IBS. The pain often is described as cramping or colicky and is usually centered in the lower quadrants though any area of the abdomen may be involved. Often patients may complain of additional GI symptoms such as pyrosis, dyspepsia, bloating, or nausea and early satiety. Female patients may mention esophageal symptoms such as chest discomfort or dysphagia more commonly than males. Symptoms may be precipitated by stress and relief often is noted after defecation. Lack of nocturnal awakening with symptoms is a clue the problem is IBS. Constitutional signs and symptoms such as night sweats, fevers, and intestinal blood loss suggest an organic illness. Weight loss is often associated with an organic illness but may be seen in IBS. Since eating may precipitate discomfort or urgency, some patients may lose weight by avoiding food. The presence of alarm symptoms does not exclude IBS nor confirm organic disease [7,8]. Patients may have IBS and another illness occurring simultaneously.

Warning Signs

Night sweats

Fevers

Intestinal blood loss

Weight loss

The next feature of IBS is perturbation of defecation. They may experience hard or fragmented stools with straining and decreased frequency or loose and frequent bowel movements accompanied by urgency. Both groups can have a feeling of incomplete evacuation. The Bristol Stool Scale Score is used as a guideline to determine the degree of constipation. The scale is scored from 1-7 with a score of one representing hard, pellet-like stools while watery movements are scored as 7 [9].

Other functional disorders seem to have a higher prevalence in patients with IBS and include migraine headaches, globus hystericus, fibromyalgia, chronic fatigue, mitral valve prolapse, and urinary bladder symptoms such as frequency or dysuria.

Pathophysiology

Several theories have been postulated to explain the causality of IBS yet all have their limitations. Research has demonstrated high propagation waves in IBS- D patients and prolonged sigmoid and

rectal contractility in IBS-C patients [10,11]. Despite the demonstration that colon transit time may be altered in IBS [12,13] no one has proven that dysmotility is constant.

The concept of visceral hypersensitivity is generally accepted as a leading factor in the development of IBS. Several mechanisms have theorized the existence of silent noviceptors or spinal hyperactivity by up-regulation of neurotransmitters or nitrous oxide. It was once postulated that hypersensitivity was limited to the GI tract but other functional disorders such as fibromyalgia also have hyperalgesia. Clinical research labs have shown multiple times that IBS patients have lower thresholds for pain than do healthy control. Current data also show higher pain responses among IBS patients subjected to electrical stimulation [14-17].

Post-infectious IBS represents a subgroup of IBS-D and some studies suggest an exposure to Campylobacter or Shigella and less frequently with Salmonella [18] though most often a pathogen is never identified. Antibiotics have been used with efficacy in the management of these patients. Objective findings in these patients have included the presence of lymphocytes and inflammatory cytokines in biopsy specimens [19,20].

Most physicians familiar with the care of functional patients will attest to the role of psychosocial factors in the pathogenesis of IBS. The role of anxiety and depressive disorders clearly are associated with flares of the condition and in some patients may be the only precipitant. Various studies have looked at psychological issues and IBS, showing that more severe cases often have psychiatric diagnoses. Those patients also are more apt to have co-existing sleep disorders, fatigue, absence from work or school, and seek medical attention [21-25]. Much work has looked at history of physical, sexual, or emotional abuse in patients with IBS and other functional disorders. Though a direct causality cannot be inferred, there nevertheless is a high percentage of IBS patients with a history of abuse. Some researchers have reported incidences as high as 40-50%. The highest rates are reported in women [26-29].

A final thought towards a mechanism of disease in IBS involves neural pathways. Traditionally attention has been focused on acetylcholine and serotonin. Studies have shown that patients with IBS have more serotonin receptors in the enteric mucosa than do controls [30]. Since serotonin plays roles in both pain perception and motility it is hopeful that greater understanding of these neurohormonal pathways will lead to better interventions.

