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Irritable Bowel Syndrome: Pathophysiology, Management and Treatment

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Abstract: *Irritable bowel syndrome (IBS) is prevalent worldwide with high prevalence in Mexico, Brazil and in Pakistan with low prevalence in Canada. The etiology of IBS is unknown with brain-gut axis and small intestine bacterial overgrowth, post-infection, genetic defects relating to immune system, high stress and anxiety levels, enteric infection causes increased gut permeability, protozoal infection are the causes, strongly associated with IBS.Genetic environmental and psychological factorsseems to be important in the development of IBS.Frequently used diagnostic algorithm include Manning criteria, the obsolete Rome 1 and 11 criteria, Kuriscriteria, Rome 111 process was published in 2006.Management include FODMAPs(fermentaleoligo-di- and monosaccharides and polyols) diet, dietary fiber with supplementation with psyllium husk,/ispaghula,with a dose of 20 g of ispaghula husk works better than 10g.Treatment include antispasmodic, antidepressant,mesalazine an aminosalicylate drug and, stress management. Probiotics may exert their beneficial effects on IBS symptoms via preserving the gut microbiota, normalizationof cytokine blood levels, improving intestinal transit time, decreasing small intestine permeability, and by treating small intestinal bacterial growth. However, more research is needed on individual strains of beneficial bacteria for more refined recommendations. Research on fecal microbiotia transplantation has been favorable.*
Key Words: *Irritable bowel syndrome, Pathophysiology, Management, and Treatment.*

I. Introduction

Irritable bowel syndrome,(IBS) or spastic colon is a symptom-based diagnosis. It is characterized by chronic abdominal pain, discomfort, bloating and alternation of bowel habits.Diarrhea or constipation may predominate, or they may alternate (classified as IBS-D,IBS-C or IBS-A, respectively)[1]First reference to the concept of an "irritable bowel syndrome" appeared in the *Rocky Mountain Medical Journal* in 1950.Early theories suggested the irritable bowel was caused by a psychosomatic or mental disorder[2].In the United States it has been estimated at 1.7-10 billion in direct medical cost, with an additional 20 billion in indirect cost of IBS patients, and 34.6% loss of productivity among workers with IBS[3,4].Population based studies on the prevalence of IBS in many geographic regions include Mexico, 46 %[5],Brazil,43%[5].Mexico City 35% [6],Pakistan,34%[7],United States,14% to 15 %,[8,9],United Kingdom,[10.5%[10].Japan,10%[5],and Canada,6%[9].Women are around two to three times more likely to be diagnosed with IBS and four to five times more likely to seek specialty care for it than men[11].As a functional gastrointestinal disorder[FGID),IBS has no known organic cause[12].Onset of IBS is more likely to occur after an infection(pos-tinfection IBS-PI) or a stressful life event, but varies with age[13-15].The most common theory is that IBS is a disorder of interaction between the brain and gastrointestinal tract[16].Risk factors of developing IBS increases six fold after acute gastrointestinal infection[17].Antibiotic use, genetic defects in innate immunity and epithelial homeostasis,and role of brain-gut"axis"and childhood physical and psychological abuse is often associated with development of IBS[18-21]No specific laboratory or imaging test can be performed to diagnose irritable bowel syndrome. Diagnosis involves excluding conditions that produce IBS-likesymptoms, and then following a procedure to categorize the patient'ssymptoms. In patients over 50 years old, recommended to undergo a screening colonoscopy[22].IBS sufferers are at increased risk of being given inappropriate surgeries such as appendectomy,cholesyctstectomy,hysterectomy due to their IBS symptoms being misdiagnosed as medical conditions[23].Effective treatment include diet, soluble fiber(Psyllium-ispaghulahusk,Isbagol-Ayurvedic),talk therapy, antispasmodic, antidepressant medication, and peppermint oil[24,25].Paper reviews the current literature, contributory factors, pathophysiology, diagnosis, management, and treatment of IBS.