Research has also looked at other potential pathways. El- Salhy and colleagues have published several works on the roles peptide YY (PYY) plays in IBS and other disorders. PYY is found in intestinal neuroendocrine cells. Their highest concentrations are in the rectum. Stimulation of these cells by lipids, short- chain fatty acids, amino acids, glucose, bile salts, vagal stimulation, vasoactive intestinal peptide, cholecystokinin (CCK) and gastrin releases PYY which affects GI motility and absorption of water and electrolytes. It has been shown that in post- infectious IBS patients there is an increase in colonic PYY producing cells and cells that release serotonin. In the duodenum we see an increase in cells that secrete CCK. Alternatively in the general IBS population we see lower densities of cells that release somatostatin, serotonin, and CCK. This data suggests that PYY availability is determined by concentration of CCK and serotonin concentrations [31].

Beta 3 - adrenoreceptors line the intestinal mucosa and upon stimulation release somatostatin from D cells found in gastrointestinal mucosa. This decapeptide inhibits cholinergic contractions in the gut. The premise is that release of somatostatin will lower secretions, decrease diarrhea, and improve visceral analgesia [32].

Diagnosis

A careful history that discusses length and quality of symptoms, a discussion of psychosocial issues (including a history of abuse), and relieving and exacerbating factors provide the basis for making an accurate diagnosis. The use of imaging studies, endoscopy, and pertinent labs are dependent upon the patient's age, infirmities, and level of suspicion for organic diseases. A minimal evaluation should include thyroid function testing, CBC, metabolic panel, celiac panel, and fecal occult blood. If gas and bloating is a major complaint then formal breath testing for bacterial overgrowth, fructose intolerance, and lactose intolerance is recommended due to the high incidence of these malabsorption syndromes [33,34]. For diarrhea that is more prominent than typically seen or awakens the patient from sleep, colonic biopsies for microscopic colitis should be considered. Non-invasive tests that can be helpful in distinguishing functional GI disorders from organic causes include fecal lactoferrin and fecal calprotectin. Calprotectin measures neutrophils and lactoferrin measures a glycoprotein expressed on neutrophils. Patients with IBD, tumors, or GI infections will have abnormally high levels as compared to IBS patients or healthy controls whom will have normal levels [35].

The standard of diagnosis thus is based upon classical signs and symptoms and the necessary exclusion of organic illnesses in the differential diagnosis. IBS is defined by criteria established by a panel of experts whom meet every few years in Rome to set diagnostic criteria for functional disorders. The current Rome III criteria [36] defines IBS as recurrent abdominal pain or discomfort at least 3 days/ month in the last 3 months with 2 or more of the following:

1. Improvement with defecation

2. Onset associated with a change in frequency of stool

3. Onset associated with a change in form (appearance) of stool.

These criteria must be met for the previous 3 months with an onset of symptoms at least 6 months prior to diagnosis. IBS is further sub-grouped according to bowel patterns:

1) IBS-C, defined as hard or lumpy stools at least 25% of the time and loose or watery stools less than 25% of time.

2) IBS-D, defined as loose or watery stools at least 25% of time and hard or lumpy stools less than 25% of time

3) IBS-M (mixed variety), defined as hard or lumpy stools at least 25% of time and loose or watery stools at least 25% of time.

4) IBS-U, defined as insufficient stool patterns to qualify as IBS -C, D, or M.

5) The Bristol stool scale score may be useful in defining subtypes of IBS.

Management

Given the complex pathophysiology of IBS it comes as no surprise that numerous treatment regimens have been developed to control symptoms. Before embarking on pharmacotherapy the foundation for success lies in a sound physician-patient relationship. Many patients come to the clinic after years of testing and without a formal diagnosis.

Providing a definitive diagnosis often reduces a patient's anxiety and ameliorates the intensity of their symptoms. Reassurance gives the patient peace of mind and is a proven tool in the management of IBS [37,38].

It is very important to assure the patient of the diagnosis of IBS and set realistic expectations of the therapy planned. The patient should know that the goals are reduction in frequency and intensity of symptoms and not a cure. This builds a patient's confidence and solidifies the doctor- patient bond [39] and reduces unnecessary calls and visits. In the next sections treatment of specific symptoms will discussed.

Bloating

Much is said about diet and each patient is unique in their responses to food. Some have no precipitants and others may note discomfort or urgency with even water. Those symptomatic owe their problem to an enhanced gastrocolic reflex. Fiber is often helpful despite lack of good clinical data but too much insoluble fiber can exacerbate symptoms [40], especially bloating. For patients whom have malabsorption of fructose or lactose an elimination diet can reduce symptoms of gas and bloating and serve as adjunctive therapy to standard IBS treatments. Avoidance of sorbitol and sugar alcohols and limitations of gas producing vegetables such as cruciferous vegetables and legumes may be helpful. Carbonated beverages cause distention and elimination of these usually reduces bloating and discomfort. A recent study showed that reduction in daily intake of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (sugar alcohols), the FODMAP diet reduces flatulence, bloating, and discomfort [41].

Role of Pharmacotherapy

Pharmacotherapy based upon an understanding of the various pathophysiological parameters has greatly improved our management of IBS patients. Some are more directed toward analgesia and others toward improving perturbation of defecation. A panel of experts reviewed the major studies on a variety of agents used to manage IBS. A grade of 1 is considered a strong recommendation and 2 as a weak recommendation. Scores of A, B, and C correlated to strong, moderate or weak evidence respectively [42].

Pain

Antidepressants, especially tricyclics have been used for years and have traditionally targeted the pain component [43,44]. The majority of studies have concluded they are efficacious. As a class they have a rating of 1B. Desipramine appears to be tolerated better than others in the TCA class [45,46]. The limiting factors with TCAs are side effects which include dryness, constipation, sleep disturbances, and rarely palpitations. To limit these adverse events a starting dose of 10mg each evening and titrating the dose every few days to 2 weeks is recommended. Selective serotonin reuptake inhibitors have shown to be beneficial in IBS-C patients since they may improve colonic transit time and modify discomfort [47-49]. As a group both TCAs and SSRIs modulate the enteric nervous system with regard to motility and visceral hypersensitivity and alter the brain- gut axis.

Anti-cholinergics and oil of peppermint have been used for years as anti- spasmotic agents yet neither have undergone vigorous placebo - controlled randomized trials with methodology required to reduce the placebo effect. The ACG position paper rates these agents as class 2C. Oil of peppermint which contains carminative has been used in Asia and peppermint candies have been a staple in American restaurants for decades to relieve the discomfort that follows indulgence.

Since the relaxation effect is not unique to the small and large intestines, it may reduce the resting pressure of the lower esophageal sphincter and produce pyrosis and regurgitation. Investigators thus advocate an encapsulated preparation that is avoids the stomach and is available in the small bowel. Like the many anti-cholinergics available on the market, peppermint oil has anecdotally been efficacious and has a following worldwide [50].

Diarrhea

Research in recent years has targeted modification of stool frequency. Alosetron, a 1B drug, is FDA approved for women with severe IBS-D, and is a 5HT3 antagonist. It also has modest relief on pain. The pharmacology of this drug is based upon the knowledge that serotonin acts on motility, secretion, and visceral pain fibers. Several studies have shown alosetron to be superior to placebo in reduction of pain, urgency, and frequency. Another pivotal trial showed durability of the drug in a yearlong study [51,52]. The recommended starting dose is 0.5 mg twice daily with a dose escalation to 1 mg twice daily if efficacy is not reached in a month. Though ischemic colitis is a concern recent experience has shown it to be uncommon in patients and physicians educated on the product. In fact one small study showed that low- dose desipramine could be added to alosetron for pain control without producing adverse events [53].

Rifaximin, is an oral antibiotic that is not absorbed and is selective for a variety of intestinal flora. It has been used in the treatment of small intestinal bacterial overgrowth [54]. Several quality studies have looked at rifaximin in the management of IBS. The major studies used rigorous methodology and used intention to treat analyses. Furthermore all patients randomized were chosen with strict Rome 3 criteria. This strategy appears best with IBS- D patients and/ or those with significant bloating. The optimal doses appear to be 1.1 g to 1.2 g/day in divided doses for 10-14 days [55-57]. Some experts argue that these trials did not account for bacterial overgrowth (SIBO), while other others believe SIBO or dysbiosis is part of the spectrum of IBS. Rifaximin is a class 1B drug.