II. Contributory Factors

The cause of IBS is unknown, a disruption of the brain-gut axis and small intestinal bacterial overgrowth are thought to be important factors [26].Research has found that genetic defects in innate immunity and epithelial homeostasis increase the risk of developing both **post-infectious** as well as other forms of IBS[19].Approximately 10 percent of IBS cases are triggered by an acute gastroenteritis infection.Genetic

defects relating to the innate immune system and epithelial barriers as well as high stress and anxiety levels appear from evidence to increase the risk of developing post-infectious IBS. Post –infectious usually manifest itself as the diarrhea predominant subtype.Evidence has demonstrated that the release of high levels of proinflammatory cytokines during acute enteric infection causes increased gut permeability leading to translocation of the commensal bacteria across the epithelial barrier resulting in significant damage to local tissues which is likely to result in chronic gut abnormalities in sensitive individuals.However, increased gut permeability is strongly associated with IBS regardless of whether IBS was initiated by an infection or not[19].
Publications suggesting the role of brain-gut "axis" in the 1990s[20] and childhood physical and psychological abuse is often associated with the development of IBS[21].Given the high levels of **anxiety seen** in IBS patients and overlap with conditions such as fibromyalgia and chronic fatigue syndrome, a potential model of IBS involves a disruption of the stress system.The stress response in the body involves the HPA axis and the sympathetic nervous system, both of which have been shown to operate abnormally in IBS patients.Psychiatry illness or anxiety precede IBS symptoms in two-third of patients, and psychological traits predispose previously healthy people to develop IBS after gastroenteritis [27].

Small intestinal bacterialovergrowth(SIB0) occurs with greater frequency in patients who have been diagnosed with IBS compared to healthy controlsSIB0 is most common in diarrhea predominate IBS but also occurs in constipation predominant IBS more frequently than healthy controls. Symptoms of SIB0 include bloating, abdominalpain, diarrhea or constipation among others.IBS may be the result of immune system interaction abnormally with gut microbiota resulting in an abnormal cytokines signaling profile[28].Researchers have focused on a possible unrecognized protozoal infection such as **blastocystosis** as a cause of SIB0[16],as certain protozoal infections occur more in IBS patients[28].

III. Pathophysiology

There is evidence that abnormalities occur in the gut flora of individuals who suffer from IBS such as loss of diversity with a decrease in Bacterioides[29].The changes in gut flora are most profound in individuals who have diarrhea predominantIBS.Antibiodies against common components namely flagellin) of the common gut flora are a common occurrence in IBS affectedindividuals[30].Chronic low –grade inflammation commonly occurs in IBS affected individuals with abnormalities found including increased enterochromaffincells, intraepitheliallymphocytes, and mast cells resulting in chronic immune mediated inflammation of the gut mucosa[31].Genetic environmental, and psychological factors seems to be important in the development of IBS.Studies have shown that IBS has a genetic component even through there is a predominant Influence of environmental factors [32].IBS has been reported in greater quantities in multigenerational families with IBS than in the regular population[33].This suggest a heritable factor.This factor does not follow classic Mendelian but is of the complex/multifactorial variety.286 genes have been identified that are variably expressed in IBS-D patients[34].Some research confirm suggest that consumption of spicy foods is directly associated with IBS, especially in women[35].Zheng and associates in a cross sectional study demonstrated that consumption of staple foods, such as rice, bread, pasta and buckwheat noodles is associated with IBS[36].Changes in the serotonin metabolism are thought to play a role in IBS development.One study found increased levels of serotonin transporters in ileum of patients suffering from IBS[37].Another study suggested that an increased expression of apoptotic genes in IBS can lead to an increase in mast cells in intestine. This may lead to internalization of cellular adhesion proteins such as Z0-1 occludin[34].Barreau and colleagues in a neonatal stress models concluded that various types of early traumatic events have long term consequences on gastrointestinal functions, and among these different models, neonatal maternal deprivation(NMD),may constitute a valuable experimental model to investigate the pathophysiology of IBS and to identify novel pharmacological targets [21].