Constipation

Lubiprostone is FDA approved for both IBS-C as well as for chronic constipation (both idiopathic and opiate -induced). The dosage for IBS-C is 8 mcg twice daily. To reduce nausea, it's most common side effect; the medication should be taken with meals. The mechanism of action is unique among agents on the market. It is a selective C-2 chloride channel activator. By opening chloride channels into the lumen, sodium follows to neutralize the charge, bringing water with it into the lumen of the small bowel. Lubiprostone is thought to work by increasing colonic motility as the increased small intestinal volume flows into the large bowel. In clinical trials 8mcg twice daily vs. placebo showed effectiveness over the course of a year. Compared to placebo, lubiprostone showed superiority with regard to global symptom relief, health concerns, and body image [58-60]. Lubiprostone is a class 1B agent.

Recently a new product, linaclotide, has been approved by the FDA for IBS-C. It acts on intestinal mucosa to increase cyclic- guanosine monophosphate (c-CMP) which works topically to increase chloride and bicarbonate secretion and adds free water to the intestinal lumen.

The end result is a decrease in intestinal transit time [61,62]. Activation of c-GMP also has an effect on intestinal noviceptors and provides pain relief [63,64]. The once a day administration (290 mcg before breakfast) and dual action make this an attractive addition to the armamentarium of agents used in the treatment of IBS-C.

There are many other agents that have been used, one tegaserod, a 5HT4 agonist with a rating of 1A, used for IBS-C was efficacious in improving spontaneous bowel movements [65], but after scrutiny arose following cardiac events, it was withdrawn from the market. As with the use of anti-cholinergics for pain, laxatives have been used forever for the constipation of IBS with effective results in some patients. The methodology of trials however has not met the standards of evidence- based practice and thus laxatives are grade as 2C agents.

Non- pharmacological Therapies

In patients with anxiety and depression that appear to exacerbate symptoms, psychotherapy has been proven by evidenced- based medicine to be effective as first line or second line therapy [66]. Many studies have shown overall improvement in all IBS symptoms and superiority to standard care practices. Psychotherapy, cognitive and behavioral therapy, and hypnotherapy are efficacious in relieving symptoms, but the same has not been shown for relaxation therapy [67-69]. The difficulty in analyzing these approaches is the inability to blind the studies. The rating for these forms of treatment is nevertheless 1C. Given the expense and accessibility of the various forms of psychotherapy, these treatments should be utilized in patients with underlying psychiatric illnesses or stressors that contribute to their symptoms [70].

Finally we have a novel treatment. It is serum- derived bovine immunoglobulin protein isolate and a medical food as labeled by the FDA. In a randomized, double-blinded, placebo-controlled study it was superior to placebo in reducing symptoms of IBS. It is thought to play a role in promoting tight cellular junctions, the reduction of mucosal inflammatory cytokines, and decrease in intestinal secretion [71].

Many published works have shown varying degrees of efficacy with regard to probiotics. It is difficult to make recommendations on their use due to this variability seen in the results of these studies. Of note is the fact that many studies have looked at different strains so comparative data is not available. A review of the trials suggests that probiotics offer at least modest benefits in treating IBS patients. The rating for these products as a group is 2C. Bifidobacteria appears to be superior to Lactobacillus as a sole agent or in combination with other species [72-74]. Given their safety profiles and lack of adverse effects it is almost certain their popularity will rise in adjunctive therapy.

There are multiple drugs in various phases of clinical trials. A promising new agent for IBS-D, eluxadoline has undergone vigorous investigation. It has simultaneous agonism of mu-opiod receptors and antagonism of delta- receptors. In a randomized, double- blinded, placebo controlled study eluxadoline proved to be superior to placebo in reduction of both pain and diarrhea and had minimal side effects [75].

Summary

IBS is an intestinal disorder of significant social and economic burden which for many leads to a poor quality of life. Effective management begins with a strong patient-physician relationship. Treatment should include attention to psychosocial issues and directing pharmacotherapy as well as psychotherapy when appropriate, toward specific symptoms. Some agents are geared toward reduction of pain and others are used to normalize abnormal stool patterns. The use of several treatments is often necessary in many patients.

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