VI. Diagnosis

No specific laboratory or imaging test canbe performed to diagnose irritable bowel syndrome.Diagnosis involves excluding conditions that produce IBS- like symptoms, and then following a procedure to categorize the patient's symptoms.Ruling out, lactose intolerance, small intestinal bacterial overgrowth, and celiac disease is recommended for all patients before a diagnosis of IBS is made.In patients over 50 years old, they are recommended to undergo a screening colonoscopy [22].IBS sufferers are at increased risk of being inappropriate surgeries and IBS symptoms being misdiagnosed as medical conditions[23].
Differential diagnosis.Coloncancer,inflammatory bowel disease,thyroiddisorders,and giardiasis can all feature abnormal defecation and abdominal pain.Less common causes of this symptoms profile are carcinoid syndrome,microscopiccolitis,bacterialovergrowth, and eosinophilic gasteroenteritis;IBSis,howevera common presentation,and testing these conditions would yield low number of results, so it is considered difficult to justify the expence[38].Because many causes of diarrhea give IBS-like symptoms, theAmerican

Gastroenterological Association published a set of guidelines for tests to be performed to rule out other causes for these symptoms.These include gastrointestinal infections, lactose intolerance, and coeliac disease.Research has suggested these guidelines are not always followed [23].Once other causes have been excluded, the diagnosis of IBS is performed using a diagnostic algorithm.Well- known algorithms include the **Manning criteria**,theobsolete **Rome 1 and 11** criteria,and **Kruiscriteria**,and studies have compared their reliability[39].The more recent Rome 111 process was published in 2006.Physicians may choose to use one of these guidelines or may simply rely on own anecdotal experience with past patients.The algorithm may include additional tests to guard against misdiagnosis of other diseases as IBS.Such "red flag" symptoms may include weight loss,gastrointestinal bleeding, anemia, or nocturnal symptoms. However, red flag conditions may not always contribute to accuracy in diagnosis; forinstance, as many as 31% of IBS patients have blood in their stool, many possibly from hemorrhoidbleeding [39].

The diagnostic algorithm identifies a name that can be applied to the patient's condition based on the combination of patient's symptoms of diarrhea, abdominalpain, andconstipation. Forexample, the statement"50% of returning travelers had developed functional diarrhea while 25% had developed IBS" would mean half the travelers had diarrhea while quarter had diarrhea with abdominal pain. While some researchers believe this categorization system will help physicians understand IBS,others have questioned the value of the system and suggested all IBS patients have the same underlying disease but different symptoms [40].

Inappropriate diagnosis. Some common examples of misdiagnosis include infectious diseases, coeliac disease[41),*Helicobacter pylori* and parasites[42].Coeliac disease in particular is often misdiagnosed as IBS.The American College of Gastroenterology recommends all patients with symptoms of IBS be tested for coeliac disease[43].Bile acid malabsorption is also sometimes missed in patients with diarrhea-predominate IBS.SeHCAT tests suggest around 30% of I-D-IBS patients have this condition, and most respond to bile acid sequestrants[44].Chronic use of certain sedative-hypnotic drugs, especially the benzodiazedipines,may cause irritable bowel-like symptoms that can lead to misdiagnosis of irritable bowel syndrome[45].*Hunginand colleagues in a series of 5009 irritable bowel syndrome cases concluded that most (76.6 %) irritable bowel syndrome sufferers in the US are undiagnosed. Irritable bowel syndrome has substantial impact on sufferers' wellbeing and health, with considerable socioeconomic consequences [8].*

Medical conditionsother than IBS.Patients with irritable bowel syndrome are frequently diagnosed with other medical conditions include psychiatric disorders [46], inflammatory bowel disease [47], abdominal surgery, gall bladder removal surgery not due to an increased risk of gallstones, but rather to abdominal pain [48],one study reported a statistically significant link between migraine headaches, IBS, and endometriosis [49].

V. Management

A number of treatments have been found to be effective including, diet fiber, talk therapy antispasmodic and antidepressant medications and peppermint oil [24].

FODMAPs-(fermentable oligo-di- and monosaccharides and polyols)diet.Studieshave shown that up to 70% of IBS patients benefited from eating a low FODMAP diet. Symptoms likely to improve from such a diet include urgency, flatulence, bloating, abdominalpain, and altered stool output. One national guideline advises a low FODMAP diet for managing IBS when other dietary and life style measures have been unsuccessful[50].This diet restricts various carbohydrates which are poorly absorbed in the small intestine, as well as fructose and lactose, which are similarly poorly absorbed in those with lactose intolerances to them .Reduction of fructose and fructan has been shown to reduce IBS symptoms in a dose-dependent manner patients with fructose malabsorption and IBS[51].Many individuals with IBS are lactose intolerant and a trial of a lactose- free diet is recommended[52].Some patients believe they have some form of dietary intolerance;however, tests attempting to predict food sensitivity in IBS have proven disappointing. A small study reported that an IgG antibody test was somewhat effective in determining food sensitivity in IBS patients, with patients with elimination diet experiencing 10% greater symptom-reduction than those on same diet[53].However more research is necessary before IgG testing can be recommended[54].No evidence indicates digestion of or absorption of nutrients is problematic for those with IBS at rates different from those without IBS However, the very act of eating or drinking can provoke an overreaction of the gastro colicresponse in some patients with IBS owing to their heightened visceral sensitivity, and this may lead to abdominal pain, diarrhea, and/or constipation[55].A diet restricted in fermentable oligo-di-and monosaccharides and polyols(FODMAP) now has an evidence base sufficiently strong to recommend its widespread application in conditions such as IBS and IBD[56].

Dietaryfiber.Some evidence suggests soluble fiber supplementation (e.g. psyllium /ispaghula husk) is effective. It acts as a bulk agent, and for many IBS-D patients, allows for a more consistent stool. For IBS-C patients, it

seems to allow for a softer, moister, more easily passable stool[57].However, insoluble fiber(e.g.bran) has not been found to be effective for IBS.In some people insoluble fiber may aggravate symptoms [58,59].Fiber might be beneficial in those who have a predominance of constipation. In some people who have IBS-C,soluble fiber can reduce overall symptoms, but will not reduce pain.The research supporting dietary contains conflicting,small studies complicated by the heterogeneity of types of fiber and doses used [60].One meta-analysis found only soluble fiber improved global symptoms of irritable bowel,but neither type of fiber reduced pain[60].An updated meta-analysis by the same authors also found soluble fiber reduced symptoms, while insoluble fiber worsened symptoms in some cases[61].Positive studies used 10-30 grams per day of psyllium[62].Kumar and associatesin one study specifically examined the effect of dose, and found 20 g of ispaghula husk were better than 10 g and equivalent to 30 g per day[63].

VI. Treatment

Therapy may consist of stool softeners and laxatives in IBS-C and antidiarrheal (e.g.,opiate, or opioid analogs such as lopermide,codeine,diphenoxylate) in IBS-D for mild symptoms and stronger opiates such as morphine andoxycodone for severe cases[64]Drugs affecting serotonin(5-HT) in the intestines can help reduce symptoms. On the other hand, many IBS-D patients report that SSRI type medications exacerbate spasms and diarrhea. This is thought to be due to the large number of serotonin receptors in the gut[65].Certain **antipsychotic**medications, such as clozapine and olanzapine,may also provide relief due to serotogeneric properties these agents possess, acting on the same receptors as other medications in this specific category[66].Benefits may include reduced diarrhea, reduced abdominal cramps, and improved general well-being. Any nausea present may also respond to 5HT3 antagonist owing to their antiemetic properties [67].The patients who do not adequately respond to dietary fiber,osmotic**laxatives** such as polyethylene glycol,sorbitol,and lactulose can helpavoid"catharticcolon"which has been associated with stimulant laxatives [68].**Antispasmodic** drugs (e.g., anti-cholinergic such as hyoscyamine or dicylomine) may help patients, especially those with cramps or diarrhea.A meta-analysis by the Cochrane Collaboration concludes if seven patients are treated with antispasmodic, one patient will benefit. Antispasmodics are divided into neurotropics and musculotropics[69].**Proton pump inhibitors(PPI)** used to suppress stomach acid production may cause bacterial overgrowth leading to IBS symptoms. Discontinuation of PPI in selected individuals has been recommended as it may lead to an improvement or resolution of IBS symptoms [[70].Strong evidence indicates low doses of **tricyclic antidepressants** can be effective for IBS However, the evidence is less robust as to the effectiveness of other antidepressant classes as SSRIs[71].**Serotonin agonists** (e.g.,Tegaserod-Zelnorm),a selective 5-HT4 agonist for IBS-C,is available for relieving IBS constipation in women and chronic idiopathic constipation in men. **Selective serotoninreuptakeinhibitors antidepressants (SSRIs),** because of their serotonergic effect would seem to help IBS,especially patients who are constipation predominant. Initial crossover studies and randomized controlled trials support this role [72,73].**Evidence is conflicting about thebenefits of antidepressants** in IBS. Some meta-analysis have found a benefit, while others have not [74].**Rifaximin** can be used as an effective treatment for abdominal bloating and flatulence[75].Statistically significant reduction in IBS symptoms occurs following antibiotics therapy for small intestinal bacterial overgrowth.However, recent research has shown that the larulose hydrogen breath test does not actually measure SIBO,and that SIBO is likely to be the cause of IBS[76.77].Preliminary research into the effectiveness of fecal microbiota transplant in the treatment of IBS has been very favorable with a 'cure' rate of between 36 % and 60% with remission of core IBS symptoms persisting at 9 months and 19 months follow up[78].There is increasing evidence for effectiveness of mesalazine an aminosalicylate drug with anti-inflammatory properties in the treatment of IBS[79].

Mental health and stress management.The mind body or brain –gut interactions has been proposed for IBS, and is gaining increasing research attention[80].Hypnosis can improve mental well-being, and cognitive behavioral therapy can provide psychological coping strategies for dealing with depressing symptoms, as well help suppress thoughts and behaviors that increase the symptoms of IBS[71],although the evidence base for effectiveness of psychotherapy and hypnosis is weak and such therapies are in general not recommended[23].NICE clinical guidelines recommend that consideration should be given to psychological treatment strategies such as cognitive behavioral therapy(CBT),hypnotherapy and/or psychological therapy[81].**Reducing stress** may reduce the frequency of severity of IBS symptoms, by relaxing, meditation, physical activities, yoga and regular exercise, swimming, walking or running[82].

Probiotics.Probiotics can be beneficial in the treatment of IBS; taking 10 billion to 100 billion beneficial bacteria per day is recommended for beneficial results.However, further research is needed on individual strains of beneficial bacterial for more refined recommendations [77].Probiotics have positive effects such as enhancing the intestinal mucosal barrier, providing physical barrier ,bacteriocin production(resulting in reduced number of

pathogenic and gas-producing bacteria),reducing intestinal permeability and bacterial translocation, and regulating the immune system both locally and systemically among other beneficial effects[23].Probiotics may also have positive effects on the gut-brain axis by their positive effects countering the effects of stress on gut immunity and gut function[83].A number of probiotics have been found to be effective, including *Lactobacillus plantarum*[23]and *Bifidobacteriainfantis*[84]but one review found only *Bifidobacteriainfantis* showed efficacy[85].*B.infantis* may have effects beyond the gut via it causing a reduction of proinflammatory cytokine activity and elevation of blood tryptophan levels, which may cause an improvementin symptoms of depression[86].A probiotic yeast called *Sccharomycesboulradi* has some evidence of effectiveness in the treatment of irritable bowel syndrome[87].Most clinical studies show probiotic do not improve straining sense of incomplete evacuation,stool consistency, fecal urgency, or stool frequency, although a few clinical studies did find some benefit of probiotic therapy.The evidence is conflicting for whether probiotics improve overall quality of life scores[88].Another study found that when (e.g.,probiotics intake) compared to a control group given placebo, those treated with probiotics have shown a significant improvement in the relief of IBS symptoms[89].Probiotics may exert their beneficial effects on IBS symptoms via preserving the gut microbiota, normalization of cytokine blood levels, improving intestinal transit time, decreasing small intestine permeability, and by treating small intestinal bacterial overgrowth of fermenting bacteria[87].**Peppermint oil** appears useful[88].Occasionally, nausea and perianal burning occur as side effects[90].**Yoga** may be effective for some IBS patients, especially poses which exercise the lower abdomen[71].**Acupuncture** might be beneficial for some patients with IBS,but current evidence does not support its use[80].A meta-analysis found no benefits of acupuncture relative to placebo for IBS symptom severity or IBS-related quality of life[91].

VII. Conclusion

The common signs and symptoms of irritable bowel syndrome (IBS) include abdominal pain, discomfort, diarrhea or constipations.IBS is considered as functional disorder with no known organiccause. Most IBS cases are misdiagnosed resulting in high impact on patient's wellbeing and health with considerable socioeconomic consequences.

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